

The AF Report

Atrial Fibrillation: Preventing A Stroke Crisis



A report for patients and those who care for them



A report for healthcare professionals



A report for policy makers and purchasers

www.preventaf-strokecrisis.org

An expert report on how we can prevent AF from causing a deadly UK stroke crisis

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Report summary

We are in the midst of a silent epidemic. Failure to act now will result in a crisis that we cannot afford.

The epidemic results from atrial fibrillation (AF), a heart rhythm disorder that causes strokes. Strokes, in turn, cause death and disability. Stroke is the brain's equivalent of a heart attack and it afflicts one person every five minutes in the UK¹ and it is also a leading cause of adult disability.^{2,3}

To prevent the tragic consequences of this epidemic it is essential that we target the prevention of stroke among the rapidly growing number of people who have AF.

Atrial fibrillation, the most common heart rhythm disorder, is less well known than stroke but it affects an estimated 1.5 million people in the UK. Aside from many other symptoms and consequences, people with AF become five times more likely to suffer a stroke.^{6,8} AF prevents blood flowing properly through the heart. This disruption allows clots to form. The most common and damaging type of stroke results from clots that have travelled to the brain where they cause a blockage in a blood vessel. Twenty percent of all strokes of this type of stroke result directly from AF.⁴

Moreover, AF-related strokes are more severe and cause greater disability than strokes in patients without AF.^{4,5} Half of all AF patients will fail to survive more than 12 months following a stroke.⁴ For many sufferers, surviving a stroke can be worse than dying; as disability and fear of death become constant companions. AF and stroke not only devastate patients' lives,⁶ but also the lives of their families and carers.⁷

Despite the availability of free and simple checks, authoritative estimates suggest around half of AF patients remain undetected. This is frequently because patients are unaware that the symptoms they experience are a sign of anything serious.^{8,10} Tragically, for many people a stroke is the first sign of underlying AF.

There remains an extremely low level of patient awareness of AF and stroke.⁹ Education is needed on the signs and symptoms of AF, on how AF is related to stroke, as well as on the risks they present both to life and health.

The current epidemic is predicted to worsen as the number of people with AF is expected to more than

double by 2050.^{11,12} AF affects a greater proportion of older people than younger. Unless we take action, our ageing population will increase both the number of people with AF and the number of strokes that result from AF.¹³ This increase will also be amplified as we become better at preventing deaths from other conditions, such as heart attacks, which themselves increase the risk of AF developing.¹⁴

Properly used, existing treatments are effective and could prevent AF-related strokes, saving thousands of lives and millions from the National Health Service (NHS) budget.^{6,8} For example, when anticoagulation therapy is used appropriately it is highly effective; lowering stroke risk by about two-thirds in AF patients.^{7,3}

Yet, despite the existence of effective guidelines, vital anticoagulation treatments are both underused and misused in clinical practice.^{15,16} This is largely due to perceived drawbacks^{16,5} associated with the most commonly used anticoagulant drug, warfarin.^{17,18} The impacts of warfarin on blood clotting need to be monitored not only to ensure that the drug is working, but also to ensure that the risk of excessive bleeding doesn't become unacceptably high. The need for monitoring and the risk of bleeding appear to have a disproportionate impact on the use of effective anticoagulation therapy that would otherwise save thousands of lives.

There is evidence that the above perceived drawbacks frequently overshadow current guidelines. This results in many doctors sticking with out-of-date treatment advice^{19,20,125,21} despite compelling evidence that following current guidelines dramatically reduces death and disability.

Today, many thousands of preventable strokes occur every year leading both to thousands of early deaths and a devastating burden on individuals, families and society. This burden takes many forms including disability, healthcare costs, social care as well as loss of working hours and tax revenues.

There is therefore an urgent need for coordinated action within the NHS to achieve earlier diagnosis and better management to reduce the risk of stroke in patients with AF. To address this need, six actions called for by the AFA and ACE are explained in the next section.

Call to action

AntiCoagulation Europe (ACE), the Atrial Fibrillation Association (AFA), and all those who endorse the recommendations in this report, call for an urgent focus on AF within the National Health Service (NHS), and call specifically for six actions that will improve and extend the lives of UK AF patients. If implemented, these actions will prevent thousands of fatal and debilitating cases of stroke; saving hundreds of thousands from stretched healthcare budgets.

Budgetary pressures within the NHS are ever-present and inevitable. Moreover, financial pressure demands sound reasoning and compelling arguments before policy change or new services. Given the weight of the evidence collated in this report, it is clear that the opportunity exists to make considerable long-term cost savings by implementing policies that today will result in the improved detection, diagnosis and management of patients with atrial fibrillation to prevent stroke.

Six actions

To achieve these goals, the six actions called for by the AFA and ACE are:

- **Targeted screening:**
The introduction of a targeted national screening programme drawing on routine manual pulse checks and ECG readings
- **Guideline adherence:**
The development and adoption of policies that increase GP motivation to follow international guidelines
- **Public awareness, patient empowerment:**
The use of existing materials to fuel a national public and patient education campaign to improve detection and patient empowerment
- **Equity of treatment:**
The imposition of equal access to AF treatments and services for all patients using the NHS regardless of location

- **GP education:**
An AF education campaign for GPs to illustrate the importance of symptomatic control, appropriate referral and the value of patient empowerment
- **AF research:**
Government support for research into the causes, prevention and treatment of AF

Targeted screening

We call for the introduction of a targeted national screening programme drawing on routine manual pulse checks and ECG readings

The prevalence of AF in our society continues to grow, but measures to detect and diagnose these patients remain insufficient. Consequently, there are many hundreds of thousands of patients with AF who are currently unaware, untreated and at substantially elevated risk of suffering a stroke. Moreover, the early diagnosis of AF is associated with an increased range of treatment options, some of which have been demonstrated to eliminate AF permanently.

A simple route to improving early detection and management of AF patients is through the introduction of an effective national AF screening programme. In chapter five of this report, the potential advantages of routine screening methods are clearly outlined. For these to be effective, a nationwide policy change is required, one which requires:

- The audit of all patients in general practice to determine and flag those at AF and stroke risk
- Manual pulse checks for all risk-flagged patients when visiting their local GP surgery
- Immediate access to an ECG for all flagged patients for whom AF is suspected
- Ready access to 24 and 48-hour heart monitoring to secure a diagnosis of intermittent AF

Guideline adherence

We call for the development and adoption of policies that increase GP motivation to follow international guidelines

Evidence discussed in chapter seven of this report illustrates that the following of guidelines is associated with improved patient treatment and a reduction in stroke. Confusingly in the UK, physicians have to draw upon two sets of conflicting guidance: the 2006 guidance from the National Institute for Health and Clinical Excellence (NICE) which all doctors in England and Wales are expected to follow; and the 2010 guidelines from the European Society of Cardiology (ESC) which represent the most current expert consensus on the affective management of patients with AF.

The existing NICE guideline for AF (CG36) is currently under review. The AFA and ACE have formally voiced their support for this review and look forward to engaging in consultation with NICE to ensure a revision that will result in harmony with European guidelines and the effective treatment of as many AF patients as possible. Specifically we call for accelerated review of the NICE clinical guideline on AF and for:

- NICE adoption of the treatment recommendations in the ESC 2010 guidelines
- NICE adoption of patient risk calculations using CHADS₂ and CHA₂DS₂VASc as described in the ESC 2010 guidelines
- NICE recommendation of a national opportunistic screening programme based upon the flagging of suitable patients, routine manual pulse checks and immediate access to ECG checks
- NICE recommendation for early referral to an appropriate specialist when many patients might be suitable for ablation and anti-arrhythmic therapy
- Replacement of the traditional but arbitrary classification of AF (based upon the duration of AF episodes) for treatment decisions

We call for changes to the GP payment system to increase patient treatment in accordance with international guidelines.

General practitioners are also currently poorly motivated by payments through the Quality Outcomes Framework (QOF) to manage AF patients in accordance with

guidelines. QOF seeks to reward doctors for the achievement of certain targets. The current system pays extra to doctors if they treat AF patients only with aspirin, despite considerable evidence that a significant additional reduction in risk of stroke is possible with anti-coagulation treatment. Importantly, these data also show that the advantages of warfarin over aspirin come without a significant increase in the risk of bleeding. At the time of preparation of this report, a revision to QOF has been proposed. We strongly support the rapid adoption of these revisions:

- Reward for a high proportion of AF patients for whom a formal stroke risk has been calculated
- Reward for a high proportion of AF patients receiving anticoagulation therapy

Public awareness, patient empowerment

We call for the use of existing materials to fuel a national public and patient education campaign to improve detection and patient empowerment

The importance of public and patient awareness and knowledge cannot be over-stressed. Almost anyone can perform a simple pulse check if they want to check for the possibility that they have AF. We have also reviewed evidence in chapter eight that greater treatment success is achieved in patients who have sufficient knowledge of their condition to contribute to treatment decisions and targets.

Yet, today, not only are there many thousands of patients unaware that they currently have AF, many of those who have been diagnosed are unaware of what is wrong with their heart or why they are taking medication.

ACE and the AFA have developed a wealth of patient information, much of which could provide source material for a national public and patient awareness and education campaign. We call for Department of Health engagement in and support of these campaigns to:

- Increase patient awareness of AF, its signs and how they can check for AF and their risk of stroke with simple checks and tests
- Increase routine supply of educational material at the point of diagnosis, and from then on, so that patients can gain sufficient knowledge to engage in treatment decisions

Equity of treatment

We call for the equal access to AF treatments and services for all patients using the NHS regardless of location

The simple presence of conflicting clinical guidelines leads inevitably to the unequal treatment of AF patients within the NHS. This is by no means the only cause of inequity for AF patients; many are reviewed in chapter eight of this report. By having the NHS, a single body responsible for almost all UK healthcare, we have an unparalleled opportunity to ensure that efficient and effective treatments and services are provided to all UK citizens regardless of local circumstances. Constant vigilance is required to identify and eliminate inequities for patients in the NHS but several targets for attention can easily be identified. We call for government policy and medical practice that ensures:

- Equity of guideline adherence among doctors
- Equity of access to services such as anticoagulation clinics
- The definition and implementation of minimum standards to eliminate or improve services and treatments that fall short of what patients deserve
- Equity of treatment decisions based on clinical status not arbitrary definitions or timing
- Equity of access to anticoagulation treatment regardless of location of the patient or the availability of local anticoagulation services
- Equity of access to ideal referral opportunities regardless of the location of the patient or the availability of local heart rhythm specialists

GP education

We call for an AF education campaign for GPs to illustrate the importance of symptomatic control, appropriate referral and the value of patient empowerment

In chapters seven and eight of this report, we document many instances where doctors over-look symptoms, under-use treatments and where they fail to interpret correctly the amount of risk that a patient is willing to accept for a given benefit.

Patients suffering from the symptoms of AF can benefit significantly from early diagnosis and referral for treatments that can have a significant positive impact. It is important

that GPs develop an understanding of how significant these symptoms are for the patient, and how effectively they can be helped once diagnosed and referred for specialist treatment.

We have also reviewed extensively, in chapter seven of this report, the discrepancies between the theoretical benefits of anticoagulation treatment and the actual benefit achieved in routine clinical practice. Much of this difference can be accounted for by deviation from guidelines founded on a misunderstanding among physicians of how their patients view the risks and benefits of treatment.

The above challenges can be met with educational efforts and tools that:

- Improve GP understanding of the impact that AF symptoms have on quality of life
- Improve GP understanding of the benefits of patient education and engagement in decisions
- Help GPs improve patient understanding of the risks and benefits of treatment
- Improve GP understanding of the potential benefits of early referral

AF research

We call for government support for research into the causes, prevention and treatment of AF

Many of the challenges faced by healthcare policy makers and doctors today arise from inadequate access to the necessary data to make effective decisions. This report and the document upon which it is based aim to help increase access to vital information. However, some data simply doesn't yet exist, highlighting an urgent need for continued research into AF so that services and policies can be developed with a firm confidence of success and cost effectiveness for the NHS. To this end, we call for government support for:

- An assessment of the burden and severity of disease for all patients with AF, based on patient experience and the impact on their quality of life
- Research to identify patients at risk of AF and AF-related stroke, and the likely impact of existing and new therapeutic approaches to the management of AF
- Multi-national registries and monitoring studies to evaluate the effect of interventions to manage AF and prevent AF-related stroke.

Chapter 1 - What is AF?

Key points

- AF is the most common sustained heart rhythm disorder
- Having AF doubles the risk of death, regardless of age
- In symptomatic patients, AF is frequently associated with a highly significant reduction in quality of life
- In all AF patients, the risk of suffering a stroke is increased nearly 500%
- AF can be detected with a simple pulse check but approximately half of all patients remain undiagnosed
- AF, and AF related illness, costs the NHS over £2.2 billion each year
- AF affects nearly 2% of the population, a number that is rising fast
- Between 100,000 and 200,000 people in the UK develop AF every 12 months

Atrial fibrillation (AF) is a common heart rhythm disorder associated with deadly and debilitating consequences including heart failure, stroke, poor mental health, reduced quality of life and death.⁷¹

AF is also the most prevalent sustained heart rhythm disorder.¹⁹³ Today, approaching a million Britons are diagnosed with AF,⁶¹ yet experts suggest that between one third and a half of all AF patients have not yet been detected. Today, everyone aged 40 or over has a life time risk of developing AF of at least one in four.²⁴ For context, this compares with one in eight for breast cancer in women of the same age.²⁵

Among many damaging and debilitating consequences, AF increases an individual's risk of suffering a stroke by five times.⁶⁸ This effect alone results in considerable disability and death,^{193,4} not to mention avoidable millions in healthcare expenditure⁶¹ that the National Health Service (NHS) cannot afford.

What is AF?

Atrial: pertaining to the atria (plural of atrium) the top two chambers of the heart

Fibrillation: the rapid, irregular and unsynchronised contraction of muscle fibres

AF is a heart rhythm disorder (a cardiac arrhythmia) of the atria. The normal beat of the heart (called sinus rhythm) is managed by a sophisticated electrical control system. This system matches heart rate with physiological demands and ensures that the four chambers of the heart contract and relax in time with one another to maintain a steady and efficient rhythm to pump blood.

The heart's natural pacemaker is a cluster of special cells in the atria called the sinus node. The sinus node controls the rate at which the atria contract and relax. In AF, chaotic electrical activity develops in the walls of the atria, over-riding the sinus node. The normal, steady rhythm of the atria is disrupted and they instead begin to fibrillate; quivering with a shallow but very fast rhythm as their muscular walls fail to contract with regularity and coordination.

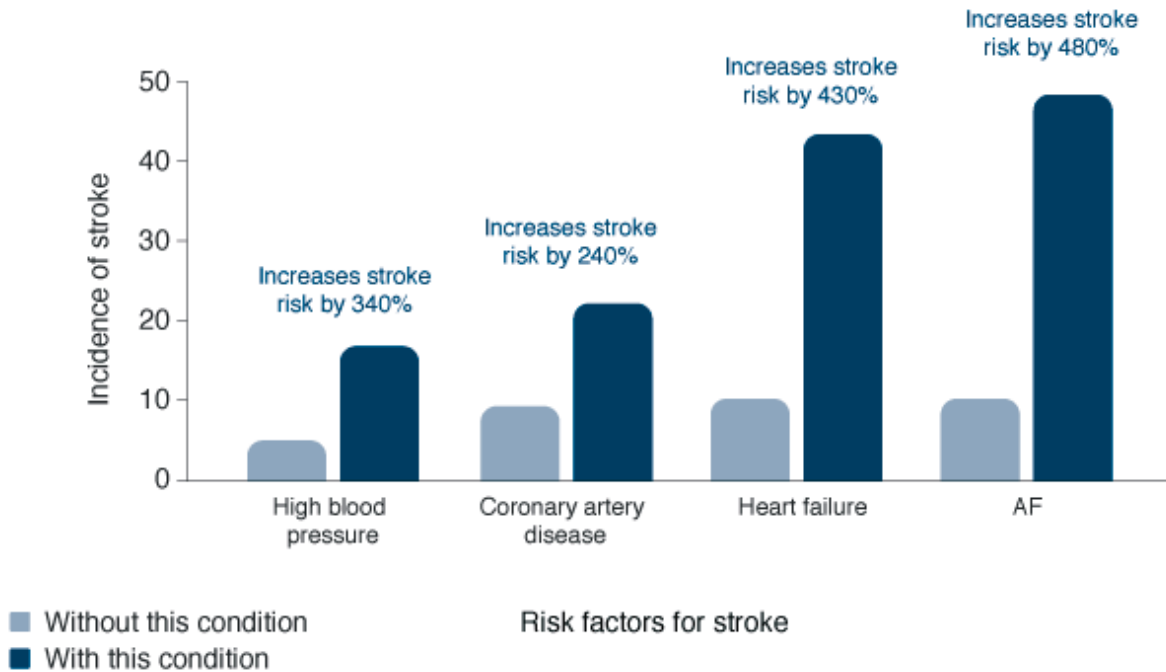
An irregular pulse

This atrial fibrillation disrupts the electrical signals that trigger the contraction of the heart's main pumping chambers, the ventricles. Consequently, the ventricles beat faster and their rhythm becomes irregular as the electrical conduction system is over-run by the fast and chaotic impulses from the fibrillating atria. This altered ventricular beating can be detected as an irregular pulse, a valuable yet simple test for AF.

A progressive condition

Initially for most patients, AF is an electrical problem in the heart that can be addressed by therapies which treat the rate and rhythm of the heartbeat, or which can immediately return the heart to normal sinus rhythm – a procedure called cardioversion.

AF increases the risk of stroke by nearly five times, more than any other cardiovascular risk factor



Over time, AF which is untreated, or which fails to respond to treatment, begins to change the anatomy of the heart muscle, interfering further with the electrical conduction necessary for a normal heart beat. Eventually, all treatments to correct the electrical system become ineffective, leading to therapy that aims only to prevent the consequences of AF.

Deadly consequences

Atrial fibrillation disrupts the efficient pumping of blood through the heart and around the body. The disturbance in flow can allow clots to form where the blood moves too slowly. The blood stream can then carry these clots to vessels in the brain causing deadly blockages that result in stroke.

Massive NHS burden

AF is a significant and growing drain on the NHS. During the past 20 years there has been a 60% increase in the number of patients being admitted to hospitals as a result of AF.²⁶ In 2008, there were an estimated 850,000 GP visits because of AF in the UK.⁶¹ When including AF as a causative secondary diagnosis, the total cost of AF to the NHS has been calculated to be nearly £2.2 billion a year.⁶¹ Some authoritative estimates predict a three-fold increase in AF over the next 50 years.^{12,27}

Signs, symptoms and consequences of AF

There are many negative consequences of AF frequently leading sufferers into a life of confusion and despair.²⁸ AF is associated with a significant increase in risk of stroke, heart failure and death.⁷¹ It has also been found that approximately one third of AF patients suffer persistent anxiety or depression. From the same research, depression was also noted to have considerable negative impact on future quality of life.²⁹ Other symptoms include palpitations, shortness of breath, light-headedness, fainting, fatigue and chest pain.³³ For emergency admissions to hospital, AF most often presents as difficulty with breathing, chest pain and palpitations.⁶⁴

A simple and easily identifiable sign of AF is an irregular pulse. For this reason, many AF experts and patient advocacy groups are calling for pulse checks to become a free, swift and routine part of every GP visit.

However, AF is frequently intermittent and many people with AF have no or non-specific symptoms.⁸ These combine to make detection and diagnosis difficult; often, AF is not apparent until a person goes to see their doctor with a serious complication such as stroke, a blood clot in the leg or heart failure.⁶⁴

Yet, even patients who do experience symptoms of AF are not always diagnosed immediately. In a recent international survey, there was an average delay of 2.6 years between the onset of symptoms and the diagnosis of AF.³⁰ In another piece of research, among patients with documented chronic AF, it was found that more than a third were not aware of their diagnosis and up to half were unaware of why they were being treated.³¹ This indicates that many patients with AF are not being detected or managed effectively and that many are at risk of serious long-term consequences such as stroke.

Efforts have already begun to increase the rates of diagnosis and effective management of AF. For example, the National Institute for Health and Clinical Excellence (NICE) recommends that doctors make assessments for the presence of AF in all people presenting with breathlessness, palpitations, fainting/dizziness, chest discomfort, stroke or mini-stroke (TIA).³²

How does AF lead to stroke?

AF results in a fivefold increase in the risk of stroke, making it the most powerful independent risk factor for stroke.⁶⁸ Moreover, strokes in patients with AF tend to be more severe than in non-AF patients.⁷² The above chart illustrates the impact that AF has on the likelihood of suffering a stroke compared to other stroke risk factors such as high blood pressure, heart disease and heart failure.

The risk of stroke increases because AF is associated with the formation of clots inside the heart. During AF, blood can slow as fibrillation prevents the normal high-pressure flow of blood through the heart and out to the arteries. When blood is allowed to travel slowly the natural formation of clots can begin. This is usually a safety mechanism to help prevent excessive bleeding at sites of injury.

In stark contrast, clots forming within the heart and arteries can be deadly. As clots travel downstream into increasingly smaller arteries, even small clots can cause blockages that prevent oxygen and nutrients reaching the tissues. If such a blockage occurs in the brain, the damage done by the lack of blood flow results in a stroke. AF is estimated to be responsible for approximately 15%-20% of all strokes.^{63,4}

Who gets AF?

It is difficult to overstate just how big a problem AF presents. To provide some perspective, one authoritative

and recent study from the Mayo clinic in the US concluded that, for anyone aged 40 or above, the lifetime risk of AF exceeds 25%;²⁴ meaning that one in four adults can expect to develop AF. This compares to the lifetime risk of breast cancer in women of the same age, which is one in eight.²⁵ However, because of improved detection methods, each new study of the prevalence of AF reports an increase for the same point in time. For example, the Mayo clinic study above was published in 2004 when AF was thought to affect less than 1% of the population they were studying.³⁴

We now know that around 2% of the population in 2004 had AF. It is predicted that by 2050, over 4% of the population will have it.¹² Consequently, it is very likely that, for those aged 40 today, the lifetime risk of developing AF in fact higher than one in four .

Given the number of people who have or will develop AF, it is not easy to define a typical AF patient. Men and women of all ages can be affected. In general terms, the likelihood of developing AF increases with age.¹⁹³

However, some people appear to be at a higher genetic risk. This predisposition to AF is most often seen in young patients.^{191,199} In addition, some studies suggest that the incidence of AF is higher than normal in athletes and others who engage in frequent, vigorous exercise regardless of age.^{35,36} For all these reasons, AF is not just a condition of the elderly.

What causes AF?

The most common underlying causes of AF are high blood pressure, thyroid disease and, to a lesser extent, coronary artery disease and diabetes.^{195,178} Dietary, lifestyle and other factors that contribute to the risk of AF include emotional and physical stress and excessive caffeine, alcohol or illicit drug intake.⁶⁴

The main causes of AF are different than they were 20 years ago. At that time, rheumatic disease commonly resulted in the hardening and narrowing of the heart's mitral valve (mitral stenosis) and was an important cause of AF. The incidence of rheumatic disease in European patients has diminished considerably in recent decades due mainly to improved living conditions. Today, AF as a result of mitral stenosis is relatively rare. The term 'non-valvular AF' is used to describe cases where rhythm disturbance is not associated with these problems.⁸ This report is concerned only with non-valvular AF, which is that most frequently encountered in the UK.

How many people suffer from AF?

As we have seen, AF is responsible for many hundreds of thousands of GP visits⁶¹ despite estimates that nearly between one third and a half of those affected are yet to be diagnosed. Over 800,000 patients in the UK are known to have AF.⁶¹ As symptoms are not always specific, and because there is no routine screening for early detection, experts estimate that the total number with AF in the UK might exceed 1.5 million.

The numbers of people affected by a condition are generally measured in two ways. Prevalence is the proportion of a population affected at any given time; usually as a percentage. The other measure is incidence, which measures just the newly affected patients in the population over a given time span, usually 12 months.

Growing and under-detected prevalence of AF

As seen in the example above from the Mayo clinic in the US, the proportion of the UK population with diagnosed AF is also growing. Today we believe the prevalence of AF in the UK to be near 2% and increasing.²⁷ Between 1994 and 2006, the UK prevalence of AF rose from 0.78% to 1.42%.²⁷ This increase appears to reflect increasing life expectancy as well as the impact of medical science that enables more people to survive conditions such as heart attacks that can add to the likelihood

of developing AF.⁶⁶ There is also the very real likelihood that an improved focus on AF, and improved methods of detection, will uncover greater numbers still.

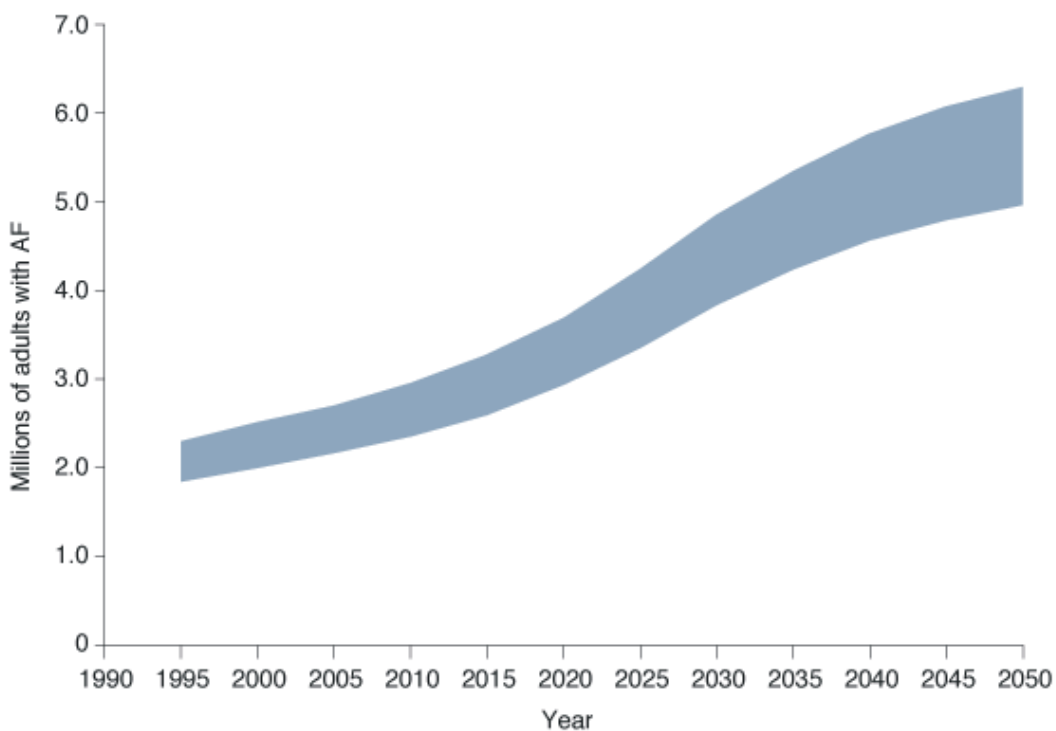
Independent of this increase in prevalence of AF over time in our society, the number of people with AF has been shown to double with each advancing decade of age, from 0.5% at age 50-59 years to almost 9% at age 80-89 years.¹⁹³ Not surprisingly, the incidence of AF also increases with age, contributing to the growing prevalence.¹⁹³

As all these factors combine, it has been predicted that the total number of people affected by AF is likely to triple by 2050.^{12,27}

Incidence of AF in the UK

The most recently published data on the number of people in the UK who develop AF is from 2002. This research reported that the incidence of AF in the UK was 1.7 per 1,000 patient years.³⁷ With today's population this would mean that 105,000 people develop AF every year. If, however, the number of people developing AF has been increasing each year since 2002, similar to the increase observed above, then it could be that approaching 200,000 people in the UK are now developing AF every 12 months.^{37,12}

The number affected by AF is predicted to double by 2050¹¹



Chapter 2 - What is stroke?

Key points

- Stroke accounts for 10% of all deaths
- Stroke affects 150,000 people in the UK, killing 53,000 each year
- Stroke-related costs in the UK NHS amount to £2.8 billion
- Surviving a stroke is frequently reported to be 'worse than death'
- Stroke is a leading cause of adult disability
- The consequences of stroke are dramatic and can negatively impact many people beyond the stroke victim

The brain requires a constant supply of blood for it to receive essential oxygen and nutrients. A stroke happens when the blood supply to any part of the brain is cut off and brain tissue is damaged.

The impact of a stroke is both instant and unpredictable. The nature and the severity of the effects depend on the amount of damage caused and the part of the brain that has been affected. Frequently people become paralysed, numb or incapable of normal speech. Vision can be impaired, as can both thoughts and feelings.

Stroke accounts for 10% of all deaths,^{43,56} and is also a leading cause of adult disability.^{3,38} The sudden nature of stroke means that sufferers, families and carers have no opportunity to prepare for what is usually a tremendous blow to their lives.

Beyond the personal impact of death and disability, stroke costs us all through the massive burden it places on National Health Service (NHS) budgets and the impact it has on the wider economy. It is estimated that the direct cost of stroke to the NHS is £2.8 billion, and that stroke patients occupy up to a quarter of all hospital beds.³

Effective methods to prevent stroke in people at high risk are both widely available and inexpensive. The potential exists to save thousands of lives and millions from health-care budgets.

What causes a stroke?

The vast majority, around 85%, of strokes are caused by a blockage in one of the blood vessels that supplies the brain.⁵⁶ The remaining 15% are usually the result of a bleed. Strokes caused by blockages are called ischaemic (ISS-KEEM-IC). Ischaemic is a medical term denoting a lack of oxygen. The most common cause of ischaemic strokes is a blockage caused by a blood clot. Most ischaemic strokes are the result of an embolism, which is a clot, or other material, that travelled to the brain in the bloodstream from somewhere else. For example, a blockage caused by a clot that formed in the heart is a cardioembolic ischaemic stroke. Strokes caused by bleeds are called haemorrhagic (HEM-UH-RA-JIC).

What's a mini-stroke or TIA?

If the blood supply to the brain is only briefly interrupted a mini-stroke might result. Also known as a transient ischaemic attack or TIA. The symptoms of a TIA are very similar to those of a stroke but last fewer than 24 hours. It is vital that medical attention is sought regardless of the temporary effects; individuals who have had a TIA are at high risk of suffering a stroke. Studies have shown that in the 90 days following a TIA, the risk of stroke exceeds 10%.³⁹

How many people does stroke affect?

Worldwide, stroke is the most common cardio-vascular disorder after heart disease, accounting for 5.7 million deaths annually, nearly one in ten of all deaths.⁴³ In the UK, 150,000 people are struck by stroke each year,¹ and 53,000 people are killed.⁴⁰ This makes stroke the third biggest killer in the UK after heart attacks and cancer.⁴¹ Stroke accounts for 9% of all deaths among UK men and 13% among UK women.⁴²

For many, surviving a stroke is a fate worse than death; stroke is the leading cause of adult disability. Over 300,000 people in the UK are living with permanent disabilities as a result of suffering a stroke.³

The total number of people living through the consequences of stroke in Europe has been estimated to be 9.6 million.⁴³ A World Health Organization (WHO) study reported that the annual number of new cases in Europe to be two million in 2004.⁴³ This was comparable to the estimated annual incidence of cancer cases at 2.9 million for the same year.⁴⁴

For countries within the EU, a study based on data from WHO estimated the number of strokes to be 1.1 million in 2000.⁶⁹ Furthermore, it has been predicted that stroke incidence will increase to 1.5 million per year by 2025, largely owing to the increasing proportion of elderly individuals.⁶⁹

The below charts illustrate authoritative estimates of stroke incidence throughout Europe. It is immediately apparent from the first chart that some countries face a greater challenge than others and that, Europe-wide, men are generally affected more than women. It is also clear that the UK has a long way to go if we are to reduce the rate of strokes to levels currently observed in France and Switzerland. Unless we act now to prevent

avoidable strokes in AF patients, this task will become immeasurably more difficult.

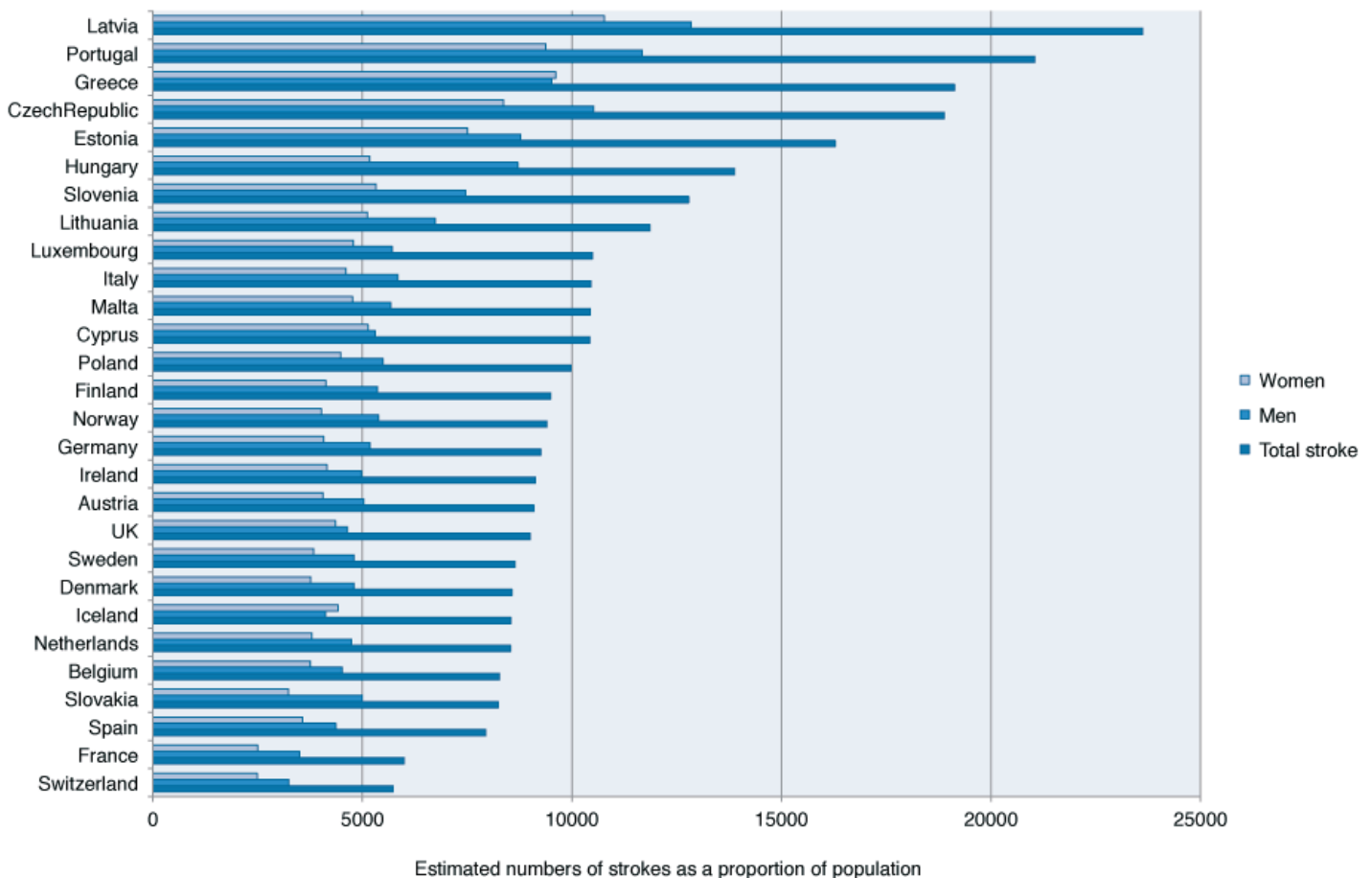
This second chart shows the same data by age. While it is clear that stroke is most commonly an affliction of the elderly, there are many countries within which a disproportionate number of those affected by stroke are aged 55-74.

Who suffers from stroke

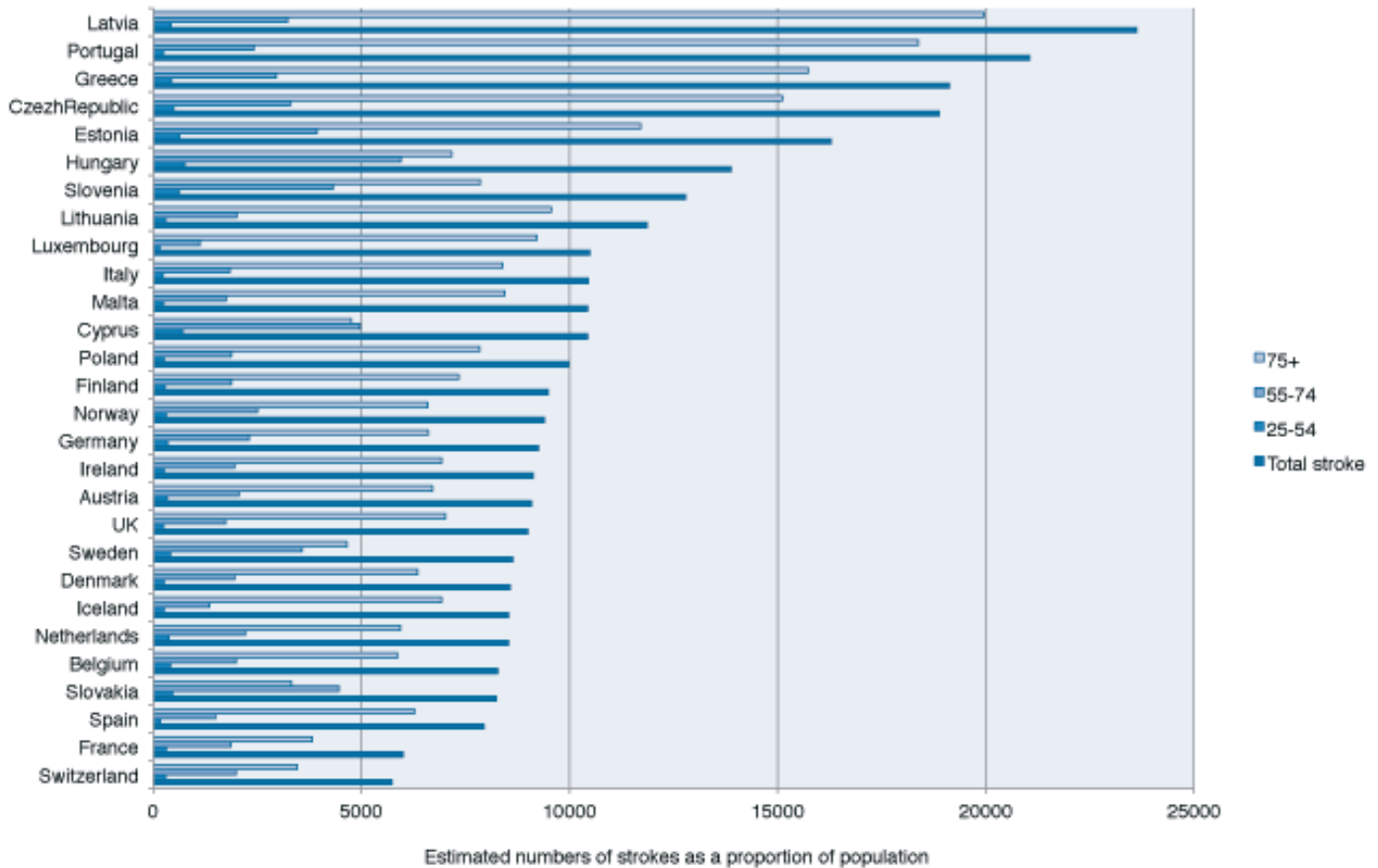
While predominantly affecting the elderly, approximately 25% of strokes occur in people aged below 65 years.²² In the UK, it has been estimated that 20,000 strokes occur in those who are 45 and younger every year.

Several risk factors other than age contribute significantly to stroke risk. Principal among them are atrial fibrillation, heart failure, heart disease and high blood pressure. Atrial fibrillation has the most powerful impact, elevating risk over a non-AF patient by five times. AF is directly responsible for 20% of strokes. High blood

Comparing stroke rates in Europe.⁶⁹



The risk of stroke generally increases with age.⁶⁹



pressure on its own elevates the risk less than each of the other three main risk factors, but because so many people have high blood pressure, it represents the single biggest cause of stroke in the UK.

Lifestyle factors also play an important role. Smoking has been shown to double a person’s risk of suffering a stroke. Poor diet, lack of exercise and excessive alcohol intake have also been shown to increase stroke risk.

Some ethnic differences may also exist, reflecting differences in the predisposition to some of the risk factors associated with stroke. For example, there is a high prevalence of high blood pressure and, as a consequence, stroke, among afro-caribbean populations. In the UK, the death rate from stroke has also been found to be higher among individuals of south asian origin than among the caucasian population.⁴⁵

What are the consequences of stroke?

As well as accounting for nearly 10% of all deaths,^{43 56} stroke is a major cause of long-term disability. World-wide, five million stroke sufferers are left permanently disabled every year.⁵⁶ In the UK, over 300,000 stroke survivors are living with permanent disabilities which leave them dependent upon others. Stroke can affect nearly all human functions, making it difficult for many patients to get out of bed, walk short distances or perform the basic activities of daily living. As well as impairing speech and physical functioning,⁵⁶ stroke can also adversely affect mental health.⁴⁶

Strokes are sudden and they frequently affect people who were unaware they were at risk. Consequently, they and their families are often poorly prepared to deal with the stroke and the damage it brings to their lives.⁴⁶ Long-term disability can dramatically affect the quality of life of both patient and relatives.

Not only does the patient and his or her family frequently have to shoulder the burden of an unexpected long-term disability, those living with the aftermath of a stroke are often in constant fear of death or another stroke.

The consequences of stroke are far from limited to the elderly. A long-term study assessing outcomes in young adults (aged 15–45) after a stroke found that within six years only 49% were still alive, not disabled, had not suffered from a recurrent event or had not undergone major vascular surgery. The majority of the survivors also reported emotional, social or physical effects that reduced their quality of life.⁴⁷

What are the costs of stroke?

Not only are strokes tragic, fatal and debilitating, they are extremely expensive. It has been estimated that a single stroke costs the NHS between £9,500 and £14,000. The factors that cause a stroke have been found to have a bearing on the severity of a stroke. For example, people with AF tend to have more severe strokes which are consequently more expensive.^{48,62}

Strokes cost more than their direct burden on healthcare budgets. The wider economy suffers from the loss of productivity associated with disability and death. The long-term care required for stroke survivors is usually informal and often overlooked. Yet this also comes with a tremendous cost to society. Then there is the human cost, which is incalculable.

Our NHS hospitals are also burdened with providing the physical space required to treat stroke patients. Stroke survivors occupy around 20% of all acute hospital beds and one quarter of all of long-term beds.³

The direct cost of stroke to the NHS has been estimated to be £2.8 billion every year. This huge sum, however, does not represent even half of the total costs. The indirect costs to the wider economy are £1.8 billion and the costs of informal post-stroke care amount to an estimated £2.4 billion.³

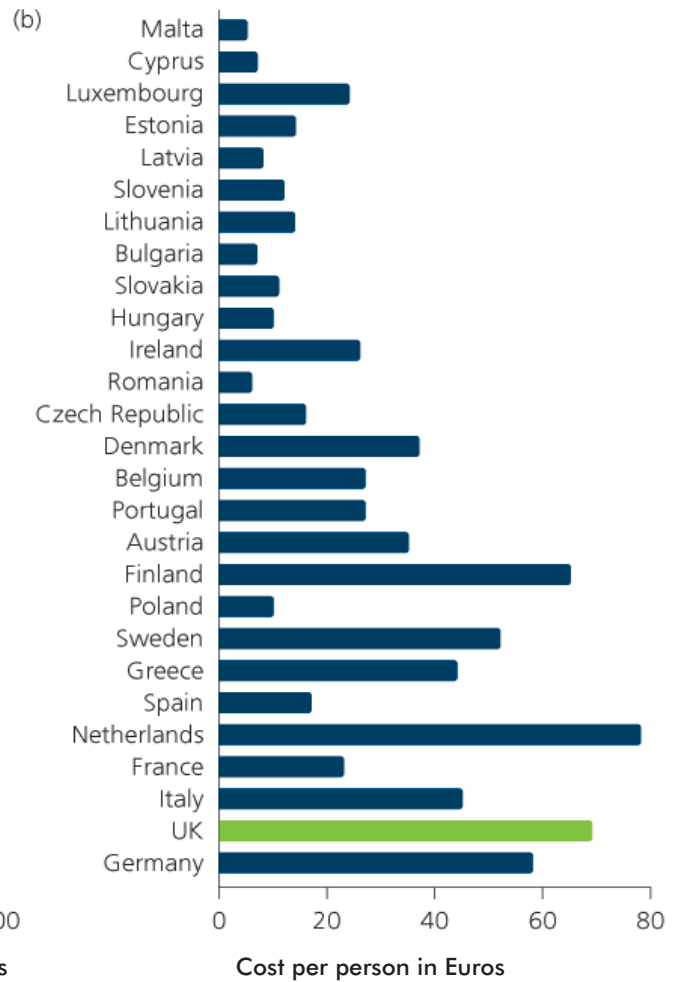
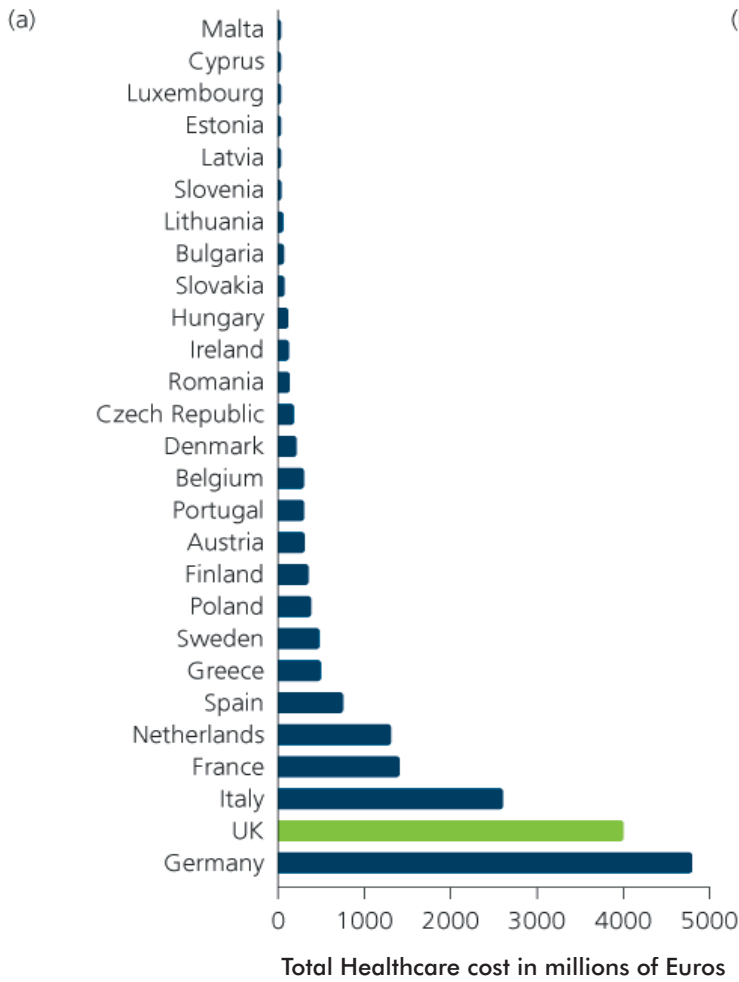
If just the avoidable strokes arising because of AF were prevented, the NHS would save nearly £60 million in direct stroke costs alone. In the chart below, the cost of stroke to the UK can clearly be seen. Both the total of stroke costs and the cost per head of population are among the highest spent of any country in Europe.

The cost of stroke for the whole of the EU was calculated to be over €38 billion in 2006. This figure included healthcare costs (about 49% of the total), productivity loss due to disability and death (23% of the total) and informal care costs (29% of the total).⁵⁷ These figures demonstrate the tremendous financial burden to society posed by stroke in Europe.

It is clear that stroke is a costly health problem in the UK and beyond. Stroke accounts for a massive burden on patients, their carers, families, friends and society. This burden falls disproportionately on the elderly, who are most at risk. Early diagnosis and effective management of atrial fibrillation would help to reduce the burden of stroke in the UK. Furthermore, the prevention of stroke with existing, cost-effective therapies in patients at high risk has the potential to reduce this huge economic burden significantly.⁵⁰

For example, in patients with AF, who are known to have a high risk of stroke, the cost of treating a stroke has been calculated to be almost four times greater than the cost of prevention with ten years' anticlotting therapy.⁹⁷

Stroke is a massive expense for the NHS and the taxpayer.⁵⁷



Chapter 3 - Why does AF matter?

Key points

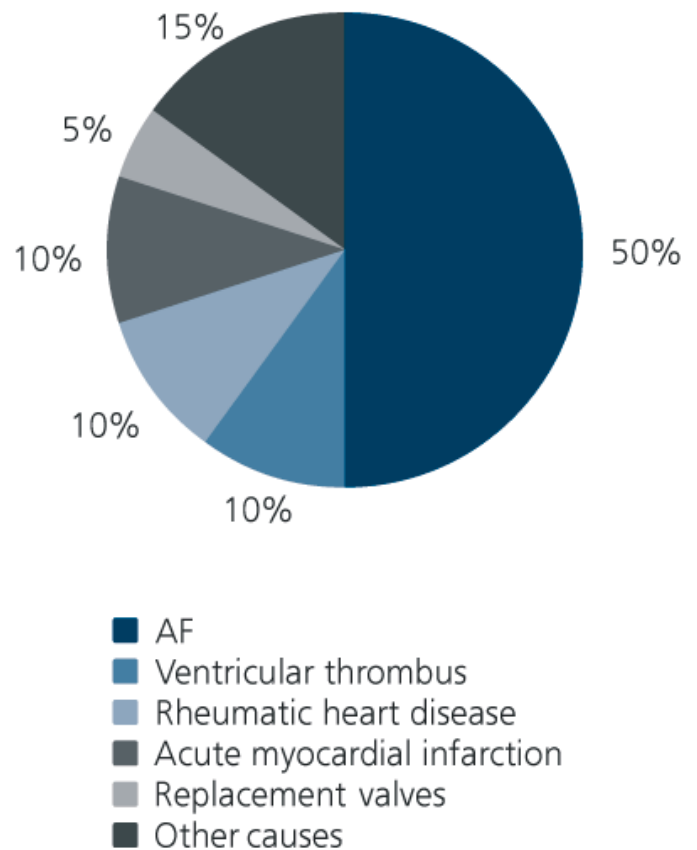
- Strokes in people with AF are more severe and have worse outcomes than strokes in people without AF
- AF almost doubles the death rate from stroke
- AF strokes are cardioembolic which leads to the increased risk of more brain damage
- AF increases disability from stroke
- AF increases the risk of a stroke happening again

The burden of stroke for patients with AF is worse than just an increase in stroke risk. The strokes suffered by people with AF are also more severe,⁷² they are more frequently fatal^{4,55} and they are more likely to lead to disability,^{4,5,178,72} increased healthcare costs¹⁰⁶ and extended hospital care than strokes in patients without AF.⁷² Moreover, AF-related strokes are more likely to happen again, adding not just to the risk of future strokes, but also to the potential for increased patient anxiety and a further reduction in quality of life.

Why does AF lead to more severe strokes?

The increased severity of strokes in patients with AF is thought to be related to the large size of the clots that ultimately block blood vessels in the brain. Almost all AF-related strokes are cardioembolic; which means that the clot forms in the chambers of the heart from where it travels downstream in the blood to the vessels of the brain. Clots will naturally grow rapidly in size as part of the body's safety mechanism to prevent bleeding. The further a clot travels, the greater opportunity it has to increase in size. Once in the brain, a larger clot can block larger vessels. The bigger the vessel that is blocked, the greater the amount of brain tissue that is likely to be affected. And so it follows that the greater the amount of brain that has its blood supply cut off, the greater the chance of a severe stroke, death and disability.

AF causes half of all dangerous embolic strokes.⁵²



AF nearly doubles the death rate from stroke

Many aspects of strokes are more severe among AF patients but one of the most dramatic is mortality; the likelihood that a stroke will kill. AF-related strokes kill nearly twice as frequently as non-AF strokes. In a Danish clinical study, stroke patients with AF were 70% more likely to be killed than those without AF.⁷² A larger subsequent study of Italian stroke patients found that the increase in death rate among AF patients after 12 months was even higher; almost double the rate of those without AF.⁴ An Austrian stroke registry also demonstrated a near doubling of death rate from stroke in the presence, compared to the absence, of AF (25% versus 14%).⁵⁵

12 months after a stroke nearly twice as many AF patients will have died compared to non-AF patients⁵⁵

Annual death rate (%)		
Year	With AF	Without AF
1	50	27
2	14	8
3	14	6
4	10	6
5	11	6
6	4	3
7	5	4
8	4	3

So powerful is this effect, AF has been found to be to be an independent predictor of death even after adjusting for age, sex and vascular risk factors.

A trend towards an increase in the overall early death rate in patients with AF over the last 20 years has also been reported,⁵¹ which may reflect the increasing age of the population. With both AF prevalence¹¹ and AF death rate increasing, there is an urgent need to improve the management of AF, in particular to prevent the most common fatal consequences, such as stroke.

For a more thorough review of the long-term consequences and costs of AF-related strokes, please see chapter four.

Patients with AF are therefore a vital target population for reducing the overall burden of stroke on society.

Chapter 4 - Cost of AF to individuals and society?

Key points

- AF-related stroke impairs stroke survivors' quality of life more than non-AF-related stroke
- Permanent disability and other consequences of AF-related stroke place a heavy burden on carers, family members and health and social services
- Healthcare costs associated with stroke are higher for patients with AF than for patients without AF

Significant impact on quality of life

Survivors of strokes have described their subsequent life as a fate worse than death. This description is not only dramatic and intuitively apparent, it is also supported in the scientific literature. For purposes of research, the impact of a stroke can be evaluated on a scale of zero to ten where 10/10 represents perfect health and 0/10 represents death.⁵³

In a study that used these scores to evaluate the impact of stroke on the quality of life for patients with AF, 83% of patients rated their quality of life after a severe stroke as equal to, or worse than, death.⁵⁴

Other scores have been developed to assess specific aspects of quality of life; such as neurological function. A comparison of AF and non-AF strokes is presented in table 4 across several of these aspects. As above, the scores in the table consistently show that AF-related stroke has a more negative impact on quality of life than non-AF-related stroke.⁷²

AF also increases the risk of medical complications following stroke. Compared with those without AF, patients with AF suffer more frequently from pneumonia, pulmonary oedema (accumulation of fluid in the lungs) and bleeding in the brain after stroke.⁵⁵

Heavy burden on carers, families and society

This sustained impact of strokes has a devastating impact not only on the individual and their carers but also on the wider family, particularly children.

Increased disability and poor health

More than one-third of patients who experience a stroke return to their home with some level of permanent disability.⁵⁶ They then rely on informal care, typically from family members, to help with their normal daily activities and to arrange the required additional assistance from healthcare services.

The disabling consequences of stroke are worse for those patients who survive an AF-related stroke, than for those without AF. The presence of AF increases the risk of remaining disabled after a stroke by almost 50%.⁵

This disability takes many forms. When compared with non-AF patients, the presence of AF at the time of stroke has been found to:

- Increase significantly the loss of ability to perform normal daily activities,
- Decrease the level of consciousness,
- Increase the partial paralysis of the arm, hand and/or leg
- Increase the difficulty in swallowing

This was found to be the case both immediately after the stroke and after rehabilitation.⁷²

Psychological impact on patients, family and carers

In addition to providing day-to-day practical care, the family also has to manage the emotional, mental and behavioural changes in the patient. These changes can be among the most difficult for family members to handle. They include mood swings, personality changes, irritability, anxiety, memory loss and depression.^{56,58} Faced with such transformations, and the corresponding effort required to provide vital care, members of the family can experience a loss of independence, identity and social life. They also suffer extreme tiredness and depression. These carers also report fears regarding the safety of the patient and distress at not having time to attend to all of the patient's needs.^{56,58}

High long-term demand on health and social services

The rehabilitation and long-term care of stroke survivors also place a significant demand on formal health and social services, often involving community nursing, social care, physiotherapy as well as speech and occupational therapy.^{56,59} Research indicates that AF increases the requirement and costs for the provision of this formal care compared to non-AF stroke patients.⁷²

Increased hospitalisation, cost and recurrence with AF-related stroke

AF has been found to be associated with a 20% increase in the length of hospital stay and a 40% decrease in the likelihood of patients returning home compared to the absence of AF in surviving stroke patients.⁷²

As described in Chapter three, almost all AF-related strokes are cardioembolic; where the clot forms in the chambers of the heart from where it travels downstream in the blood to the vessels of the brain. Compelling research has shown that those who suffer cardioembolic strokes have a poorer clinical condition on admission to hospital, experience a longer stay and endure a worse recovery following discharge than those with non-cardioembolic stroke.¹⁰⁶ The same study also found that costs were higher. The average cost per patient of initial hospital care for cardioembolic stroke was €4,890 per patient, compared with €3,550 for non-cardioembolic stroke, representing an increase of almost 40%.¹⁰⁶

In addition to being more severe, cardioembolic strokes are associated with a higher risk of recurrence than other types of stroke.⁶⁰ The increased severity and risk of recurrence of strokes in patients with AF compared with other strokes suggests that these patients will experience a greater impairment in quality of life than patients without AF.

Case study: a carer's perspective

"For the past nine months my sister and I have been acting as full-time carers to our mother, who is bedridden following a stroke. She is unable to do anything for herself and needs 24-hour care in her own home, where she feels comfortable and safe. We have had to leave our husbands and our own homes to give mother our full support.

Full-time carers can lose their sense of identity and independence as their social life is curtailed. I am also concerned for my husband's welfare."

Case study: a child's perspective

"The first time I saw Daddy again, he was sitting in a wheelchair tied on with a sheet so that he would not fall. His mouth was drooping and he was making funny noises which we could not understand. I was scared of him, I didn't want to see him any more. I was ashamed of him... he does not remember much about it. He doesn't look like Daddy any more."

High economic cost

As explored in chapter two, strokes are extremely expensive, each one costing the NHS between £9,500 and £14,000. AF strokes are more severe⁷² and consequently can be expected to account for a greater proportion of the more expensive strokes. This impact of AF becomes of considerable importance when considering that the cost of stroke to the UK economy has been estimated to be £2.4 billion,⁶¹ and the cost of stroke to Europe is likely to be over €38 billion.⁵⁷

AF-related strokes cost more

In a clinical study that investigated the cost of different severities of stroke, it was found that the average cost of a severe stroke was more than three times higher than the average cost for a mild stroke.⁴⁸

There is also direct evidence for the increased cost of stroke in patients with AF. In one study, the average direct costs of stroke per patient were found to be over a third higher in patients with AF than in patients without AF.⁶² The effect of AF on stroke-related inpatient costs was also recently analysed. The inpatient costs over just a three-month period were on average 8% higher for each patient with AF compared to patients without AF.¹⁹⁶ As AF is estimated to be responsible for approximately between 15-20% of all strokes,⁶³ the increased cost of AF-related strokes compared with other strokes represents a significant economic burden.

Direct costs of AF to NHS are huge

All the above studies were focused on the economic burden of AF associated only with the elevated risk and severity of strokes. A study from the Office of Health Economics published in 2009 deliberately set out to

evaluate the direct costs to the NHS of all AF. The study investigated the costs of AF alone, as well as the costs of secondary problems such as AF-related stroke and AF-related heart failure.

For 2008, it was calculated that AF accounted for 5.7 million days in hospital beds and a total direct cost to the NHS of £2.2 billion.⁶¹ AF patient days spent in hospital beds cost the NHS over £1.8 billion. Non-bed in-patient costs were £124 million and outpatient costs completed the total at £205 million.

Together with loss of time in employment and contribution to the community of the patient, and most probably also to those providing informal care, this amounts to a significant burden on society and on thousands of individuals.

Strong rationale for stroke prevention in patients with atrial fibrillation

In conclusion, patients with AF have a higher risk of stroke and suffer from more severe strokes than patients without AF. Thus, AF-related stroke imposes an even greater burden on individuals, carers, families, society and healthcare resources than stroke in patients without AF, providing a strong rationale for effective management of AF and prevention of stroke in this high-risk population.

Chapter 5 - Who is at risk of AF?

Key points

- For many people AF is silent, with no symptoms to prompt either concern or medical consultation
- AF is often not detected until the development of a serious complication such as stroke or heart failure
- Routine opportunistic pulse checks represent an effective and cost-effective method of improving the detection of AF in patients at risk of stroke
- Many methods are used by doctors to determine stroke risk for an individual patient, and hence the ideal treatment to prevent stroke
- Patients in the UK may currently be receiving inconsistent advice and therapy, due to a lack of consensus on AF risk stratification

Atrial fibrillation is often present without symptoms

AF patients, because of their elevated risk both of having a stroke and having a severe stroke, represent an ideal focus for stroke prevention. However, we have also discussed in earlier chapters that a substantial proportion of AF patients are currently undiagnosed or inappropriately treated. This chapter reviews detection, diagnosis and decisions on who and how to treat for the prevention of stroke.

Although AF may be recognized by symptoms such as palpitations or dizziness it is commonly asymptomatic, when the patient is unaware of anything that might indicate that they have AF. This is commonly called silent AF. Consequently, many people have undetected AF, and might have had it for some time.⁸ Studies using heart monitors that record heart rhythms 24 hours a day have shown that it is common for a patient to have periods of both symptomatic and asymptomatic AF.⁸ It is often the case that a diagnosis of AF is only made following a serious complication such as stroke or heart failure.⁶⁴

Detection and diagnosis of atrial fibrillation

Effective AF detection and diagnosis strategies are essential before treatment and the prevention of deadly and debilitating strokes become possible. Steps to improve the detection of AF have already been made; guidelines from the National Institute of Health and clinical Excellence (NICE) recommend that an ECG is required for all patients with an irregular pulse whether symptomatic or not.⁶⁴ ECG stands for electrocardiogram and is the method doctors use to capture the electrical signature of heart rhythm problems. However, for this recommendation to be effective, patients first need to have their pulse checked for irregularity. Modern electric pulse meters have all but taken over this job from doctors and nurses. Unfortunately, extremely few modern electrical pulse check machines are capable of detecting an irregular rhythm. Consequently, one of the most valuable detection methods for AF has largely been eradicated from the NHS by the advance of technology.

Many patients have other risk factors for stroke, such as high blood pressure, diabetes and heart disease. For these conditions they will already be receiving frequent check ups. The introduction of opportunistic screening by making routine manual pulse checks during these check ups would appear to be a prudent, simple and low cost method to increase the detection of AF and prevent strokes.

Opportunistic pulse checks are a low cost option

A UK study, involving almost 15,000 patients, compared opportunistic screening for AF, as described above, with another, systematic, method. Compared to routine clinical care, opportunistic screening identified approximately 50% more cases of AF. Systematic screening identified approximately 70% more case than routine clinical care, but was associated with a high cost per patient, nearly five times the cost of the opportunistic approach.¹³⁹ The opportunistic screening was associated with a cost of only £363 per patient. However, only a tiny fraction of this was for the inclusion of a manual pulse check at routine appointments. The majority of the cost was ac-

counted for by the subsequent ECG and interpretation;¹³⁹ steps already required by the NICE Guidelines upon detection of an irregular pulse.

The study highlighted the important role of a simple, routine pulse check, in helping to improve detection of AF. The policy implications arising from the results of this study are that an opportunistic approach using pulse-taking followed by ECG is probably the most cost-effective option for any screening programme implemented through primary care.¹³⁹

Despite these results, today there is no policy, formal target or recommendation from the Department of Health that recommends or mandates the routine manual pulse checks for any group of patients at GP surgeries.

The role of ambulatory monitoring

Episodes of AF can be both short and infrequent which adds to the difficulty of detection and diagnosis. For some patients, for example those who have reported instances of their own pulse being irregular, there is potential value in the use of heart rhythm monitors that record the pulse constantly for up to several days at a time. A patient would need to wear the device for between 12 and 72 hours but the constant monitoring would greatly increase the likelihood of a positive diagnosis. When prolonged monitoring is used in ischaemic stroke patients, AF is detected in one in 20 cases, providing powerful evidence for the routine adoption of such monitoring in these stroke patients.

Making treatment decisions based upon risk of stroke

Once an AF patient is identified, it becomes necessary to make a treatment decision that best addresses the needs of the patients; lowering risk of stroke as much as possible while not adding further unnecessary risks to the patient's health. The treatment options to prevent stroke will be covered in more detail in the following chapter but in short; patients at low risk of stroke are often candidates for treatment with the antiplatelet drug aspirin.¹¹⁶ For patients at moderate and high risk of stroke, aspirin has been shown to offer only modest efficacy despite having a similar risk for major bleeding as warfarin,^{65,104} that is therefore recommended for these patients. To determine who receives which of these two drugs, much attention has been given to this risk factors for stroke in AF patients.

Factors reported to increase further the risk of stroke in patients with AF include:^{8,66}

- Being female
- Being elderly
- Having previously had a stroke or TIA (mini stroke)
- Having high blood pressure
- Having heart failure or valvular heart disease
- Having diabetes
- Having vascular disease

Furthermore, the factors contribute in different ways and by different amounts to the risks of an AF patient having a stroke.

For example, a history of stroke or TIA is the strongest independent predictor of stroke in patients with AF, increasing the risk of another stroke approximately three-fold.⁸ Increasing age also has a marked effect on the risk of stroke: among patients with AF, the incidence of stroke is approximately sevenfold higher in patients in their 80s compared with those in their 40s.⁶⁷ High blood pressure increases the risk of stroke approximately threefold in patients with AF.⁶⁸ Vascular disease also independently increases the risk of stroke and death in AF patients.^{81,194,197} Specifically, the development of coronary artery disease in AF patients has been found to be predictive of the formation of stroke-causing clots.²⁰³

Although stroke and AF are both more prevalent in men than in women,^{69,70,71} the literature shows that death rate from stroke is increased fourfold in women with AF compared with twofold in men with AF.¹⁰⁵ However, it should be noted that not all studies have demonstrated such a significant difference between the genders.^{105,72}

Given that every patient is different, it is necessary for doctors to work out individual AF patient risk of stroke from all the above factors. This is called risk stratification. Many approaches to evaluating individual stroke risk in AF patients have been developed. Using these, doctors can quickly assess the patient's risk and make the necessary treatment decisions.

Approaches to risk stratification

Several different methods are used by UK doctors when seeking to determine the risk of stroke among AF patients. These all provide risk scores based upon the presence of risk factors including those reviewed above.^{73,74} Risk calculation schemes vary by the risk factors they incorporate and in their methods of scoring and risk evaluation. Schemes in current use are, usually known by their acronyms, include: AFI, SPAF, ACCP, Framingham,

CHADS₂ and CHA₂DS₂VASc. Furthering potential for the adoption of different methods among doctors, NICE developed its own new scheme instead of adopting an existing option.

NHS Improvement GRASP-AF tool

NHS Improvement has sought to assist GPs with the adoption of risk stratification among AF patients through the introduction of the GRASP-AF tool. GRASP-AF is made available free to all GPs, allowing them to analyse patient records swiftly and easily for those at risk of stroke because of AF. The tool automatically calculates CHA₂DS₂VASc and CHADS₂ scores for all patients, identifying all those in need of anticoagulation. The GRASP-AF tool automates multiple steps for GPs, it:

- Identifies AF patients
- Searches for risk factors
- Calculates CHA₂DS₂VASc and CHADS₂ scores
- Searches for current medication status
- Searches for reasons for not treating with an anticoagulant
- Alerts GPs to those patients at risk of stroke but not receiving anticoagulation medication

Considerable advances could be made in the identification and appropriate treatment of AF patients if GPs made routine use of this free and powerful tool. More information on GRASP-AF can be found in the next chapter and at www.improvement.nhs.uk.

The role and limitations of CHADS₂

CHADS₂ is a simple algorithm that is an evolution of the AFI and SPAF risk schemes. It is based on clinical trial results and works on a simple points system:

CHADS₂ and how it's calculated

C	Congestive heart failure:	1 point
H	Hypertension (high blood pressure):	1 point
A	Age greater than 75 years:	1 point
D	Diabetes:	1 point
S ₂	Stroke or TIA:	2 point

From these risk factors, the acronym CHADS is derived. The '2' is then added denoting that Stroke and TIA attract double the risk score of the other factors. The points for a particular patient are then added up allowing doctors to assign the patient to low, moderate or high risk and prescribe the appropriate treatment.

An authoritative comparison of CHADS₂ and 11 other schemes concluded that there were substantial, clinically-relevant differences between them. Most were found to have only a modest ability to predict stroke and that the proportion of patients assigned to low, moderate and high risk categories varied widely between the schemes.

For example, while CHADS₂ has been found to be a more accurate predictor of stroke, in patients not on anti-coagulation treatment, than the older AFI¹¹⁷ and SPAF¹¹⁸ schemes (from which it was derived), it does not take account of several common stroke risk factors. Consequently, CHADS₂ categorises many patients as at moderate risk despite evidence that many of them would derive benefit from taking an anticoagulant instead of aspirin.¹¹⁶

The development and validation of CHA₂DS₂VASc

Because of these limitations, a further development was made called CHA₂DS₂VASc, to complement the CHADS₂ scheme. CHA₂DS₂VASc extends CHADS₂ by considering additional common risk factors and focusing on a continuum of risk as opposed to arbitrary levels of low, moderate and high risk. The risk factors and scores for CHA₂DS₂VASc are listed below.

CHA₂DS₂VASc and how it's calculated

C	Congestive heart failure	1 point
H	Hypertension (high blood pressure)	1 point
A ₂	Age greater than 74 years	2 point
D	Diabetes	1 point
S ₂	Stroke or TIA	2 point
V	Vascular disease	1 point
A	Age 65-74	1 point
Sc	Sex (i.e. female)	1 point

CHA₂DS₂VASc was validated in an analysis from the Euro Heart Survey⁷⁹ and in several other studies.^{75 76 77}

The most recently published international consensus guidelines, from the European Society of Cardiology, have adopted the CHA₂DS₂VASc scheme and endorses use of the scheme to categorise the stroke risk among patients with a CHADS₂ score lower than two, to ensure the most appropriate treatment decision is made.¹¹⁶

Subsequent to the publication of the ESC guidelines, CHA₂DS₂VASc has received further support from new data illustrating that the scheme performs better than CHADS₂ in predicting patients at high risk of stroke.

The new data also showed that patients categorised as low risk by CHA₂DS₂VASc were indeed at truly low risk for stroke, unlike similarly categorised patient under other schemes.⁸¹

Having different schemes, while confusing, becomes inevitable as scientific understanding increases and evidence builds for one method versus another. For example, at least until the next revision of the NICE guidelines on the management of AF, many British doctors will be in the challenging position of having different risk assessment and treatment advice being endorsed by different authorities. As a result, patients in the UK may receive inconsistent advice and therapy, depending on local preferences.

Calculating the risk of treatment-related bleeding

Despite increasing pressure from advanced stroke risk calculation schemes and recommendations of new guidelines, many physicians hesitate to use an anticoagulant because of perceived risks of the patient suffering from dangerous excessive bleeding. This perception is frequently unjustified. To address this concern with bleeding risk, the authors of the ESC consensus guidelines included an additional risk calculation scheme for bleeding among AF patients.

Using data on risk factors for major bleeding from the Euro Heart Survey as well as from a systematic review of the literature, a simple bleeding risk scheme, HAS-BLED, was derived for patients with AF.⁸⁰

HAS-BLED and how it is calculated

H	Hypertension	1 point
A	Abnormal renal/liver function	1 point each
S	Stroke	1 point
B	Bleeding history/predisposition	1 point
L	Labile INR (unstable warfarin impact)	1 point
E	Elderly (eg, >65 years)	1 point
D	Drugs/alcohol	1 point
	for certain drugs plus 1 for alcohol excess – max 2	

HAS-BLED aims to provide a simple way to evaluate risk of bleeding in AF patients so that effective treatment decisions can be made. HAS-BLED has also been developed to encourage doctors to consider reducing the risk of bleeding by focusing on correctable risks such as high blood pressure and poor warfarin control. The HAS-

BLED score has been validated in large independent groups of AF patients^{80,200,201} and has also been recommended in recent Canadian treatment guidelines,¹⁹⁸

The new ESC guidelines state that it would seem reasonable to use the HAS-BLED score to assess bleeding risk in AF patients on the basis that a score of three or greater indicates 'high risk'.¹¹⁶ In the light of growing evidence, the more recent Canadian guidelines recommend that bleeding risk is assessed using the HAS-BLED score.¹⁹⁸

Chapter 6 - Treating AF and preventing stroke

Key points

- Direct treatment of AF is frequently necessary to control distressing and intrusive symptoms; some heart rhythm treatments also reduce the risk of stroke
- It is recommended that patients receiving antiarrhythmic treatment for AF also receive therapy to reduce the risk of blood clots
- Warfarin is safe, effective and cost effective for the prevention of stroke in the majority of AF patients
- Warfarin is used less in the UK than recommended in authoritative guidelines; this under use results from practical obstacles and, frequently unfounded, safety concerns
- High blood pressure and diabetes, which commonly affect patients with AF, also require management to reduce the risk of stroke

Aims of AF management

The immediate aim of AF clinical management concentrates on the relief of symptoms and the assessment of AF-associated long term risk.¹¹⁶ The greater proportion of this document is focused on the serious complications of AF, specifically stroke. For many patients, however, addressing the symptoms of AF represents a much greater concern than preventing long-term complications. The symptoms of AF can be debilitating and unpredictable. Many AF patients report a dramatic fall in quality of life. As we have learned in previous chapters, many also suffer from a pronounced decline in mental health. At diagnosis, it is common for a patient to have endured a considerable period of time living in fear of symptoms over which they had no control and of which they had no understanding. Treatments such as ablation that achieve the desired symptomatic control by returning the heart to a normal rhythm also offer the potential benefit of eliminating the threat of long-term complications such as heart failure and stroke.

For these reasons, it is vital that the drugs and procedures that treat the underlying AF are used in appropriate patients whenever possible.

In a considerable proportion of patients, control of the AF itself proves unsuccessful and treatment becomes entirely targeted at assessing and reducing the risk that a patient will suffer serious long-term consequences of AF, particularly stroke and heart failure.

This chapter reviews current treatments both for AF directly and for managing the risk of long term complications independently of the underlying AF.

Rhythm and clotting

Two treatment approaches underpin the management of AF. One is to correct the faulty heartbeat,¹⁷⁸ and the other is to manage the risk of stroke by preventing the formation of clots in the fibrillating heart.

Rate control, rhythm control and cardioversion

Several strategies are commonly used to treat the heart-beat:

Strategies for treating a faulty heart rhythm

Rate control	Slowing an excessively fast pulse with sustained drug treatment Rate control is used to treat symptoms and to relieve stress to the cardiovascular system
Rhythm control	Returning the heart to a normal rhythm with sustained drug treatment Rhythm control is achieved with antiarrhythmic drugs that reduce the fibrillation to control symptoms
Cardio-version	Resetting the heart rhythm suddenly, usually with an electric current
Ablation	Returning the heart to a normal rhythm permanently by surgically blocking chaotic electrical activity in the atria

Reducing the risk of stroke

Regardless of the course chosen to address the underlying heart rhythm problem, AF patients almost always need additional management of stroke risk by preventing clots from forming and blocking blood vessels in the brain.

AF disrupts the blood flow through the heart allowing the formation of a blood clot, or thrombus. Most strokes are the result of a thromboembolism which is a clot that travelled to the brain in the bloodstream. Strategies for the prevention of stroke in patients with AF primarily involve the use of anticlotting drug therapy. It is recommended that AF patients receiving treatment to correct their heart rhythm also receive some form of anticlotting therapy.⁸²

There are three main classes of ‘blood-thinning’ drugs currently used in the prevention of stroke in patients with AF

The main types of antithrombotic (‘blood thinning’) drugs

Anticoagulants	Which interrupt the pathway of chemical reactions that result in the formation of a blood clot Warfarin is the recommended oral anticoagulant (OAC) for stroke prevention in AF patients
Antiplatelet drugs	Which limit the aggregation of platelets; components of the blood that form a significant part of the blood clot Aspirin is the most widely used antiplatelet agent for the reduction of stroke risk in AF patients
Thrombolytics	Which break up blood clots once they are formed. Thrombolytics are generally reserved for use in the acute setting and do not play a role in long-term stroke prevention

Warfarin

Warfarin belongs to a class of drugs called vitamin K antagonists, (VKAs) meaning that they interfere with the normal action of vitamin K which is involved in the blood clotting process. Specifically, four proteins that play key roles in the blood coagulation pathway require vitamin K for their production. Warfarin inhibits the action of vitamin K, limiting the production of these four anticoagulation proteins.^{4,17} The anticoagulation pathway is a series of enzyme-controlled chemical reactions that ultimately produces fibrin, an insoluble protein that combines with platelets to form blood clots.

A narrow effective range and a need for monitoring

Despite this useful anticoagulant activity, warfarin has only a narrow range of concentration in the blood in which it is both safe and effective. Maintaining warfarin within this range is also complicated by interactions with food and other drugs¹⁸ that can significantly alter blood levels of warfarin regardless of the dose taken.

If the level of warfarin is too low then the patient is not benefiting from a reduced risk of stroke. If the level is too high, the anticoagulation properties put the patient at an increased risk of bleeding.

Thus, the management of patients on warfarin can be challenging, and frequent monitoring is required so that the dose can be adjusted to maintain effective and safe therapy. For monitoring, a measure of clotting time is taken (called the pro-thrombin time). If clotting takes too long then the dose needs to be reduced. If clotting happens too quickly, the dose of warfarin needs to be increased.

Understanding clotting time and INR

So that all pro-thrombin tests can be compared accurately with one another, the result of the test is converted to a ratio between the test result and a standard pro-thrombin time. This ratio is called the international normalised ratio (INR). Consequently, it is the INR that a physician and patient will try to keep within a target range to ensure warfarin remains at ideal levels in the blood. A target INR of 2.0 - 3.0 is typically recommended for patients receiving warfarin.^{8,83} If the INR is too high, a patient is at increased risk of bleeding; too low, and the risk of a blood clot becomes high.

Drawbacks of warfarin are not insignificant and include unpredictable interactions with food which often necessitate significant lifestyle changes. One of the many drugs with which warfarin interacts is amiodarone, an anti-arrhythmic drug used in the treatment of AF.⁸⁴ The inconvenience of INR monitoring and frequent dose adjustment also represents a burden for many patients.

Efficacy of warfarin in clinical trials

Warfarin has been shown to be very effective at reducing stroke in AF patients. Systematic reviews of clinical trials in patients with AF have shown, compared with no therapy, that warfarin can provide a 62-68% reduction in stroke and a 26-33% reduction in the death rate^{85,87,88} without significantly increasing the risk of major bleeding. This means that for every 1,000 patients treated with warfarin, 31 strokes will be prevented each year.⁸⁵ Given the cost and harrowing consequences of stroke, this is an equation that strongly favours the use of warfarin.

Importantly for patients with AF, it has been shown that, when the dose is monitored and adjusted, warfarin is effective in preventing both mild and severe strokes.^{89,90}

Warfarin in clinical practice

The practical difficulties in maintaining the target INR, understandably raise concerns that the efficacy and safety observed with warfarin in clinical trials might not reflect what can be achieved in routine clinical practice.⁹¹ Clinical trials monitor patients very closely, more than might be practical or possible in routine clinical practice. Also, to meet trial design and ethical requirements, clinical trials often exclude patients at high risk of bleeding while also recruiting relatively few elderly patients.^{85,91}

These concerns were largely refuted by observational studies that reviewed the history of large groups of patients cared for in routine clinical practice. In a large-scale study of more than 11,500 AF patients, warfarin provided a 39-60% reduction in the risk of thromboembolic events (stroke and peripheral embolism) and a 31% reduction in the risk of death compared with either patients taking therapy or patients only taking aspirin.⁹² The risk of an intracranial bleed was almost doubled with warfarin, but still remained low with no significant association between warfarin and non-intracranial bleeding. The authors concluded that the results of clinical trials of warfarin translate well into clinical care for patients with atrial fibrillation.⁹²

Further investigations in the clinical practice setting in Italy and the UK have demonstrated reductions in the risk of stroke of between 26-66% in patients with AF receiving warfarin compared with those not receiving warfarin.^{93,95} Despite an increased risk of bleeding, the overall rates of ill health and death were significantly lower in the Italian patients receiving warfarin than in those not receiving warfarin.^{94,95} However, the risk reduction observed in the UK study (26%) was substantially lower than in clinical trials.⁹⁴ Further analysis has highlighted management differences between anticoagulation clinic care and routine medical care, with patients in routine clinical care spending less time within the target INR range.^{94,150} While the efficacy and safety profiles of warfarin do appear to be somewhat less favourable in routine medical practice than in clinical trials, the benefits outweigh the risks in the majority of patients.

Improving warfarin use with GRASP-AF

Warfarin is currently recommended in UK and European guidelines as first-line therapy in patients with AF and a moderate or high risk of developing stroke.^{8,83} Despite evidence that following the guidelines results in improved patient outcomes,¹⁰⁶ there is significant under-use of warfarin illustrating that the guidelines are not always followed. Thus, many patients with AF and a moderate-to-high risk of stroke do not receive anticoagulant therapy and therefore remain at high risk for stroke.^{112,19}

As introduced in the previous chapter, GRASP-AF is a tool for GPs that automates the identification of patients for whom warfarin treatment should be started. GRASP-AF data, collected from use in over 1,500 English GP practices, supports the NICE statistics that only around half (55%) of those with AF at high risk are prescribed warfarin.

GRASP-AF is part of a broad NHS Improvement programme to raise awareness of AF and stroke risk, thereby reducing the number of AF-related strokes. An important element of this work is improving the management of stroke risk in patients with AF by promoting appropriate risk assessment, and the prescribing of appropriate anticoagulation. This is achieved through the use of the GRASP-AF tool that is free for GPs to download from the NHS Improvement web site. The GRASP-AF tool identifies patients with AF, calculates their stroke risk, and also details their current management. This information is simply summarised, allowing GPs easily to audit their current management of AF against best practice guidelines.

There is also a facility to upload the data to CHART, a web-based comparative analysis tool. This enables anonymous comparison of data with other practices.

Local and regional analyses are also made possible by comparisons between Primary Care Trusts, Cardiac and Stroke Networks and Strategic Health Authorities. To date, 1,500 GP practices in England have run GRASP and uploaded their data to CHART – this growing database is probably the largest AF database in the world.

Illustrating the potential of warfarin to reduce stroke risk, GRASP-AF is already leading to improvements in anticoagulation and management of AF in general practice.

Cost of warfarin in stroke prevention in atrial fibrillation

In a UK study, the cost of preventing one AF-related stroke per year using warfarin was estimated to be £5,260.⁹⁶ This cost of prevention appears to be favourable when compared with a European average cost of £11,799 for treating a stroke.⁶² In another study of patients with AF in the UK, the cost of treatment of a stroke over a 10-year period was estimated to be almost four times greater than the estimated 10-year direct costs of anticoagulation,⁹⁷ further indicating that prevention is a cost effective option, regardless of the costs associated with warfarin and its challenges. Numerous other studies have provided additional evidence that anticoagulation with warfarin is cost-effective in patients with AF at a moderate or high risk of stroke when compared with no therapy or aspirin.^{105,99}

As well as efficacy and safety, modern health providers also have to take into account the cost-effectiveness of a treatment. This can be challenging as it necessarily puts a price on human health and life. However, done carefully, cost-effectiveness comparisons allow many different treatments to be assessed on a level playing field. In the absence of unlimited funding, cost-effectiveness comparisons allow the NHS to make treatment decisions that will have the greatest benefit for the most people.

To make these comparisons, health economists use the QALY; a quality-adjusted life-year. To illustrate, a year in perfect health is equal to a QALY of one. A year in less than perfect health would have a QALY less than one. The worse the health, the closer the QALY becomes to zero.

Treatment of AF patients with warfarin has been found to be cost effective, i.e., associated with a low cost per QALY, particularly in patients considered to be at moderate-to-high risk of stroke.⁹⁹ In one study, the cost of warfarin for AF patients with one additional stroke risk factor was reported to be \$8,000 per QALY saved¹⁰⁹ well below the threshold of acceptable cost effectiveness of £20,000 - 30,000 per QALY established by NICE in the UK.¹⁰⁰

It should be noted that the cost effectiveness of warfarin is dependent on achieving a significant reduction in the risk of stroke. Practical difficulties in maintaining target INR values may result in warfarin being less cost effective in clinical practice than in clinical trials. INR monitoring in clinical practice may also incur additional costs, to the patient, carer and society, not captured in the cost-effectiveness studies.

Thus, it is important that stroke prevention in clinical practice is improved so that it is as cost effective as in clinical trials. This might be achieved through new strategies that deliver optimal management with warfarin. It might also be achieved following technological advances, or new treatments that overcome the current challenges of warfarin.

Aspirin

One of many actions of aspirin is to reduce the activity of platelets during clotting. Limited platelet aggregation reduces the risk of a clot from forming which, in turn, helps to prevent a stroke.¹⁰¹

In patients with AF, aspirin reduces the risk of all strokes by approximately 22% compared with placebo. For severe, disabling strokes, the reduction in risk with aspirin compared to placebo is smaller (13%).⁸⁶ Clinical trials directly comparing aspirin with warfarin in the prevention of stroke in AF have shown warfarin to be significantly superior, reducing the risk of a stroke by approximately half compared with aspirin.^{107,129} Despite perceptions that it may be safer than warfarin, a major drawback of aspirin is that it increases the risk of bleeding, particularly in the gastrointestinal tract.^{65,104}

Aspirin is therefore recommended only in patients with a low risk of stroke and in those who cannot take warfarin.^{8,83} It should be noted, however, that there is doubt as to the benefit of aspirin in patients at low risk of stroke.^{108,98}

Managing other conditions that increase stroke risk

AF commonly co-exists with other conditions, such as high blood pressure and diabetes, which themselves can contribute to the risk of blood clots and stroke. The risk in patients with several of these conditions is cumulative that is, the more conditions that predispose to stroke, the greater the risk. Even in patients who are receiving antiarrhythmic and anticlotting therapy, effective management of these other conditions can further reduce the risk of stroke.

Blood pressure control is particularly important in the management of AF, as uncontrolled blood pressure increases the risk of stroke three-fold.^{68,110}

AF in patients with diabetes is also associated with a very high risk of stroke. One study in patients with diabetes found that those who also had AF had a more than 60% greater risk of death from all causes than patients without AF; they also had an increased risk of death from stroke and heart failure.¹¹¹

It is therefore clear that conditions which increase the risk of stroke and that co-exist with AF must be carefully managed.

The outlook for stroke prevention in patients with atrial fibrillation

To summarise, patients with AF should be managed holistically and treated with drugs or other strategies that control the abnormal heart rhythm itself, as well as with anticlotting therapy to reduce the risk of blood clots and, hence, stroke. Warfarin has been shown to reduce the risk of stroke in patients with AF in both clinical trials and clinical practice. Importantly, warfarin has proven efficacy in reducing the risk of severe, fatal or disabling strokes. In addition, anticoagulation with warfarin has been demonstrated to be cost-effective in patients with AF and a moderate-to-high risk of stroke. Warfarin is, however, associated with major, well-recognised drawbacks. Nevertheless, it remains frontline therapy in this indication. Thus, in the immediate term, improved detection of asymptomatic AF and increased use and optimisation of warfarin therapy is important to reduce the incidence of severe strokes in patients with AF.

In the medium-to-long term, alternative therapies that combine convenience with a efficacy and safety could help to improve further the prevention of stroke in patients with AF. The development of such treatment promise considerable improvements in the management of patients with AF. Several clinical studies of potential new treatment are ongoing and early indications are positive. New and emerging treatments and recently-published clinical trial results are discussed in more detail in the chapter “New developments for stroke prevention in patients with atrial fibrillation”.

Chapter 7 - The importance of guidelines

Key points

- Patients at moderate and high risk of stroke should receive anticoagulation therapy such as warfarin
- Aspirin is currently recommended only for patients at a low risk of stroke
- Robust evidence for the effectiveness of aspirin in AF patients is limited
- Aspirin is associated with major bleeding risks
- While two sets of guidelines are directly applicable to the UK, neither benefits from widespread adherence
- In the UK fewer than 55% of at-risk patients receive adequate, guideline-adherent therapy to prevent blood clots
- The drawbacks of current therapies, a lack of physician and patient education, and poor motivation of GPs to change practice, may contribute to this problem

Summary of guidelines

Data show that under-use of anticoagulant therapy in AF patients at a high risk of stroke is associated with a significantly greater rate of thromboembolism, while over-treatment is not associated with a significantly higher risk of bleeding.¹¹² Given this evidence, and that reviewed in the previous chapter, the importance of clinical guidelines which advocate the use of warfarin in patients at moderate and high risk for stroke cannot be overstated.

Different recommendations in NICE 2006 and ESC 2010 guidelines

Several sets of guidelines exist for the treatment of AF and the prevention of stroke. In the UK, however, there are two guidelines that have direct relevance: those published by the National Institute for Health and Clinical Excellence (NICE) in 2006 and those published by the European Society of Cardiology (ESC) in 2010.

The ESC 2010 guidelines have replaced many earlier international publications, including those cited by NICE in its 2006 guidelines.¹¹³ However, clinical guidance from NICE has a special status in the UK; as the formal guidance that all health professional are expected to take into account when making treatment decisions.¹¹⁴ It is important to note that the NICE guidelines reflect the start of the art in 2005. However, until and unless NICE updates its guidance to accommodate the more recent ESC 2010 publication, healthcare professionals in England and Wales will remain in the challenging situation of having to decide between two, occasionally conflicting, guidelines.

The clinical guidelines from NICE are based on systematic reviews and cost-effectiveness analysis.³² This differs from the methodology of expert consensus that was used to produce the ESC 2010 guidelines, as well as most others.¹¹⁵

The guidelines differ in the specific treatment recommendations that they make regarding stroke prevention in patients with AF. Until the publication of the ESC 2010 guidelines, there was a general agreement between international expert consensus guidelines that patients at low risk of stroke should receive aspirin therapy, those at moderate risk should receive aspirin or oral anticoagulant therapy (eg, warfarin) and those at high risk should only receive therapy with warfarin. This raises therapeutic uncertainty for the doctor when faced with moderate risk patients; should aspirin or warfarin be given? Stroke risk classification schemes that assign a high proportion of patients to moderate risk compound this therapeutic uncertainty and are less helpful.

New guidance that all 'low' and 'moderate' risk patients should be on warfarin

In contrast, the ESC 2010 guidelines recommend a risk factor approach and a reduction in emphasis on the artificial categories of low, moderate and high, which have been found to be poor predictors of stroke risk. The ESC guidelines recommend that those at genuinely low risk (with a CHA₂DS₂-VASc score of zero) should receive no antithrombotic therapy or, in some cases, aspirin. For those with risk factors for stroke (ie, with a CHA₂DS₂-VASc score of one or higher) most should receive oral anticoagulation therapy.¹¹⁶

Treatment implications of not using ESC 2010 guidelines

Risk of stroke	NICE 2006 Guidelines	ESC 2010 Guidelines
Low	Aspirin	No antithrombotic therapy (or *aspirin)
Moderate	Aspirin or Warfarin	Warfarin (or *aspirin)
High	Warfarin	Warfarin

* indicates the guidelines' preferred choice

The ESC 2010 guidelines draw upon CHA₂DS₂VASc, a new method of risk stratification that was introduced in chapter five. CHA₂DS₂VASc is an evolution of the stroke risk scheme developed by NICE for its 2006 guidance and is more inclusive of common stroke risk factors. One recent analysis of patient registry data (registry data can provide insights into outcomes within routine clinical practice) found that the benefits of oral anticoagulation therapy outweigh bleeding risks in all but those patients at genuinely low risk, ie, those with a CHA₂DS₂VASc score of zero.²⁰²

CHADS₂ has been found to be easy to use, but still a modest predictor of stroke; similar to earlier schemes, in patients not on anticoagulation treatment.^{117,118} CHADS₂ does not take account of several common stroke risk factors, categorising many patients at moderate risk despite evidence that many of them would gain significant benefit from taking an anticoagulant instead of aspirin.¹¹⁶

Until the 2006 NICE AF guidelines are updated to reflect this advance in understanding of stroke risk, many patients will continue to receive aspirin when they could derive a significantly increased reduction in stroke risk, with no additional risk of major bleeding, if they were to take warfarin instead.

Guidelines: theory versus practice

Regardless of the difference between these two authoritative guidelines, neither is uniformly followed and warfarin treatment remains underused in the UK. Even NICE's own data shows that of all those with AF who should be on warfarin, almost half are not.¹¹⁹

This is not just a UK problem; in a study conducted in seven European countries, it was found that only 8.4% of patients with AF who had a stroke were receiving anticoagulants at the time of their stroke, and the proportion decreased by 4% per year with increasing age.⁵ A review of the scientific literature from 2000 indicated that only 15–44% of eligible patients with AF were receiving warfarin.²³

Yet, when asked, physicians demonstrate both awareness of the guidelines and agreement with them. For example, a questionnaire was used to examine the adherence of Swedish physicians to European and national guidelines.¹⁹ Of 498 physicians who responded, more than 94% stated that patients at risk of blood clots with chronic AF should receive long-term anticoagulation therapy. The investigators also evaluated the records of 200 patients hospitalised for AF to check whether or not treatment matched the answers to the questionnaire. In total, 108 patients had chronic AF with one or more risk factor for stroke, and no other reason not to take to warfarin, but only 40% of these patients received warfarin.¹⁹ This study further highlights the discrepancy that is often found between guidelines and what happens in clinical practice.

Another study documented the medications being taken by AF patients when they suffered an ischaemic stroke. It found that only 10% of these patients had been taking an effective dose of an anticoagulant. Nearly a third were on no antithrombotic treatment at all (29%). A further 29% were on aspirin and another 29% were on a non-therapeutic dose of warfarin.

Not all studies into the use of warfarin in AF patients provide evidence of under-use.^{121,143} According to recent surveys in different parts of Europe, the proportion of patients with AF at high risk of stroke who are receiving adequate anticoagulation is most commonly around 54–61%,^{122,112} but this figure is as high as 88% in settings where guidelines are being more successfully applied in the real world.^{123,124}

Reasons for poor adherence to guidelines

Adherence to guidelines for the prevention of stroke in patients with AF may be low for several reasons. These include difficulties in maintaining INR within the therapeutic range¹⁸ and physicians' concerns about bleeding risk, particularly in the elderly.¹²⁵ This section reviews some of these challenges, and also examines the way in which the Department of Health rewards GPs for reaching targets, and how that might contribute to poor adherence to guidelines in the UK.

The motivation of general practitioners

When the payment of UK general practitioners was reviewed in 2004, a new scheme was introduced called the Quality Outcomes Framework (QOF).¹²⁶ QOF was designed to reward GPs for the quality of the care that they provided, instead of for how many patients they treated. The scheme also provided additional resources that could help GPs implement new services to address local needs. Currently, GPs can work to secure up to 1,000 QOF points by meeting predetermined performance targets in four broad areas: Clinical, Organisational, Patient Experience and Additional Services. A total haul of 1,000 points represents an additional payment to GPs of over £13,000.

Specifically for AF, within the current QOF scheme, up to 12 points are available for GPs achieving a high percentage of...

'... patients with atrial fibrillation who are currently treated with anticoagulation drug therapy or antiplatelet therapy.'¹²⁶

It is reasonable to expect that many patients diagnosed with AF will already be taking aspirin for another condition. It is also relatively simple to start and manage a patient on aspirin (antiplatelet therapy) compared to warfarin (anticoagulation therapy). Consequently, the way the target is written enables GPs to receive the maximum QOF reward just by having AF patients on aspirin, even if none of them is on warfarin.

Consequently, QOF today provides virtually no motivation for GPs to put patients on warfarin in accordance with the NICE 2006 or the ESC 2010 guidelines. The QOF target described above is, within the scheme, called an indicator. In March of 2011, NICE opened a consultation on proposed revisions to the QOF indicators for AF. Encouragingly, the proposed revisions represent the possibility that GPs might become more effectively motivated to adhere to guidelines.¹²⁸ Specifically, two new indicators were submitted for consultation. If these new indicators are adopted, GPs will receive QOF rewards dependent upon:

- The percentage of patients with Atrial Fibrillation in whom stroke risk has been assessed using the CHADS₂ risk stratification scoring system in the previous 15 months

- In those patients with Atrial Fibrillation in whom there is a record of a CHADS₂ score of less than one, the percentage of patients who are receiving anticoagulants

Both of these proposals are to be welcomed by those seeking better adherence to clinical guidelines and more effective treatment of UK patients at risk of stroke because of AF. Moreover, the second of the two proposed new indicators specifically addresses the failing of the current QOF indicator to provide GPs with motivation to prescribe anticoagulation therapy.

The proposed QOF reward for prescribing an anticoagulant in patients at moderate or high risk appears reflective of the ESC 2010 guidelines and perhaps demonstrates that UK policy makers are keen to accommodate the recommendations of the new ESC guidelines even before there is opportunity to accommodate them in revised NICE guidelines.

Difficulties of keeping warfarin within the therapeutic range

Many patients find the frequent monitoring and necessary dose adjustments associated with warfarin inconvenient and time consuming, and may miss appointments. Research has shown that AF patients in routine clinical care were able to maintain a target INR for over half the time (56%). Of the considerable remaining time, patients were above the target range for 30%, and below the target range for 14%.¹⁴³

This has unsettling implications. If around half of all patients in need of anticoagulation aren't prescribed warfarin¹¹⁹ and if those who are have either ineffective or unsafe blood levels of warfarin for nearly half of the time,¹⁴³ then perhaps only a quarter of patients at any one time is receiving the therapy they need to safely lower their risk of stroke.

This becomes ever more worrisome when remembering experts' estimates that only about half of all AF patients are actually diagnosed. The vast majority of these undiagnosed patients would be expected to be at moderate or high risk of stroke,¹²⁷ and, hence, in need of warfarin therapy according to the ESC 2010 guidelines. As illustrated in the table below, perhaps only a fifth of patients in need of warfarin to reduce risk of stroke actually receiving safe and effective anticoagulation treatment at any time.

Very few warfarin patients receive effective and safe treatment

	Percentage	Of every 100 AF patients
AF patients diagnosed	c.60%	60
AF patients at moderate or high risk	97% ¹²⁷	58
Number anticoagulated	54% ¹¹⁹	31
Number in INR range	56% ¹⁴³	18

Even if the estimated for the number diagnosed is incorrect and, for example, only 30% of AF patients are undiagnosed, the estimate for the number of patients receiving safe and effective anticoagulation would rise only to 21%.

When patients do not receive close monitoring, which is not usually available in routine clinical practice, they have been found to be outside the target INR range for longer than when strict monitoring is imposed upon them.¹⁴² Clearly patients are facing challenges with their therapy when not under close supervision, and are therefore put at increased risk of a potentially-dangerous blood clot or of uncontrolled bleeding.

Physician concerns about bleeding risk

Many physicians resist the use of warfarin in the elderly, largely on grounds of safety. The evidence, however, strongly favours the use of warfarin in older patients. The incidence of stroke among patients aged 75 years or more with AF is lower in those who are receiving warfarin than in those taking aspirin, without increasing the risk of haemorrhage.¹²⁹

Despite this, research has demonstrated repeatedly that many physicians over-estimate the risk of bleeding associated with the use of warfarin and under-estimate its benefits in preventing thromboembolism and stroke; conversely, they have been shown to under-estimate the bleeding risk of aspirin therapy and over-estimate its benefits.^{20,125,21} As a result, eligible patients are not receiving therapy that could prevent strokes.¹⁶ For many physicians, bleeding risk is a particular concern in the elderly, who are more prone to falls, more likely to have suffered previous major bleeds and who are subject to

many additional problematic factors associated with old age.^{132,134} However, evidence has shown that none of these factors, not previous bleeds, falls or old age itself has any impact on increased risk of bleeding associated with warfarin.

While the bleeding risk with warfarin is no worse than that with aspirin, especially in the elderly, physician experience of major bleeding events associated with warfarin can profoundly reduce prescription of warfarin.¹³⁵ A study investigated the behaviour of physicians treating AF patients who had bleeds while on warfarin. Patients treated in the 90 days after the physician had encountered a bleeding event were significantly less likely to receive a prescription for warfarin than patients treated before the bleed.¹³⁵ In contrast, having a patient who experienced a stroke while not receiving warfarin did not influence prescribing behaviour with subsequent patients.¹³⁵

In other words, a bleeding event may make a physician less likely to prescribe an anticoagulant but a stroke does not increase the likelihood that a physician will prescribe and anticoagulant.

Two theories have been put forward to explain this phenomenon. The first is based upon a theory that when we predict the probability of an event, we are influenced by the ease with which those events can be remembered. Since a major bleed is likely to be memorable, this might create a perception among physicians that bleeds are more likely than is actually the case.¹³⁶ A second theory suggests that when making choices, we tend to select the one we will least regret.¹³⁷ It is arguable that a decision to add to bleeding risk by making a change (prescribing warfarin) is less appealing than a decision to add to stroke risk by doing nothing. This may also be in keeping with a principle of the Hippocratic oath, to 'do no harm'.¹³⁵ While of interest, there is no evidence that an understanding of these two possible influences on prescribing behaviour has any impact on the number patients who remain at high risk of stroke despite strong evidence that warfarin would reduce that risk without a prohibitive risk in bleeding.

Discrepancies between patients' and physicians' perceptions of stroke and bleeding risk

Much of proposed future NHS policy is founded on a desire to engage patients in the path of treatment recommended to them, giving them both choice and control. This is neatly captured in the line, 'no decision about me, without me'.

A study that compared patients' and physicians' perceptions of risk illustrates how such a shift toward patient-centred care might influence the prevention of stroke in AF patients.

A group of physicians, and another of patients at high risk of stroke, were asked the same set of questions about when anticoagulation therapy was justified according to the reduction in stroke risk. Following in-depth explanation of the bleeding risks involved, 74% of the patients were willing to take warfarin if prevented just one stroke in 100 patients over two years. Yet, when confronted with the same question, only 38% of physicians were willing to prescribe warfarin for the same risk reduction.¹³⁸ This result suggests that if patients were sufficiently informed about, and then involved in, treatment decisions, many more of them would receive stroke-preventing anticoagulation therapy than if just left to the doctors.

The same study also asked questions about the number of bleeds that were acceptable with warfarin and aspirin, having first explained the stroke risk reduction with which each treatment is associated. Of the physicians, 46% were willing to accept more than ten bleeds in 100 patients treated with warfarin over two years. In stark contrast, the patients were much more willing accept bleeds on warfarin given the stroke risk reduction possible. Of the patients, 85% were willing to accept more than ten bleeds in 100 patients over two years.

The study also suggested that physicians perceive the risk of bleeding to be higher with warfarin than with aspirin, perception that we know is not supported by the clinical evidence.¹²⁹

These results indicate that patients place more value than physicians do on the avoidance of stroke, and less value on the avoidance of bleeding.¹³⁸ For the effective prevention of strokes, it appears important that the views of the individual patient are taken into account when assessing whether to use anticoagulant therapy.

To summarise, adherence to guidelines for the prevention of stroke in patients with AF is often poor. The reasons for this appear to be related primarily to the drawbacks associated with warfarin therapy and to a lack of physician and patient education regarding the benefit-to-risk ratio of therapy. There is also a clear need for a change in the way that UK GPs are rewarded for treating AF patients. The current system fails to provide motivation to follow guidelines. The proposed change to this system is to be welcomed, as is the indication that UK policy makers appear to endorse elements of the most recent international guidelines from the ESC.

Chapter 8 - Current challenges

Key points

If the prevention of a silent epidemic of AF-related stroke is to be prevented, it is vital that we address the following barriers to reduced stroke risk:

- Insufficient detection and diagnosis strategies
- Low patient awareness and understanding
- Limitations of current treatments
- Incomplete knowledge among healthcare professionals
- Inequity of patient access to effective management
- Insufficient communication to ensure a continuum of care for patients
- Guideline differences and low guideline adherence

As has been discussed at length in this report, there are many and varied obstacles to the effective prevention of stroke in AF patients. This chapter identifies and summarises seven major challenges to effective stroke prevention among AF patients, as captured above in the key points.

Insufficient detection and diagnosis

Without effective detection and diagnosis of AF between a third and a half of patients affected will only be identified once it is too late; having suffered a potentially debilitating or lethal stroke. If a lack of detection and diagnosis continues, then many patients will be denied the opportunity to benefit from treatments that can dramatically reduce their risk of stroke.

Strategies are urgently needed to improve detection and diagnosis of AF. Existing research suggests that routine pulse screening has a role to play,¹³⁹ as does public education on the need to investigate an irregular pulse. Any solution will need to involve promoting pulse checks among the general public, and the importance of having an irregular pulse investigated. The role and value of screening programmes will need serious review, especially following the positive results of the SAFE study.¹³⁹ Many pieces are already in place; NICE already recommends that all patients with an irregular pulse receive an

ECG to make a diagnosis and the SAFE study uncovered the marginal additional costs of taking a manual pulse.

The SAFE study also found that GP and practice nurse performance in interpreting ECGs was not encouraging,¹³⁹ identifying another potential challenge to the effective diagnosis of AF in primary care.

Low patient awareness and understanding

Wider access to information

Many patients have poor understanding of AF and of the treatments they take because of it. We know from one study that 37% of documented chronic AF patients were unaware that they had AF and nearly half didn't know why they were taking warfarin. A similar number didn't know they were at risk of clots that could cause stroke. Sixty percent felt that their underlying condition (AF) was not severe.¹⁴⁰

These findings are backed up by other sources including surveys of patients from patient advocacy organisations and from qualitative research among patients.

An extensive international survey conducted by the patient organisation, AntiCoagulation Europe (ACE), revealed that a quarter of the surveyed patients did not remember receiving any information on AF at diagnosis, and over one-third felt that their doctor could have told them more regarding their medication and how it would affect their lives. Particular lack of awareness among patients was noted with regard to the potential interactions of warfarin with common over-the-counter medicines and herbal remedies.¹⁴¹

From a qualitative study of AF patients' experiences it is clear that the above findings should not have been surprising. The study reported common and disturbing patient experiences during particular phases of the pathway of care. All patients involved in the research had AF which was both recurrent and symptomatic. Before being diagnosed, patients reported confusion and fear of symptoms, and were often puzzled during a search to understand what they meant. Patients reported that fre-

quently no explanation of symptoms was given by health-care professionals, and that symptoms were dismissed as ‘panic attacks’.

At diagnosis, patients reported relief, hope for the future and validation of their search for understanding of the symptoms. However, the time of diagnosis was also associated with many less positive experiences with health-care professionals:

- Lack of information and support from healthcare professionals
- No education of the course of AF, or information on what to expect in the future
- No acknowledgement of the negative impact that symptoms were having on patients’ lives
- Inadequate education on how to manage symptoms

Following the initiation of management, a new range of negative patient experiences were reported. The unpredictable recurrence of symptoms was associated with distress, anxiety and a loss of control. Recurrent symptoms were commonly associated with a perception of treatment failure and accompanied by a fear of suffering a debilitating stroke.

So not only are patients not receiving or retaining information during consultations with their doctors, there is also evidence that AF patients feel abandoned, dismissed, without support and without understanding at the hands of the healthcare professionals charged with the care of their AF.²⁸

Better adherence to therapy

According to AntiCoagulation Europe, adherence to therapy is strongly dependent upon patients’ understanding of their condition. Without the proper information or guidance, adherence can be poor, leaving patients at risk of bleeding or stroke. This report is supported by data showing that adherence to warfarin therapy increases when patients are supervised and have easy access to professional support.¹⁴²

We know that AF patients in routine clinical care were able to maintain a target INR for over half the time (56%). Of the considerable remaining time, patients were above the target range for 30%, and below the target range for 14%.¹⁴³

Insights into these research findings were uncovered by the ACE patients survey. It was found that, while nearly three-quarters of patients knew their target INR, over a

third believed that being outside the target range had no major effect on their health. Only 30% of patients had been in their target INR range in all of their last 5–10 monitoring sessions, and 7% had not been in their target INR range in any of their last 5–10 sessions.¹⁴¹

Greater patient empowerment

Patient empowerment is associated with improved clinical outcomes,¹⁴⁴ and has been made central to the current focus of the NHS. For a patient to be empowered, it is necessary that he or she has sufficient knowledge to be actively engaged in treatment decisions, in the setting of treatment goals and in evaluating the outcomes. Specific to the stroke prevention efforts required in AF, patient education and involvement in the management of warfarin therapy have been shown to reduce the risk of major bleeding.¹⁴⁵ Patients cannot become empowered without access to information which needs to be accurate, consistent and easy to understand. Limits on the accessibility should also be removed wherever possible by addressing different levels of literacy, by not relying on a single format (e.g., print or internet) and by making the information available in appropriate languages.

Barriers to patient empowerment extend far beyond the accessibility of information; they include factors such as time pressure on healthcare professionals, their misperceptions of patient needs and poor continuity of care between healthcare professionals.

Limitations of current treatments

The limitations of current treatments represent a significant challenge to the effective reduction of stroke risk in AF patients. Among the group of patients who are diagnosed, and who would benefit from warfarin, nearly half don’t receive it.¹¹⁹ And that those taking warfarin, are only benefiting from reduced stroke risk, with no increase in bleeding risk, for about half the time.¹⁴³ As we have seen in earlier sections, there are many drawbacks with warfarin and almost all of these can be traced back to the narrow therapeutic range and the ease with which lifestyle choices, foods and other drugs can push blood levels outside of that range.

There is clearly a need for new therapies that treat AF, prevent blood clots and prevent AF-stroke without the inconvenience and disadvantages of warfarin and aspirin. Understandably, AF patients currently taking anticlotting therapy are all too aware of this need. When surveyed, 68% of chronic AF patients expressed their interest in new anticoagulation drugs for which routine monitoring was not needed.¹⁵¹

Progress in this area of new therapies is discussed in more detail in the earlier section but new anticoagulant drugs are in development. Available clinical data suggests that some of these new drugs might match the stroke risk reduction of warfarin while being convenient, having more predictable effects and a better safety profile. These agents they have the potential to increase adherence to therapy and to guidelines, and most importantly to the number of AF patients at reduced risk of stroke.

Incomplete knowledge among health-care professionals

The importance of patient empowerment has been stressed already. Unless healthcare professionals are equipped with a high knowledge of AF-patient management, it will remain almost impossible to engage patients in decision making and target setting for their own management.

Benefits of current treatments to prevent stroke

The reasons for poor adherence to guidelines have been reviewed in earlier sections. Many of these reasons are rooted in the degree of understanding and concern that physicians have about the safety and effectiveness of warfarin. We have seen that doctors both underestimate the benefits of warfarin and over estimate the risks. There is also evidence that the safety of aspirin and effectiveness is overestimated by prescribers. This highlights an urgent need for improved awareness and understanding among physicians of the existing antithrombotic treatments and their essential role in the prevention of stroke among AF patients.

The barriers of low awareness and knowledge among healthcare professionals is also evident from survey data. Physicians have reported that increased training and availability of consultant advice or guidelines specifically on managing anticoagulation therapy would increase their willingness to prescribe warfarin.¹⁵³

Evidence also suggests that healthcare professionals need greater awareness of their patients' ability to retain information at the point of diagnosis, as well as greater insight into the negative effects that the symptoms of AF have on patients' lives.

Provision of information

There is a large amount of information for patients to absorb in one consultation with the physician. Physicians

need to understand the enormous value of supplying written information covering critical advice and facts, and that this is vital to ensure patient understanding and engagement. Physicians also need to revisit this information in subsequent consultations to confirm and reinforce patient understanding so that patients can become involved in the making of informed decisions about their care.

Physicians need also to recognise the negative impact that symptoms are having on patients lives. Failure to do this results in a feeling of abandonment and dismissal, which will likely undermine efforts to educate and engage the patient in the management of AF, achieving the opposite of patient empowerment.

Finally, efforts are required to ensure that always patients receive consistent and accurate information and advice that is uniformly specific to individual circumstances. This is only possible if there is effective communication between the various healthcare professionals involved in the patient's care.

Management of patients receiving warfarin

There is evidence to suggest that patients adhere to warfarin therapy more closely when closely supervised or routinely managed by a dedicated anticoagulation service.¹⁵² However, there are great differences between the many dedicated anticoagulation services provided throughout the UK, but a distinct lack of information on the effectiveness, quality and range of services that they provide. Physicians need to become aware of the strengths and limitations of their local anticoagulation clinic, and remain mindful of alternatives such as home testing. The roles of self-management and anticoagulation clinics is covered more closely at the end of this chapter under Access to care and information.

Awareness of treatment innovations

Novel anticoagulants currently in advanced stages of development may simplify the management of patients with AF. As with any chronic intervention, however, high-quality guidance and education for doctors, patients and their carers will be essential. Healthcare professionals will need to identify and manage eligible patients and know how to deal with emergency situations. Increased resources for education and rapid dissemination of information will allow faster introduction and uptake of new therapies.

Inequity of access to effective management

There is a considerable body of evidence that supports the accuracy and reliability of self-testing.^{146,147,148,149}

There is also high-level endorsement of home testing from NICE which recommends that it is considered in all AF patients in need of long-term anticoagulation, if they would prefer self-management. The Department of Health has committed to help fund home testing and self-management is very much in line with government strategy promoting patient choice and patient empowerment.

However, there are major disincentives for patients to self-manage their warfarin treatment in the UK. The testing machines are not available on the NHS, preventing their use among many patients who would benefit from a high degree of involvement with their own treatment. Furthermore, while the Department of Health has committed to funding the testing strips that the machines use, many Primary Care Trusts (PCTs) are not currently funding the strips in line with this commitment. The result is that the cost falls to patients who should not have to face this financial burden. Many patients simply can not afford the strips and become failed by the system responsible for their care. This situation also creates imbalance and 'postcode prescribing' where patients in one part of the country are denied access to a therapy which is provided routinely elsewhere.

There is need not only for agreed standards of care and service from anticoagulation services, there is also need for much greater consideration and support of home testing for those patients likely to benefit. When the risks and benefits of home testing are properly explained to patients, nearly all (94%) find the option to be acceptable.¹⁴⁷ In a study that investigated the role of self-testing, 87% of patients reported that they felt it to be straightforward and that they were confident with the results they obtained. Research from outside the UK has also indicated that cost benefits might also be possible with home testing.¹⁵⁵

In further support of home testing and patient empowerment, there is general agreement among both primary care physicians and specialists that anticoagulation therapy is best managed by general practitioners, rather than hospital doctors to ensure optimal access to, and continuity, of care.¹⁵³

Anticoagulation clinics – a potential educational resource

Anticoagulation clinics may be run from a hospital or attached to a primary care practice. They have sometimes

been considered the gold standard of warfarin management¹⁵² helping to increase the time that a patient's INR values are within the target range, improve the overall cost-effectiveness of therapy, increase patient adherence and provide valuable information for both healthcare professionals and patients.^{150,154} However, information of the quality and range of services of these clinics in the UK is poor. When the effectiveness of dedicated clinics is compared with home-monitoring, the results are positive for self-testing.¹⁴⁹ Self-testing also avoids much of the time and financial commitment required to make frequent journeys to the clinic, and it frees patients from feeling a need to remain close to their clinic at all times. This can interfere considerably with daily life as patients avoid travel and holidays because of such fears.

If patients are referred to an anticoagulation clinic, communication between all the healthcare professionals involved is crucial: assigning one part of patient care to an external clinic can weaken the relationship between the primary care physician and patient and may lead to disruption of care if communication breaks down.¹⁵² Therefore, healthcare providers may need education and support in ensuring a seamless transition between the different strands in the patient pathway. As management of patients receiving anticoagulants evolves, anticoagulation clinics will need to adapt.¹⁵² The organisation and running of anticoagulation clinics might gain cost and efficiency benefits through the adoption of technology. Computer programs to calculate the required dose adjustment of warfarin have been found to perform just as well as clinic staff.^{157,158} Anticoagulation clinic staff may have an increasing role as educators and coordinators of anticoagulation therapy, providing support and communications links for other healthcare providers.

Moves towards patient-centred care

Access to, and the quality of, management of patients with AF is also likely to be greatly improved by a move to more patient-centred care and patient empowerment. Under current Department of Health policies, the consideration of patients' needs, preferences and concerns relating to overall health, rather than just to a specific condition will become increasingly important. Although a patient-centred approach is widely advocated, it is not always implemented.¹⁵⁹ Instead, health care is typically centred on treating the disorder, rather than considering patients' individual needs.^{159,160} There is evidence that anticlotting therapy tailored to patients' preferences is more cost-effective than giving the same therapy to every patient.¹⁰⁹ There is therefore a need to provide physicians with further education on the benefits of patient-centred care and with support in implementing this approach locally.

Interruptions in the continuum of patient care

Continuity of care, involving timely communication between healthcare providers, is essential for high-quality care. As the provision of health care often involves several different service providers, continuity of care is defined as 'coherent health care with a seamless transition over time between various providers in different settings'.¹⁶² By empowering patients and adopting a patient-centred approach to management, many factors that interrupt the continuum of care can be identified and eliminated.

Clinical research supports the need for an optimised continuum of care. In one paper, the defining characteristics of an ideal continuum were established; the seven Cs) of optimal continuity of care.¹⁶²

- Regular contact between patients and healthcare providers.
- Collaboration between healthcare professionals and patients in educating and 'empowering' the patient.
- Communication between healthcare providers.
- Coordination of the multidisciplinary teams involved, with clear identification of different roles.
- Contingency plans in the form of access to healthcare professionals out of hours to answer questions and address concerns.
- Convenience – achieved, for example, by avoiding the need for patients to keep repeating information and by considering home monitoring.
- Consistency of the advice provided by different professionals and adherence to clinical practice Guidelines.

The close monitoring required in patients receiving warfarin therapy can be problematic in ensuring continuity of care. When patients are transferred to other healthcare providers or to different settings, such as during hospitalisation or at discharge from hospital, critical information can be lost. Comprehensive, timely and appropriate discharge information is essential – possibly in some portable format¹⁶³ – so that the primary care practice has all it needs for appropriate follow-up care. Insufficient discharge information can contribute to hospital readmission.¹⁶⁴ Education of carers also plays a key role in the success of therapy, and the availability of a healthcare provider to answer questions and address concerns is likely to improve continuity of care.

Conflicting guidelines and GP targets

When guidelines provide conflicting information or when outcomes rewards fail to motivate treatment in accordance with guidelines, there is significant opportunity for patient management that falls short of what is ideal. In the UK, healthcare providers have a choice of two conflicting sets of authoritative guidelines; those from NICE and those from ESC.

It is essential that the planned review of the existing NICE 2006 guidelines are updated to reflect not only the existing ESC guidelines, but also to reflect improvements that the authors of the ESC guidelines are already considering.

It is also necessary to change the current QOF scheme that rewards physicians for achieving targeted patient outcomes. In the previous chapter, this topic was addressed in more detail, but the current scheme provides virtually no motivation for GPs to put patients on warfarin in accordance with either the NICE 2006 or the ESC 2010 guidelines. Proposed changes to this scheme would help eliminate this barrier to effective AF patient management.

Summary of current challenges

In summary, numerous challenges remain in the prevention of stroke in patients with AF. Increased detection of AF by physicians is vital, and improved education is needed among patients and healthcare professionals on the benefit-to-risk profile of aspirin and warfarin, and on the optimum management of patients receiving warfarin. Healthcare professionals need to be aware of new anticoagulants and other therapeutic strategies that are emerging, as well as advances in the treatment of the underlying AF. It is also vitally important to encourage patient empowerment and patient-centred care and ensure equity of access to advances such as self-management. Finally, improved adherence to guidelines, consistent recommendations between guidelines and collaborative approaches to the development of revised guidelines are essential, as are revisions to schemes that exist to motivate GP to achieve outcome targets among AF patients. All of these factors will contribute to the prevention of stroke in patients with AF.

Chapter 9 - New treatments in development

Key points

- Practical and perceived drawbacks of warfarin are limiting its potential to prevent stroke
- alternative anticoagulants in development aim to offer efficacy, safety and convenience, without need for monitoring or dose adjustment
- Three oral anticoagulants are in the final stages of development for the prevention of stroke in AF
- Promising minimally-invasive procedures have also been developed for correcting abnormal heart rhythms and eliminating the source of AF-related blood clots

Limitations of warfarin and aspirin restrict their use and effectiveness in the prevention of stroke in patients with AF. These limitations have led to an ongoing search for alternative effective and convenient therapies. In addition, there have been developments in anti-arrhythmic drugs used to treat AF. These developments are discussed in more detail below.

Anticoagulant agents

There are many challenges involved in the effective use of current anticoagulants to prevent stroke. Taken together, they point clearly to what might be the ideal characteristics of an anticoagulant for long-term use in AF.¹⁶⁵

- As effective as warfarin
- A large therapeutic window (a wide separation between blood levels that reduce the risk of a blood clot and those that substantially increase the risk of bleeding)
- A good safety profile in a wide range of patients, including the elderly
- A low tendency to interact with food and other drugs
- No need for regular monitoring and dose adjustment
- Easy and simple to take (i.e., by mouth in pill or capsule form on daily basis)

Warfarin can be very effective, is relatively simple to take, and is somewhat safer than many physicians appear to believe, but it does not fulfil the remaining criteria for an ideal anticoagulant. Warfarin interacts with food and other drugs in a way that can lead to blood levels far outside a very narrow therapeutic window. Consequently, warfarin requires frequent monitoring and dose adjustments. When monitoring and adjustment are lax, both the effectiveness and safety of warfarin are compromised.

Understandably, there has been a long search for alternative anticoagulants. The clotting process is a complicated cascade of biological reactions providing many potential targets for a new drug. Yet it has taken decades of research to uncover new compounds that are effective in tackling some of these targets. The agents that are most advanced in their development act on single proteins in the coagulation pathway; either clotting factor Xa (pronounced 'ten A') which is involved in the amplification of the clotting response, or on thrombin which enables the final step of the clotting process to take place.¹⁶⁵ Today, development of a handful of new oral anticoagulants has advanced to human trials in large numbers of patients.

The below table summarises the new anticoagulation agents which have filed, or which plan imminently to file, applications for European regulatory approval. These and other agents in the final stage of development are discussed below.

New anticoagulant agents offer potential alternative to warfarin in some patients^c

Agent	Commercial Name	Class	Current indications	Status of AF indication
Rivaroxaban	Xarelto	Direct factor Xa inhibitor	VTE ^a	Licensed Dec-2011
Apixaban	Eliquis	Direct factor Xa inhibitor	VTE ^a	Plans to file before end 2011
Dabigatran	Pradaxa	Direct thrombin inhibitor	VTE ^a AF ^b	Licensed Sep-2011

^a The prevention of venous thromboembolism in adults after hip or knee replacement

^b To prevent strokes and the formation of clots in adults who have an abnormal heart beat called 'non-valvular atrial fibrillation' and are considered to be at risk of stroke

^c Accurate at 1-Oct-11

Oral factor Xa inhibitors

Clotting factor Xa has few functions in the body outside coagulation, making it an excellent target for potential new anticoagulants as this may result in fewer side effects.¹⁶⁶ Inhibition of factor Xa inhibits thrombin generation, while allowing existing thrombin to continue its vital role in blood clotting.¹⁶⁶ Oral inhibitors of factor Xa in late-stage development include rivaroxaban, apixaban and edoxaban. Two factor Xa inhibitors are currently licensed in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA); rivaroxaban,¹⁷⁰ and apixaban.¹⁶⁷ Both are available Europe-wide following authorisation from the European Medicines Agency. Both agents are available for the prevention of clotting problems in the veins in adults after hip or knee replacement surgery. For this indication, called venous thromboembolism (VTE), rivaroxaban is taken orally, once daily at a fixed dose; apixaban is taken orally, twice daily at a fixed dose.

Unlike warfarin, rivaroxaban and apixaban have a wide therapeutic window and do not require routine monitoring. The manufacturers of rivaroxaban have also now submitted additional indications for licence, including stroke prevention in patients with AF and the treatment of deep vein thrombosis. The manufacturers of apixaban have announced plans to make regulatory filings in 2011 for stroke prevention in AF patients.

Rivaroxaban

The pivotal clinical study of rivaroxaban is called ROCKET AF.^{168,169} The results of the study showed that AF patients taking rivaroxaban had a comparable risk of stroke and a similar risk of bleeding compared to patients taking warfarin.¹⁶⁹

ROCKET-AF was a randomised, double-blind study that compared the efficacy and safety of rivaroxaban 20 mg once daily with warfarin for the prevention of stroke in approximately 14,000 high-stroke-risk patients with AF.^{168,169}

Apixaban

Two pivotal studies of apixaban have recently released results. The AVERROES study compared apixaban with aspirin in 5,599 AF patients who were unable to take warfarin. The study was stopped early having demonstrated clearly that apixaban was associated with a significant reduction in strokes when compared with aspirin. A second pivotal trial, ARISTOTLE, compared apixaban with warfarin in over 18,000 AF patients. Results from this trial show that apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

Edoxaban

Pivotal studies of edoxaban have yet to complete but earlier trials indicated that AF patients taking edoxaban had a similar incidence of bleeding to those assigned to warfarin.¹⁷² A pivotal phase III study (ENGAGE- AF TIMI 48) is underway to demonstrate the safety and efficacy profile of different edoxaban doses compared to warfarin.¹⁷¹

Indirect factor Xa inhibitors

Another group of factor Xa inhibitors are under investigation. These agents, instead of acting directly, limit the activity of factor Xa via antithrombin. Among these indirect factor Xa inhibitors, biotinylated idraparinux is the most studied and the only example to have been involved in a late-stage clinical study. Unlike the direct Factor Xa

inhibitors above, biotinylated idraparinux is administered by subcutaneous injection.¹⁶⁵ A study called BOREALIS-AF was evaluating whether subcutaneous biotinylated idraparinux administered once a week was at least as effective as warfarin for the prevention of stroke in patients with AF.¹⁷¹ However, the trial was halted by the sponsor. This is the second trial of biotinylated idraparinux to have been stopped early. However, unlike a predecessor BOREALIS-AF was not stopped because of a safety concern. This earlier trial, which used a different formulation of the drug, was stopped as a result of bleeding concerns.

Thrombin inhibitors

Dabigatran

Dabigatran etexilate directly inhibits the action of thrombin, blocking the final step of the clotting cascade which converts fibrinogen to fibrin. Similar to apixaban and rivaroxaban, throughout Europe dabigatran has been approved for the prevention of VTE in adults after total hip replacement or total knee replacement surgery.¹⁷³ The pivotal, late-stage clinical study of dabigatran is called RE-LY, which compared the efficacy and safety of dabigatran with warfarin in^{18,113} AF patients. RE-LY compared two doses of dabigatran, taken orally, twice daily, to warfarin. The lower dose was associated with a stroke rate comparable to that seen with warfarin, but with a lower rate of major bleeds. The higher dose resulted in a significantly lower rate of stroke compared to warfarin and a similar rate of major bleeds.¹⁷⁴ Further studies of dabigatran and other direct thrombin inhibitors are ongoing.^{176,55}

Antiplatelet agents

Clopidogrel is an inhibitor of platelet aggregation. Reduced platelet aggregation reduces the risk of a blood clot forming. In a study called ACTIVE-A, clopidogrel in combination with aspirin was compared to aspirin alone for the prevention of stroke in AF patients for whom warfarin therapy was unsuitable. While clopidogrel in combination with aspirin significantly reduced the risk of stroke in patients with AF, it was also associated with a significantly greater rate of major bleeding.¹⁷⁷

Additional studies are under way to assess the efficacy and safety of clopidogrel for stroke prevention in patients with AF.¹⁷¹ Clopidogrel is currently licensed for other indications including the prevention of atherothrombotic events in patients suffering from heart attack.¹⁸⁵

Alternative strategies

Current strategies are focused on drugs that target the process of clot formation. However, other strategies are emerging for patients with AF. These include:¹⁷⁸

- Drugs and procedures that target AF itself
- Drugs and procedures to control heart rhythm and heart rate
- Drugs and procedures to prevent blood clots reaching the brain

New rate and rhythm control drugs

In rhythm control, drugs are used to restore and maintain the sinus rhythm of the heart; in rate control, drugs are used to maintain a suitably low heart rate. Examples of drugs used for rhythm or rate control include amiodarone, digoxin and beta-blockers.

Dronedarone is a new anti-arrhythmic drug licensed for use in clinically stable patients with non-permanent atrial fibrillation, to prevent recurrence of AF or to lower the pulse rate. In trials dronedarone has been shown to reduce the incidence of death or hospitalisation due to cardiovascular events compared with placebo.¹⁸⁸

Non-pharmacological methods

Non-pharmacological interventions for stroke prevention in AF concentrate on eliminating the AF itself; stopping potentially harmful blood clots from reaching the brain, or by preventing the formation of clots.

Non-pharmacological management of abnormal heart rhythm

There are numerous non-pharmacological methods for the management of abnormal heart rhythm.¹⁷⁸ These include:

- Electrical cardioversion: the process by which an abnormally fast heart rate or disturbance in heart rhythm is terminated by the delivery of an electric current to the heart at a specific moment in the heart cycle
- Radiofrequency (RF) catheter ablation: a minimally-invasive procedure used to correct a faulty electrical pathway in the heart
- Non-RF ablation: open surgical or minimally-invasive procedures that correct the faulty electrical pathways from the heart

- Left atrial appendage (LAA) occlusion: minimally-invasive procedure that either prevents clots from forming or prevents them from leaving the site of formation in the heart

Current data suggest that catheter ablation is more effective than anti-arrhythmic drug therapy in maintaining normal heart rhythm.¹⁷⁹ Whether or not this intervention affects the incidence strokes requires further evaluation in clinical trials.

Procedural interventions to reduce stroke risk

One procedural approach to preventing stroke in AF patients seeks to remove an anatomical contributor to clot formation. More than 90% of blood clots in AF patients form in the left atrial appendage (LAA) of the heart.¹⁷⁸ The LAA is a small sac behind an opening the wall of the left atrium. It has been suggested that AF particularly degrades the normal flow of blood in the LAA, allowing clot formation.

Sealing the left atrial appendage, isolating it from the main atrial chamber, may therefore prove to be an effective and permanent way to reduce the risk of blood clots and stroke. Several new occlusion devices have been developed that block the LAA. Such devices are designed to be placed permanently, sealing the opening of the LAA. Once in place, potentially harmful blood clots no longer have opportunity to form in the LAA and any thrombotic material in the LAA is prevented from entering the bloodstream and causing stroke.^{180,181} One of these devices, Watchman, recently received approval for use in Europe.¹⁸¹ The results of a recently published trial, PROTECT-AF, showed that closure of the LAA with Watchman was comparable to warfarin for stroke prevention. The study authors noted caution, having observed an overall increase in the rate of adverse events in the LAA group compared to warfarin. However, unlike drugs, device-related interventions frequently demonstrate substantial safety improvements associated with increased operator experience. A subsequent paper from an extension of the same study investigated this effect. A significant reduction in safety events was observed during the second half of the study period compared to the first. It was also noted that the impact of these safety events, as defined by significant disability or death, was statistically superior in the Watchman group compared with the warfarin group. The authors concluded that closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with AF.^{182,183}

Summary

To summarise, there are several pharmacological agents in development for use in patients with AF, including the new oral anticoagulants rivaroxaban, dabigatran and apixaban. Minimally-invasive device interventions for the management of arrhythmias and the reduction of stroke risk are also being developed.

Valuable insights into the impact of these new therapies on the prevention of stroke in patients with AF can be gained from real-life registries. A number of registries of AF patients are in existence, most of which are country specific or focused on North America.

A new global registry has now been established, the Global Anticoagulant Registry in the FIELD (GARFIELD). GARFIELD will prospectively follow 50,000 newly-diagnosed AF patients and 5,000 patients with previously-diagnosed AF, over six years.¹⁹² Patients will be included and followed, regardless of whether or not they receive appropriate therapy. The GARFIELD registry will document details such as the risk factors, treatment patterns and clinical events associated with AF, and will provide a picture of the real-life global burden of the condition. It is also hoped that GARFIELD will show how the new advances in therapy can contribute to the prevention of stroke in patients with AF.¹⁸⁶

It is hoped that the availability of new therapy options, together with a greater understanding of their impact on the burden of stroke, will pave the way for better management of patients with AF.

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