

ATRIAL FIBRILLATION AND STROKE

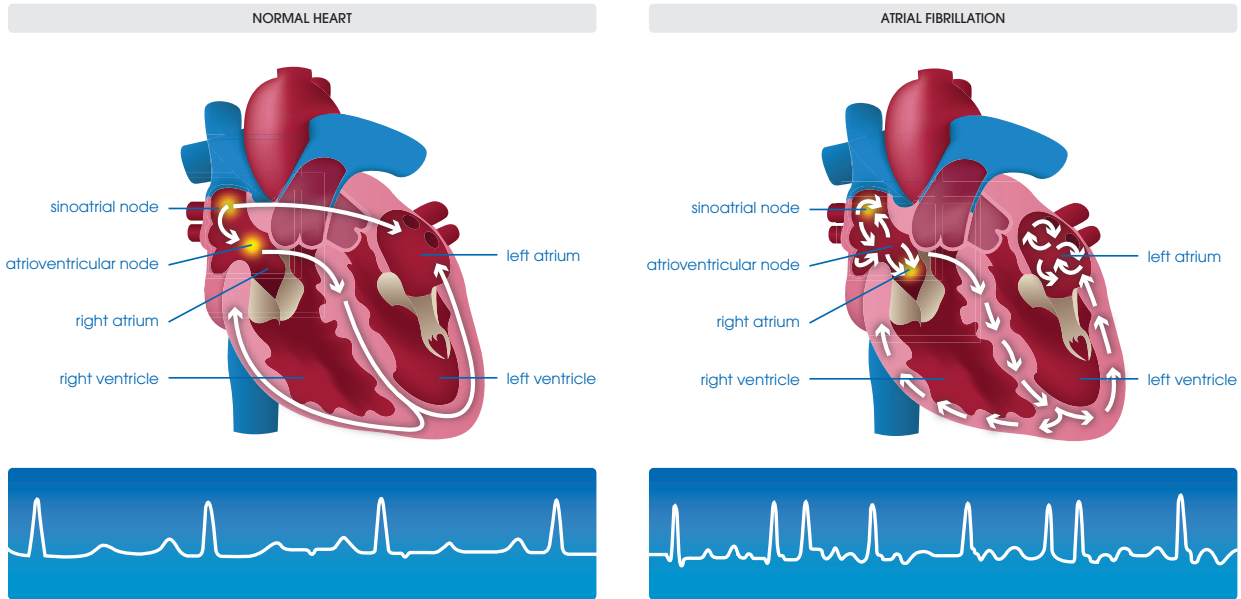
KEY SUMMARY

- Nearly one in four people over the age of 40 will develop atrial fibrillation (AF)¹, making it the most common heart rhythm abnormality.²
- People with atrial fibrillation are five times more likely to have a stroke³, but many are unaware of the increased risk
- Atrial fibrillation-related strokes are more likely to be severe, disabling and fatal than non atrial fibrillation-related strokes⁴
- Many atrial fibrillation-related strokes can be prevented with appropriate antithrombotic therapy⁵
- The key goals of therapy in atrial fibrillation (AF) are stroke prevention and the control of heart rhythm and rate
- Clinical trial results have shown that well controlled vitamin K antagonist therapy can prevent two out of three strokes due to atrial fibrillation⁵
- VKAs have several limitations resulting in only 51% of diagnosed patients living with atrial fibrillation and at risk of stroke receiving appropriate anticoagulation therapy.⁶



What is atrial fibrillation?

- In patients with atrial fibrillation (AF), the normal control of heart rhythm by the sinoatrial (SA) node is disrupted, leading to rapid and irregular electrical signals (tachyarrhythmia), which cause the atria to quiver rather than contract in a coordinated fashion.⁷ This reduces the efficiency with which blood is pumped from the atria to the ventricles and blood stasis (pooling) can occur.



How atrial fibrillation affects the heart

- AF alters the electrophysiological properties of myocardial cells so that disturbances in electrical signalling tend to be self-perpetuating.⁸
- Pathophysiological causes of AF include abnormal electrical activity in pulmonary veins (PVs), atrial dilatation and atrial fibrosis.
- For those who experience symptoms of atrial fibrillation, they include palpitations, dizziness, chest pains and breathlessness. Although some people with atrial fibrillation can experience the symptoms on a regular basis, others may never, or rarely, experience symptoms.^{9,10}

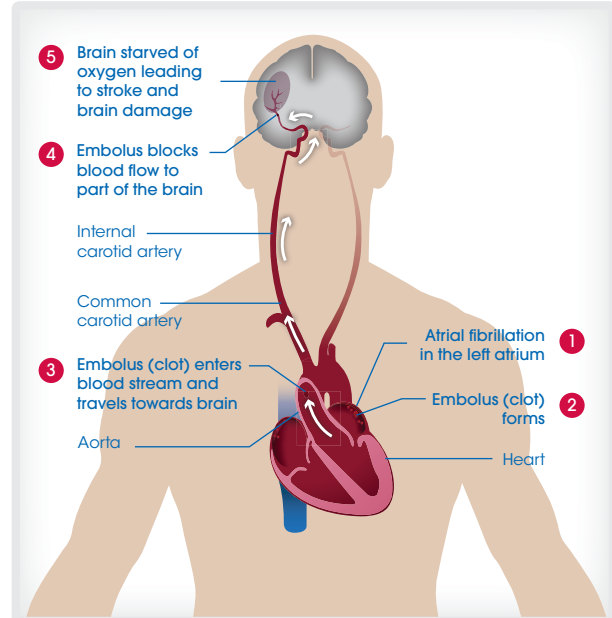
What are the risk factors for atrial fibrillation?^{11,12}

Family history of AF	Echocardiographic abnormalities
Advancing age	Thyroid disorders
Cardiovascular disease	Sleep apnoea
History of heart disease	Excessive alcohol intake

- The risk of atrial fibrillation increases with age. It affects 1% of adults worldwide. Nearly one in four people over the age of 40 will develop the condition¹ and it affects 10% of people above the age of 80.²

Consequences of AF

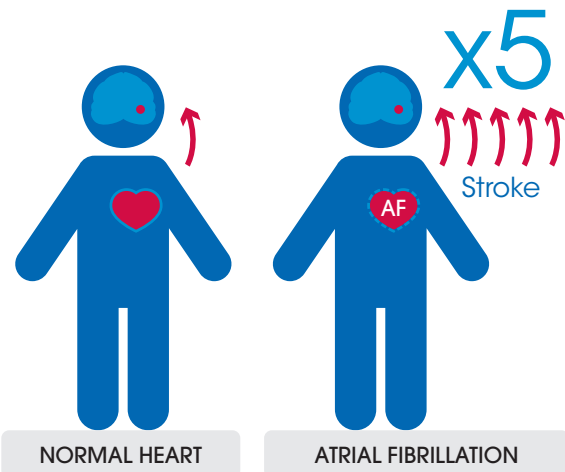
- Atrial fibrillation (AF) is associated with several serious consequences. The rapid and irregular atrial activity in AF reduces the efficiency with which blood is pumped from the atria to the ventricles.⁷ Blood clots (thrombi) can form in the atria following the pooling of blood (stasis) that can dislodge and travel in the bloodstream, potentially blocking blood vessels in the brain and leading to ischaemic stroke.
- The reduction in cardiac output observed in AF can precipitate heart failure, leading to accumulation of fluid in the legs (peripheral oedema) and lungs (pulmonary oedema), or dyspnoea, fatigue and chest pain.¹³
- AF has also been associated with poorer clinical outcomes in patients suffering a myocardial infarction and in patients with acute coronary syndromes.¹⁴



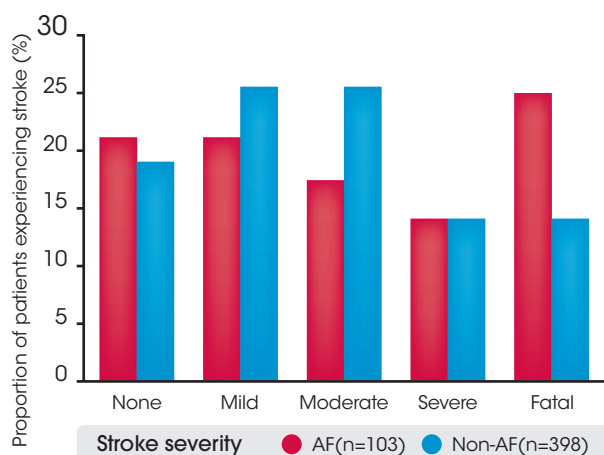
How atrial fibrillation leads to stroke

Stroke is the leading complication of AF

- AF increases the risk of stroke approximately five-fold.³ It is responsible for nearly one-third of all strokes¹⁵ and is the leading cause of embolic stroke.¹⁶ Without preventive treatment, approximately 1 in 20 patients with AF will have a stroke each year.¹⁷



Atrial fibrillation and the risk of stroke



Lin HJ et al. Stroke 1996;27:1760-4

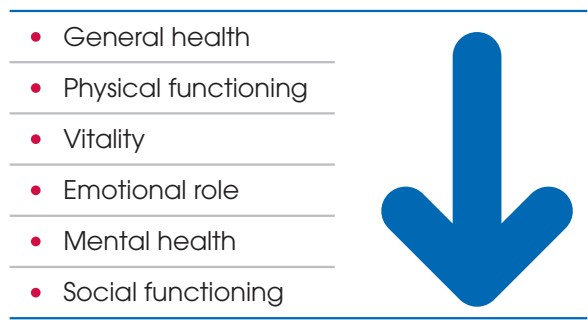
Stroke is more likely to be fatal in patients with AF

(AF vs. non-AF: P=0.048)

- AF-related stroke is associated with a heavy burden of morbidity and mortality. For example, stroke is more likely to be fatal in patients with AF, and those who survive face persistent neurological deficits, persistent disability and poorer functional performance.^{4,18}

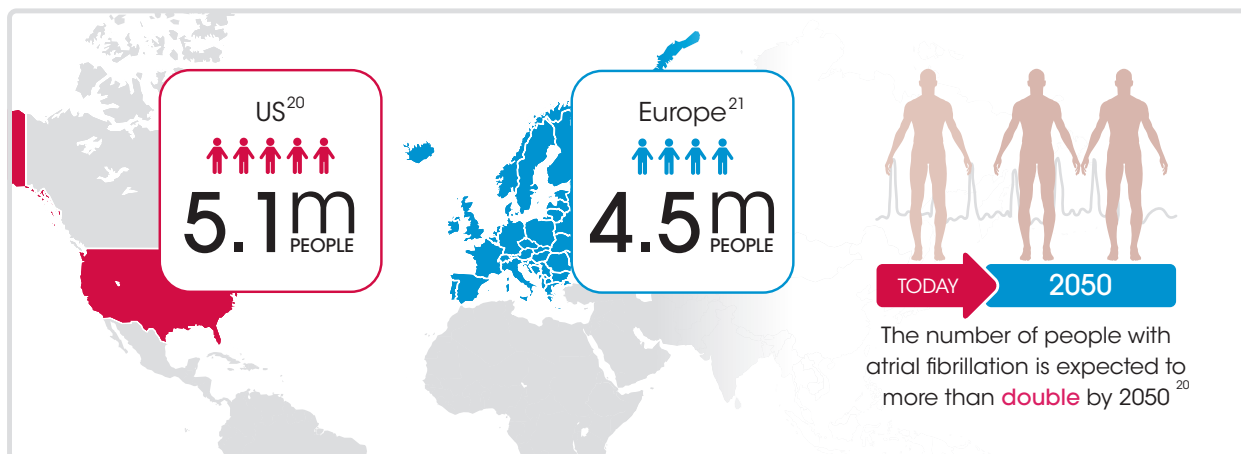
The personal burden of atrial fibrillation and stroke

- Atrial fibrillation negatively impacts on people’s quality of life affecting both physical functioning and emotional wellbeing.^{17,19}
- For people with atrial fibrillation, mental health, emotional wellbeing and social functioning are more negatively affected compared to people with other cardiac conditions.^{17,19}
- Many people with atrial fibrillation live with a constant fear about what the future might hold, worrying about becoming a burden on their families should they have a stroke.
- AF is also associated with a number of serious and potentially life-threatening complications including heart failure² and death.



The personal burden of atrial fibrillation and stroke

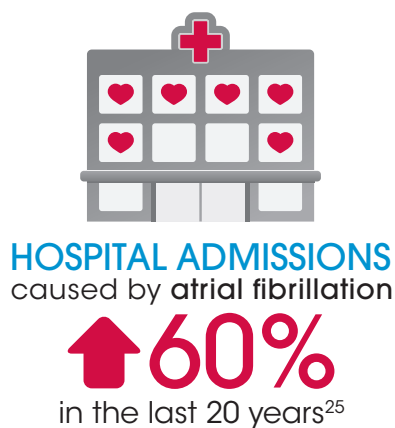
Atrial fibrillation – an increasing problem



Atrial fibrillation – An increasing problem

Cost burden

- Stroke increases costs by approximately 30% in patients with AF compared with those without the arrhythmia.²²
- Treating atrial fibrillation costs the US \$6.65 billion and Europe €6.2 billion per year.^{23,24}
- Atrial fibrillation costs healthcare systems across Europe up to €13.5 billion per year.²¹



Managing atrial fibrillation

- The management of atrial fibrillation (AF) has two broad objectives. These are the prevention of complications, including stroke and heart failure, and the relief of symptoms from the arrhythmia itself.¹⁹
- Symptom relief can be achieved by either controlling the heart rate or restoring sinus rhythm. The choice between a rate- or rhythm-control strategy depends on individual patient characteristics.¹⁹

Rate-control aims to normalise the heart rate and relieve symptoms of AF

- Clinical targets for rate-control vary between patients depending on age, but generally aim to achieve a resting heart rate of 60-80 beats per minute.¹⁹ First-line therapies for pharmacological control of heart rate include beta-blockers and calcium channel blockers, which can be used either alone or in combination.²⁶
- Non-pharmacological methods include atrioventricular nodal ablation and use of a permanent pacemaker.²⁶ However, rate-control does not address the atrial arrhythmia.

Rhythm-control aims to restore normal sinus rhythm and eradicate AF

- By restoring and maintaining normal control of heart rhythm by the sinoatrial node, successful rhythm-control corrects the underlying arrhythmia.¹⁹ The process of restoring normal sinus rhythm is also referred to as "cardioversion". This can be achieved by pharmacotherapy with anti-arrhythmic drugs, or the use of electrical shocks to reset the heart rhythm, which is known as direct-current cardioversion.¹⁹

Treatment strategies should be tailored to the patient

- The goals of therapy need to be individualised for each patient. Studies have demonstrated that rate-control has similar efficacy to rhythm-control and that rate-control is generally better tolerated.²⁷⁻³⁰ Consequently, rate-control is recommended as the first-line strategy for many patients. Restoration of sinus rhythm is still more advantageous than controlling heart rate, and criteria favouring rhythm-control include patients being younger and the heart rate, and criteria favouring rhythm-control include patients being younger and the existence of troublesome symptoms of AF despite treatment with rate-control.¹⁹

A majority of patients with AF should receive antithrombotic therapy

- For stroke prevention, antithrombotic therapy is recommended for all patients with AF and at least one risk factor for stroke, other than those with lone AF or contraindications.¹⁹ Risk factors for thromboembolism and bleeding must be considered when deciding on a stroke prevention strategy. Risk stratification schemes such as CHADS₂ and HEMORR₂HAGES can be used in clinical practice to stratify a patient's risk of stroke and bleeding, respectively.^{31,32}

CHADS₂ score is a simple index that is widely used to assess the risk of stroke of a patient with atrial fibrillation. It can be used to guide antithrombotic therapy. The name CHADS₂ comes from the components included in the index: **C**ongestive Heart Failure history (1 point), **H**ypertension history (1 point), **A**ge ≥ 75 years (1 point), **D**iabetes mellitus history (1 point), **S**troke or TIA history (2 points).

HEMORR₂HAGES is a stratification scheme for assessing the risk of bleeding complications in patients with atrial fibrillation, which assigns a score based on the presence of risk factors. The name HEMORR₂HAGES comes from the components included in the index. The HEMORR₂HAGES score assigns 2 points for a prior bleed and 1 point for each of the other risk factors: **h**epatic or renal disease, **e**thanol abuse, **m**alignancy, **o**lder (age > 75 years), **r**educed platelet count or function, **h**ypertension (uncontrolled), **a**nemia, **g**enetic factors, **e**xcessive fall.

Fuster V, et al. *Circulation* 2006; 114:e257-e354, Gage et al. *Am Heart J.* 2006 Mar;151(3):713-9

Vitamin K antagonists vs. Aspirin

- Treatment guidelines for stroke prevention in AF are based on oral anticoagulation with vitamin K antagonists (VKAs), such as warfarin, and the antiplatelet agent Aspirin.¹⁹ VKAs and Aspirin are proven to reduce the risk of stroke in patients with AF. For example, in a meta-analysis of 29 key clinical trials, warfarin reduced the risk of stroke by approximately 64%, whereas Aspirin reduced stroke risk only by approximately 20% compared with placebo.⁵
- Although warfarin is more effective than Aspirin, treatment is lifelong and it may be associated with a higher risk of bleeding complications as well as being more difficult to manage in clinical practice.
- Treatment with VKAs requires intensive monitoring of blood coagulation to ensure it remains within a safe and effective INR range.

International normalized ratio is a measure of how fast the blood clots and shows the amount of anticoagulant in the bloodstream to help determine the correct dose. A high INR means that the patient is more likely to bleed and a low INR means that a patient is at higher risk of clot formation.

- Doctors aim to extend patients' time in therapeutic range (TTR) by regulating the INR. For patients treated with warfarin, the target INR is between 2 and 3.
- VKAs are very effective with long term use, preventing two out of three strokes in patients with atrial fibrillation.⁵ However VKAs can be difficult for people to take as they can interact with other common medications, alcohol and certain types of food, including green tea, avocados (large amounts), and food with high vitamin K content including broccoli and spinach.
- Around half of all AF patients do not receive anticoagulation therapy due to the contraindications and limitations associated with current agents, particularly warfarin.⁶



Food interactions with VKAs

Drug	Examples
Analgesics	Acetaminophen, popoyphene, salicylates
Anti-arrhythmics	Amiodarone, propafenone, quinidine
Antibiotics	Ciprofloxacin, erythromycin, metronidazole
Antifungals	Fluconazole, itraconazole, miconazole
Beta blockers	Propranolol
H ₂ -receptor antagonists/PPIs	Cimetidine, omeprazole
Lipid-lowering agents	Lovastatin, atorvastatin
Supplements	Examples
Herbal products, dietary supplements	Vitamin E, garlic, devil's claw

Drug	Examples
Antibiotics	Dicloxacillin, nafcillin, rifampicin
Antifungals	Griseofulvin
Immunosuppressants	Azathioprine, cyclosporine
Lipid-lowering agents	Cholestyramine
Miscellaneous	Carbamazepine, sucralfate, trazodone
Supplements	Examples
Herbal products, dietary supplements	Coenzyme Q10, ginseng, St John's Wort

PPIs = proton pump inhibitors; VKAs = Vitamin K antagonists

Holbrook AM *et al.* *Arch Intern Med* 2005;165:1095-106
 du Breuil AL & Umland EM. *Am Fam Physician* 2007;75:1031-42

Drug interaction associated with an **increased** potency of VKAs

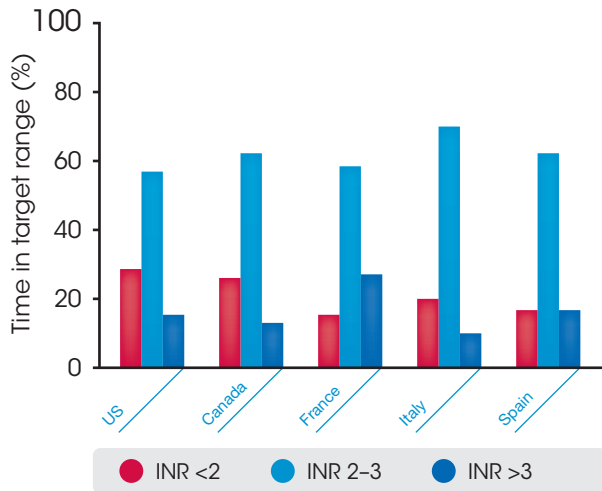
Holbrook AM *et al.* *Arch Intern Med* 2005;165:1095-106
 du Breuil AL & Umland EM. *Am Fam Physician* 2007;75:1031-42

Drug interaction associated with a **reduced** potency of VKAs

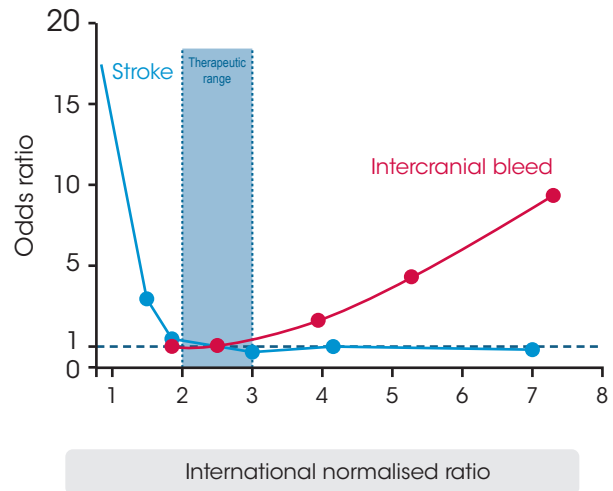
Implications of VKA's limitations

Registries have shown patients receiving warfarin only spend half their time within the narrow therapeutic range.³³ When INR control is not well controlled, the therapeutic benefit is reduced:³³⁻³⁵

- Under-anticoagulation (INR<2) increases stroke risk significantly, doubling at INR of 1.7, tripling at 1.5 and increasing 6-fold at INR of 1.3³⁶
- Over-anticoagulation (INR>4.0) increases risk of brain haemorrhage sharply.³⁵



Ansell J et al. *J Thromb Thrombolysis* 2007;23:83-91



ACC/AHA/ESC guidelines: Fuster V et al. *Circulation* 2006;114:e257-354 v& *Eur Heart J* 2006;27:1979-2030

INR time in target therapeutic range

The INR for VKAs is often outside the therapeutic range.

VKAs have a narrow therapeutic window.

Unmet need in anticoagulation

- Due to the limitations of current anticoagulant therapy there is a need for an effective, safe and convenient oral anticoagulant with predictable anticoagulant effects, fewer drug-drug interactions, no drug-food interactions and no requirement for routine coagulation monitoring.

Dabigatran etexilate and anticoagulation

- Dabigatran etexilate, an oral reversible direct thrombin inhibitor, is the most advanced novel oral anticoagulant in clinical development for stroke prevention in AF, and provides predictable, consistent anticoagulation without the need for routine coagulation monitoring, has a low potential for drug-drug interactions and no drug-food interactions.³⁷⁻⁴⁰ Results from RE-LY® (Randomized Evaluation of Long-term anticoagulant therapy) trial show that the novel oral direct thrombin inhibitor dabigatran etexilate, demonstrates superior outcomes vs. warfarin.⁴¹
- Dabigatran etexilate provides its anticoagulant effect by specifically and selectively blocking the activity of thrombin (both free and clot bound).^{42,43} Thrombin is the central enzyme in the process responsible for clot (thrombus) formation.

RE-LY® study

- Results from the landmark phase III global RE-LY® (Randomized Evaluation of Long term Anticoagulant therapy) study - the largest atrial fibrillation outcomes study ever completed (18,113 patients in 44 countries worldwide) compared the long-term efficacy and safety of dabigatran etexilate with warfarin for the prevention of stroke in patients with AF.⁴¹

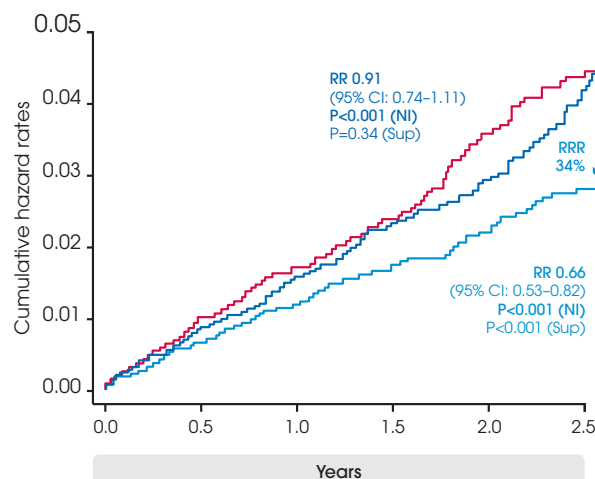
Results

150 mg dabigatran etexilate BID* vs. warfarin:

- provides superior stroke prevention - 34% reduced risk of stroke or systemic embolism⁴¹
- prevents three out of four AF related strokes⁴¹ – warfarin prevents 64% of strokes¹ and dabigatran etexilate prevents an additional 34% of the remaining strokes or embolisms⁴¹
- superior reduction of intracranial bleeding – 60% reduced risk vs. warfarin⁴¹
- effective across all major patient sub-groups including age, gender, co-morbidities (symptomatic heart failure, hypertension, diabetes, prior stroke or transient ischaemic heart attack) and irrespective of stroke risk^{41,42,43}
- reduced risk of total and life threatening bleeding (except for gastrointestinal bleeding).⁶

110 mg dose vs. warfarin:⁴¹

- comparable rates of stroke/systemic embolism
- statistically significant reduction in hemorrhagic stroke
- statistically significant reduction in major bleeding rates
- significant reduction in total bleeds, life threatening bleeds and intracranial bleeds.



BID = twice daily; NI = non-inferiority; RR = relative risk; RRR = relative risk reduction; Sup = superiority
 Connolly SJ et al. N Engl J Med 2009;361:1139-51

Time to first stroke or systemic embolism

Disclaimer

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation prevention. This information is provided for medical education purposes only.

*BID: Twice a day

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Atrial fibrillation and stroke

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