

About Stroke Prevention in Atrial Fibrillation



What is Atrial Fibrillation (AF)?

AF is the most common sustained cardiac rhythm disorder and affects more than 6 million people in Europe¹, up to 5.1 million people in the U.S.² and more than 800,000 people in Japan³.

In AF, the upper chambers (atria) of the heart contract irregularly⁴. As a result, the atria do not empty completely and blood does not flow properly, potentially allowing blood clots to form. These blood clots can break loose and travel to the brain, resulting in a stroke⁵.

What is Stroke?

A stroke is the rapidly developing loss of brain function(s)⁶. Strokes are caused by a lack of blood supply to the brain due to a blood clot or haemorrhage, causing rapid brain-cell death that may result in severely restricted movement paralysis, loss of speech or vision which may be permanent, or even death. Strokes can be classified into two major categories:

- ◆ Ischaemic strokes occur due to an interruption of the blood supply due to a blockage (e.g. a blood clot)⁶
- ◆ Haemorrhagic strokes occur due to rupture of a blood vessel which leads to bleeding inside the brain⁶

Stroke, from any cause, is the second most common cause of death worldwide, responsible for 5 million deaths each year⁷. Stroke is also the leading cause of permanent disability among adults in the US⁸.

AF-Related Stroke

AF-related stroke devastates lives and is major healthcare burden. AF is a strong independent risk factor for stroke⁹ and accounts for approximately 1 in 5 ischaemic strokes (strokes caused by a blood clot blocking a blood vessel in the brain)¹⁰. Patients with AF are five times more likely to have a stroke compared with the general population¹¹. Moreover, previously undiagnosed AF is a probable cause of many strokes of unknown origin (so-called 'cryptogenic' strokes), and stroke may be the first manifestation of AF.



The risk of stroke in patients with AF increases with age and with the addition of other risk factors (e.g. high blood pressure, previous stroke, and diabetes)¹².

The Burden of AF-Related Stroke

Patients with AF who have multiple co-morbidities have a greater risk of stroke¹² and represent the population most difficult to protect. Furthermore, AF-related strokes are more severe, causing disability in more than half of patients and a worse outcome than strokes in patients without AF^{13,14,15}. AF-related strokes are also associated with a 50% likelihood of death within one year¹⁵.

Importantly, the burden of AF-related stroke is likely to become more marked in years to come because the number of people with AF is forecast to increase approximately 2.5-fold by 2050^{16,2} due to ageing of the population¹⁷ and to improved survival following conditions that predispose to AF (such as heart attack)¹⁸.

Current Treatments and Clinical Challenges

Current Clinical Guidelines state that anticoagulation with oral anticoagulants (OACs) is the cornerstone of stroke prevention. Medications known as vitamin K antagonists (VKAs), which reduce blood clotting, are widely regarded as the current standard of care. VKAs, including warfarin, are effective in preventing AF-related stroke. Warfarin has been shown to reduce the risk of stroke by 64%¹⁹. Despite this effectiveness, the limitations of VKAs undermine long-term efforts to protect patients with AF from stroke. Problems with VKAs include unpredictable levels of anticoagulation, the need for frequent blood monitoring and dose adjustments, drug-drug interactions and dietary restrictions²⁰.

When taking VKAs, patients can be 'over-anticoagulated', which can lead to bleeding, particularly intracranial haemorrhage, or 'under-anticoagulated', which increases the risk of a stroke. Currently, approximately 50% of patients with AF who are eligible for VKA treatment do not receive the therapy²¹. Additionally, only 10% of patients with AF who experience a stroke are being adequately anticoagulated at the time of admission¹⁴. There remains a clear unmet need for simple, effective and well-tolerated anticoagulation with comparable safety to existing treatments.





New oral anticoagulants hold the promise of overcoming the limitations of traditional anticoagulants, thereby enabling their use to prevent and or treat more venous and arterial thromboembolic (VAT) conditions.

- ◆ Benefits of new oral anticoagulants include predictable anticoagulation without the need for routine coagulation monitoring or frequent dose adjustment, low risk of drug-drug interactions and no dietary restrictions
- ◆ Xarelto[®] (rivaroxaban) combines highly effective stroke protection and similar overall bleeding rates to the VKA warfarin, but importantly with less intracranial and fatal bleeding²²
- ◆ In ROCKET AF, once-daily 'Xarelto' met the primary efficacy outcome – the prevention of stroke and non-CNS systemic embolism in patients with non-valvular AF, and was shown to be non-inferior to warfarin. This was achieved with a mean time in therapeutic range (TTR) of 55% (INR values within the therapeutic range 2.0 to 3.0) among patients receiving warfarin²²
- ◆ ROCKET AF results were achieved with a simple fixed one-tablet, once daily dosing regimen unique to 'Xarelto' (including a reduced fixed 15mg dose in patients with moderate renal impairment), in patients at risk of stroke, including those with multiple comorbidities, who are considered more difficult to protect
- ◆ In ROCKET AF, 'Xarelto' was shown to have a reassuring cardiovascular profile with no increase in myocardial infarctions²²
- ◆ In the study 'Xarelto' was also shown to be well tolerated by patients, with no significant increase in dyspepsia²³
- ◆ 'Xarelto' is approved in the United States to reduce the risk of stroke and systemic embolism in patients with non-valvular AF
- ◆ In September 2011, 'Xarelto' was recommended for European approval by the European Committee for Medicinal Products for Human Use (CHMP) for the prevention of stroke and systemic embolism in adult patients with non-valvular AF, as well as for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults



References

- 1) Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am.* 2008;92:17-40
- 2) Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation.* 2006;114,(2)119-125
- 3) Inoue H, Fujiki A, Origasa H, et al. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. *Int.J.Cardiol.* 2009;137,(2)102-107
- 4) NHS choices. Atrial fibrillation. Available at <http://www.nhs.uk/Conditions/Atrial-fibrillation> Last accessed November 2011
- 5) NHS choices. Atrial fibrillation. Available at <http://www.nhs.uk/Conditions/Atrial-fibrillation/Pages/Complications.aspx> Last accessed November 2011
- 6) News Medical. What is a stroke? Available at <http://www.news-medical.net/health/What-is-a-Stroke.aspx> Last accessed November 2011
- 7) Mackay, J, Mensah, G. Global burden of stroke. The Atlas of Heart Disease and Stroke. United Kingdom. World Health Organization 2004. Available at http://www.who.int/cardiovascular_diseases/resources/atlas/en/ Last accessed November 2011
- 8) Internet Stroke Center. About stroke. Available at <http://www.strokecenter.org/patients/stats.htm> Last accessed November 2011
- 9) Benjamin E, Wolf P, D'Agostino R, et al. Impact of Atrial Fibrillation on the Risk of Death. *Circulation.* 1998;98:946-952
- 10) CDC. Atrial Fibrillation Fact Sheet. Available at: http://www.cdc.gov/dhdsdp/data_statistics/fact_sheets/docs/fs_atrial_fibrillation.pdf Last accessed November 2011
- 11) Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol.* 1998;82(8A):2N-9N
- 12) Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* 2001;285,(22)2864-2870
- 13) Lin HJ, Wolf P, Kelly-Hayes M, et al. Stroke Severity in Atrial Fibrillation: The Framingham Study. *Stroke.* 1996; 27:1760-1764
- 14) Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke.* 2009;40(1):235-240
- 15) Marini C, De SF, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke.* 2005a;36,(6)1115-1119
- 16) Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA.* 2001;285,(18)2370-2375
- 17) United Nations. World Population Ageing. 2009. Available at: <http://www.un.org/esa/population/publications/WPA2009/WPA2009-report.pdf>. Last accessed November 2011
- 18) Briffa T, Hickling S, Knuiman M, et al. Long term survival after evidence based treatment of acute myocardial infarction and revascularisation: follow-up of population based Perth MONICA cohort, 1984-2005. *BMJ.* 2009;338,b36
- 19) Hart RG, Pearce LA, & Aguilar MI Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann.Intern.Med.* 2007;146,(12)857-867
- 20) Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126,(3 Suppl)204S-233S
- 21) Ezekowitz MD & Falk RH The increasing need for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. *Mayo Clin.Proc.* 2004;79,(7)904-913
- 22) Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891
- 23) Data on file. Bayer Pharma AG, Berlin, Germany





About Rivaroxaban (Xarelto®)

Rivaroxaban is an oral anticoagulant that was discovered in Bayer HealthCare's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for routine coagulation monitoring, and a limited potential for food and drug interactions.

Rivaroxaban is marketed under the brand name Xarelto® for VTE prevention in adult patients following elective hip or knee replacement surgery, and it is the only oral anticoagulant that has consistently demonstrated superior efficacy over enoxaparin in this indication. Rivaroxaban is approved in more than 110 countries worldwide and marketed outside the U.S. by Bayer HealthCare in this indication.

In the U.S., where rivaroxaban has been available since July 2011 for VTE prevention in adult patients following elective hip or knee replacement surgery, Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company) holds marketing rights. The Bayer HealthCare sales force is supporting Janssen Pharmaceuticals, Inc. in designated hospital accounts. On November 4, Xarelto® received further marketing approval in the U.S. for the prevention of stroke in patients with Atrial Fibrillation.

The extensive clinical trial programme supporting rivaroxaban makes it the most studied and widely published oral, direct Factor Xa inhibitor. The studies, reported and ongoing, involve over 75,000 patients for the prevention and treatment of venous and arterial thromboembolic (VAT) disorders across a broad range of acute and chronic conditions, including stroke prevention in patients with Atrial Fibrillation, DVT treatment and the prevention of recurrent DVT or PE, and the secondary prevention of Acute Coronary Syndrome.

**To learn more about thrombosis, please visit www.thrombosisadviser.com
To learn more about 'Xarelto' please visit www.xarelto.com**

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