

## Background: The Risk of Stroke in Atrial Fibrillation (AF)

### What is Atrial Fibrillation?

Atrial fibrillation (AF) is the most common type of arrhythmia, a problem with the rate or rhythm of the heartbeat. During an arrhythmia, the heart can beat too fast, too slow, or with an irregular rhythm. AF occurs if rapid, disorganised electrical signals cause the heart's two upper chambers, the atria, to fibrillate.<sup>1</sup>

In atrial fibrillation, the heart does not contract as strongly as it should. This can cause blood to pool in the heart and form clots. When the blood clots dislodge, they may move to the brain, where they can become trapped in a narrow brain artery, blocking the blood flow and causing a stroke. Research suggests that over 90 percent of blood clots responsible for stroke in patients with AF originate in a pouch on the left side of the heart called left atrial appendage (LAA).<sup>2</sup>

Atrial Fibrillation may be brief, with transient symptoms and it is possible to have an AF episode that resolves on its own. However, AF may be persistent and require treatment. Sometimes AF is permanent, and medications or other treatments cannot restore a normal heart rhythm.

### Risk factors for AF include<sup>3</sup>:

- Haemodynamic stress (i.e. heart failure or hypertension)
- Atrial ischemia
- Inflammation
- Non-cardiovascular respiratory causes
- Alcohol and drug use
- Endocrine disorders (i.e. diabetes)
- Neurologic disorders
- Genetic factors/Advancing age

### Prevalence and death rates

Atrial fibrillation affects approximately 1.5 to 2 percent of the general population worldwide.<sup>4</sup> Over six million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double over the next 50 years as the population ages.<sup>5</sup>

### The global burden of atrial fibrillation

Atrial fibrillation is an increasing burden on the global healthcare system because of the numbers of patients affected, the impact of stroke, and the cost of both inpatient and outpatient therapy.<sup>6</sup>

Atrial fibrillation is associated with significant economic costs from the perspective of statutory health insurance, with the largest part of costs attributable to inpatient stays and drug usage.<sup>7</sup>

### What is stroke?

A stroke is a vascular event in the brain that causes abnormal neurological function lasting for more than 24 hours. The World Health Organisation (WHO) defines stroke as a clinical syndrome which consists of rapidly developing clinical signs of focal (or at some times global) disturbances of cerebral function.

Symptoms last 24 hours or longer and can lead to death with no apparent cause other than of vascular origin.<sup>8</sup> The most common symptom of a stroke is sudden weakness or numbness of the face, arm or leg, most often on one side of the body. Other symptoms include confusion, difficulty speaking or understanding speech, difficulty seeing with one or both eyes, difficulty walking, dizziness, loss of balance or coordination, severe headache with no known cause, fainting or unconsciousness.

Stroke can be caused either by a clot obstructing the flow of blood to the brain, *an ischemic stroke*, or by a blood vessel rupturing and preventing blood flow to the brain, *a haemorrhagic stroke*. A transient ischemic attack (TIA) is caused by a temporary clot and related symptoms will go away completely within 24 hours. People who have a TIA are very likely to have a stroke in the near future.

### **Prevalence of stroke and death rates**

According to the WHO, stroke is the most common cardiovascular disorder after heart disease and affects 17 million people worldwide each year. The WHO estimates that stroke is the number two cause of death worldwide; of the 17 million people who suffer a stroke annually, 6.7 million of them die.<sup>9</sup> The total number of stroke deaths in 51 European countries is currently estimated at 1,074,000 per year.<sup>10</sup>

### **AF-related stroke risk**

AF is a major risk factor for stroke, making a person with AF five-times more likely to suffer from it in comparison to the general population.<sup>11</sup> Overall, AF is estimated to be responsible for approximately 15 percent of all strokes<sup>12,13</sup> and for 20 percent of all ischemic strokes.<sup>14</sup> As the population ages, the global burden of AF-related stroke will continue to increase.

The prevalence of stroke in AF patients older than 70 years doubles with each decade.<sup>15</sup> Furthermore, AF-related strokes are associated with poorer outcomes than non-AF-related strokes. This increased severity of strokes in patients with AF is thought to be related to the large size of the clots that will block a larger-sized intracranial artery depriving a larger territory of the brain of blood flow.<sup>16</sup>

### **The global burden of stroke**

Stroke presents a major public health challenge, with a high case fatality and a large proportion of survivors dependent on nursing and other types of care.<sup>17</sup> The average medical cost alone of stroke per patient with AF has been calculated to approximately €12,000.<sup>18</sup> This cost is set to increase dramatically as the size of the aging population continues to rise.

### **Reducing the risk of stroke in Atrial Fibrillation (AF)**

Management of AF patients is aimed at reducing symptoms and the risk of severe complications associated with AF such as stroke. The cornerstone of stroke risk reduction in AF patients is oral anticoagulation (OAC) therapy, with warfarin as the current standard of care. In addition, non-pharmacological approaches such as closing off the left atrial appendage (LAA) offer treatment alternatives, e.g. for patients with non-valvular AF who require treatment for potential thrombus formation in the LAA and have a contraindication to anticoagulant therapy. These one-time procedures offer a permanent solution for AF patients and eliminate the need for lifelong oral anticoagulation therapy.

## **Treatment Guidelines**

To assess the right course of treatment in AF-related stroke prophylaxis, several sets of international, European and country-specific guidelines are available and various methods exist to categorise stroke risk.

In order to reduce risk of AF-related strokes, the ESC recommends the initiation of anticoagulation therapy. When this therapy is appropriately used and monitored, it is highly effective, lowering stroke risk by about two thirds.<sup>19</sup> However, current data indicates that the management of AF is still sub-optimal, with many of those receiving anticoagulation consistently outside the optimal therapeutic range.<sup>20,21</sup>

## **Anticoagulation therapy**

The goal of anticoagulant therapy is to administer the lowest possible dose of anticoagulant to reduce the risk of clot formation or expansion. Anticoagulation therapy with warfarin (Coumadin™) is widely considered the standard of care for stroke prophylaxis in patients with AF who are at high risk of stroke.<sup>22</sup>

However, the therapeutic effect of warfarin is highly unpredictable and can change due to a variety of factors, such as changes in diet or concomitant medications. As a result, safe and effective utilisation of chronic warfarin therapy requires frequent monitoring.<sup>23</sup> The FDA's Adverse Event Reporting System indicated that warfarin is among the top 10 drugs with the largest number of serious adverse event reports submitted during the 1990 and 2000 decades.<sup>24</sup>

Over recent years, new oral anticoagulants have entered the market. Substances such as apixaban, dabigatran, edoxaban or rivaroxaban can are now available as an alternative to warfarin to aim at stroke prevention in AF patients.<sup>25,26</sup> According to the ESC new oral anticoagulants tested in clinical trials have all shown non-inferiority compared with warfarin, offering better efficacy, safety, and convenience for a vast majority of patients with non-valvular AF, when used as studied in the clinical trials performed so far. Additional data are necessary before conclusions can be drawn on the potential for these new anticoagulant drugs to replace warfarin in patients with AF. Thus, strict treatment adherence and careful surveillance are strongly recommended, since patient adherence and bleeding risk continue to remain major challenges of stroke risk reduction in AF patients.<sup>27,28</sup>

## **LAA closure for AF-related stroke risk reduction**

Research shows that in over 90 percent of patients with non-valvular atrial fibrillation the stroke-causing blood clots are developed in the left atrial appendage (LAA). Currently, these patients, being at high risk of stroke, are treated with warfarin or other anticoagulant drugs. However, by closing off the source of blood clot formation, the risk of stroke may be reduced and could eliminate the need for long-term OAC therapy.<sup>29,30</sup>

LAA closure is a minimally-invasive procedure that usually only lasts about an hour and presents a permanent therapy option for stroke prophylaxis in patients with non-valvular AF, who require treatment for potential thrombus formation.

This has already been reflected by the following revisions of common treatment guidelines:

- In August 2012, ESC announced the inclusion of LAA closure devices like Watchman™ Left Atrial appendage Closure Device in the revised “Guidelines for Management of Patients with Atrial Fibrillation”. The 2016 ESC guidelines<sup>31</sup> recommend LAA closure as a class IIb, level of evidence b, for patients with a high stroke risk and contraindications for long-term oral anticoagulation, based on existing clinical evidence such as the PROTECT AF trial. Previous versions of the guidelines had already suggested that occlusion of the LAA may reduce stroke in AF patients.<sup>32</sup>
- Guidelines of the American Heart Association (AHA) recommend the removal of the LAA during cardiac procedures such as coronary bypass or valve repair surgery for patients at risk of developing post-operative AF.<sup>33</sup> This is mainly due to the fact that surgical approaches to LAA ligation using sutures or staples have failed to demonstrate consistent closure.
- According to the guidelines of the National Institute for Health and Clinical Excellence (NICE), the percutaneous occlusion of the LAA is efficacious in reducing the risk of thromboembolic complications associated with non-valvular AF. NICE also recommends that the procedure should be carried out by clinicians with specific training and appropriate experience in the procedure.<sup>34</sup>

For additional information about the Watchman LAA Closure Device, please refer to the product factsheet.

## Media Contacts

Sharron Tansey  
Market Access, Health  
Economics & Government Affairs  
+44 7770 834 947  
[TanseyS@bsci.com](mailto:TanseyS@bsci.com)

Chiara Ennas  
Media Relations and Corporate  
Communications Europe  
44 7766 086882  
[ennasc@bsci.com](mailto:ennasc@bsci.com)

## References

- <sup>1</sup> National Lung Blood and Heart Institute, National Institutes of Health (NIH), July 1, 2011.
- <sup>2</sup> Randall J. Lee, MD, PhD; Krzysztof Bartus, MD; Steven J. Yakubov, MD, Catheter-Based Left Atrial Appendage (LAA) Ligation for the Prevention of Embolic Events Arising From the LAA: Initial Experience in a Canine Model, *Circ Cardiovasc Interv* 2010;3:224-229.
- <sup>3</sup> Medscape: <http://emedicine.medscape.com/article/151066-overview#aw2aab6b2b3aa> (Accessed: November 3, 2015 – 12:53 am).
- <sup>4</sup> Camm JA et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation, *European Heart Journal* 2012, 33:2719–2747.
- <sup>5</sup> AFA, Anticoagulation Europe UK The AF Report. Atrial Fibrillation: Preventing A Stroke Crisis <http://www.preventaf-strokecrisis.org/report/chapter1/> (Accessed: November 3, 2015 – 12:55).
- <sup>6</sup> Mayo Clinic: <http://www.mayoclinic.org/documents/mc5234-23-pdf/doc-20079137> (Accessed: November 3, 2015 – 12:59 am).
- <sup>7</sup> Reinhold T, Lindig C, Willich SN, Brügggenjürgen B. The costs of atrial fibrillation in patients with cardiovascular comorbidities—a longitudinal analysis of German health insurance data. *Oxford Journals Medicine, EP Europace*, Volume13, Issue 9 Pp. 1275-1280.
- <sup>8</sup> Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bulletin of the World Health Organisation* 1976;54: 541-53.

- <sup>9</sup> WHO Cardiovascular Diseases Fact Sheet No. 317. Updated January 2015 <http://www.who.int/mediacentre/factsheets/fs317/en/> (Accessed November 4, 2015 – 10:09 am).
- <sup>10</sup> European cardiovascular disease statistics 2012. European Heart Network, Brussels.
- <sup>11</sup> Stroke Association:  
[http://www.strokeassociation.org/STROKEORG/LifeAfterStroke/HealthyLivingAfterStroke/UnderstandingRiskyConditions/When-the-Beat-is-Off---Atrial-Fibrillation\\_UCM\\_310782\\_Article.jsp#.VjnO8tLtlY](http://www.strokeassociation.org/STROKEORG/LifeAfterStroke/HealthyLivingAfterStroke/UnderstandingRiskyConditions/When-the-Beat-is-Off---Atrial-Fibrillation_UCM_310782_Article.jsp#.VjnO8tLtlY) (Accessed November 4, 2015 – 10:30 am).
- <sup>12</sup> Wolf CD, Rudd AG. The Burden of Stroke White paper: Raising awareness of the global toll of stroke-related disability and death.
- <sup>13</sup> World Health Organisation. The atlas of heart disease and stroke.
- <sup>14</sup> Avoiding heart attacks and strokes: don't be a victim – protect yourself. Publications of the World Health Organisation, 2005.  
[http://www.who.int/cardiovascular\\_diseases/resources/cvd\\_report.pdf](http://www.who.int/cardiovascular_diseases/resources/cvd_report.pdf) (Accessed: November 3, 2015 – 13:14 am).
- <sup>15</sup> Rathore SS, Berger AK, Weinfurt KP, Schulman KA, Oetgen WJ, Gersh BJ, et al. Acute myocardial infarction complicated by atrial fibrillation in the elderly: prevalence and outcomes. *Circulation*. Mar 7 2000;101(9):969-74.
- <sup>16</sup> Tu HT et al. Pathophysiological determinants of worse stroke outcome in atrial fibrillation, *Cerebrovascular Disease* 2010;30(4):389-95.
- <sup>17</sup> Richard F. Heller, Peter Langhorne, Erica James. Improving stroke outcome: the benefits of increasing availability of technology. *Bulletin of the World Health Organisation*, 2000, 78: 1337–1343.
- <sup>18</sup> Bruggenjurgen B, Rossnagel K, Roll S et al. The impact of atrial fibrillation on the cost of stroke: the Berlin acute stroke study. *Value Health* 2007;10:137-43.
- <sup>19</sup> National Health Services (NHS): <http://www.preventaf-strokecrisis.org/report/report-summary> (Accessed: November 3, 2015 – 13:18 am).
- <sup>20</sup> National Health Services (NHS). Anticoagulation for Atrial Fibrillation Report:  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3324990/> (Accessed: November 3, 2015 – 13:20 am).
- <sup>21</sup> Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011;106:968–977.
- <sup>22</sup> Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. *Pharmacoeconomics*. 2006; 24(10):1021-33.
- <sup>23</sup> Jacobson AK. Warfarin monitoring: point-of-care INR testing limitations and interpretation of the prothrombin time. *Journal of Thrombosis and Thrombolysis*, Volume 25, Number 1, 10-11, DOI: 10.1007/s11239-007-0098-5.
- <sup>24</sup> Wysowski DK, Nourjah P, Swartz L. Bleeding Complications With Warfarin Use-A Prevalent Adverse Effect Resulting in Regulatory Action. *ARCH INTERN MED/VOL 167 (NO. 13), JULY 9, 2007*.
- <sup>25</sup> National Center for Biotechnology Information. New oral anticoagulants in patients with nonvalvular atrial fibrillation: a review of pharmacokinetics, safety, efficacy, quality of life, and cost effectiveness, issued in June 2014. Available at:  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4069048/> (Accessed: November 4, 2015 – 10:38 am).
- <sup>26</sup> Granger CB, Alexander JH, McMurray JJV et al. for the ARISTOTLE Committees and Investigators. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2011; 365:981-992 September 15, 2011.
- <sup>27</sup> Altman R, Vidal HO. Battle of oral anticoagulants in the field of atrial fibrillation scrutinised from a clinical practice (the real world) perspective. *Thromb J*. 2011; 9: 12.
- <sup>28</sup> Camm JA et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation, *European Heart Journal* 2012, 33:2719–2747.
- <sup>29</sup> Alberg H. Atrial fibrillation: a study of atrial thrombus and systemic embolism in a necropsy material. *Acta Med Scand*. 1969;185:373–379. Medline.
- <sup>30</sup> Stoddard MF, Dawkins PR, Price CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 1995;25:452–459.
- <sup>31</sup> Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Defferere S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorennek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016 Oct 7;37(38):2893-2962.