



THE BURDEN OF ATRIAL FIBRILLATION

2018 Full Report

**Understanding the Impact of the New Millennium
Epidemic across Europe**



OVERVIEW	3
Atrial Fibrillation	3
EPIDEMIOLOGY OF AF	5
How common is AF?	5
Who is at risk for AF?	7
Which type of AF is most common?	8
How will AF affect Europe in the future?	9
CAUSE AND RISK FACTORS OF AF	11
What cause AF?	11
What factors lead to AF?	12
CLINICAL BURDEN	13
What are the symptoms of AF?	13
How does AF change over time?	15
What are the consequences of AF?	16
What is the risk of mortality?	18
What is the risk of stroke?	19
What is the risk of a heart attack?	21
What is the risk of heart failure?	22
What is the risk of cognitive dysfunction?	23
How does obstructive sleep apnea impact AF?	24
PATIENT BURDEN	25
How long do people live with AF?	25
Why do people with af seek medical treatment?	26
How does AF impact patient quality of life?	27
How does AF impact family members?	31
How does stroke impact quality of life?	33
How does stroke treatment affect quality of life?	34
How does AF treatment affect quality of life?	35
ECONOMIC BURDEN	36
What is the total cost of AF to national healthcare systems?	36
What are the direct and indirect costs of AF?	38
What factors influence direct costs of AF?	40
Why are AF patients admitted to hospital?	42
How does stroke affect the cost of AF?	43
CONCLUSION	45
REFERENCES	47

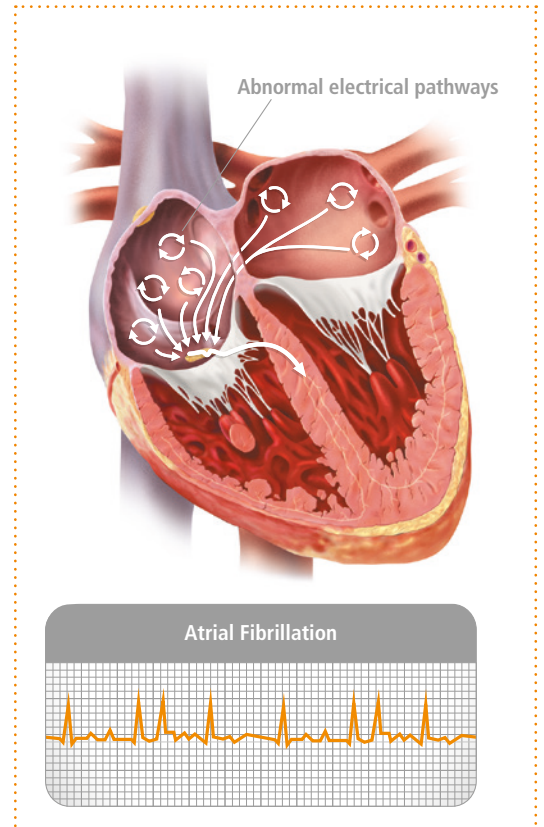
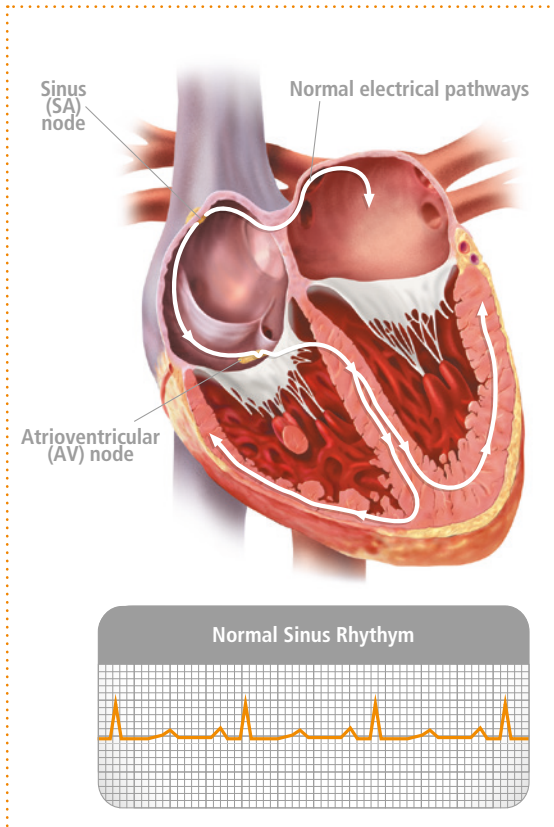
Atrial Fibrillation is fast becoming one of the world's most significant health issues that places a critical burden on healthcare systems

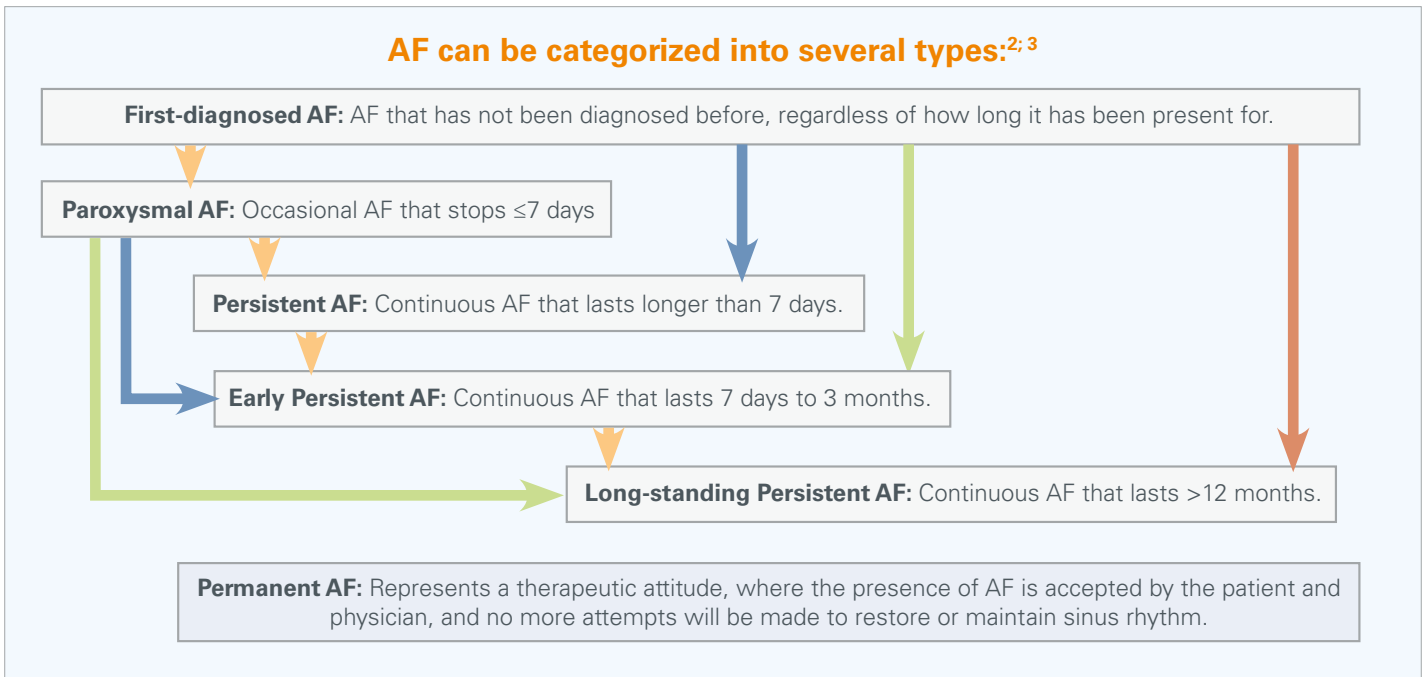
ATRIAL FIBRILLATION

What is Atrial Fibrillation and why is it important?

■ The heart normally contracts in a coordinated manner, with a steady beat (i.e., rhythm) and at a consistent speed (i.e., rate).¹

■ Atrial fibrillation (AF) is **characterized by an irregular and often fast heartbeat** that results in uncoordinated contraction of the top 2 chambers of the heart (i.e., atria).¹





■ Patients may have episodes of AF that fall into one or more of the above categories; patients are categorized based on their most frequent pattern of AF.^{2,3}

■ Early detection and diagnosis of AF may help improve patient outcomes, since long history and duration of AF have been associated with recurrence.⁴⁻⁷



15%-30%
OF PATIENTS
EXPERIENCE
NO SYMPTOMS
(ie, silent AF)⁸




PAROXYSMAL AF

1 in 5
PATIENTS
PROGRESS
IN 1 YEAR⁹⁻¹²



PERSISTENT AF

Patients with AF have an increased risk for life-threatening complications and other diseases:¹³

5x Increase heart failure 

2.4x Increase stroke 

2x Increase cardiovascular mortality 

■ AF worsens quality of life for patients, which can be burdensome to caregivers.¹⁴⁻¹⁹

■ AF increasingly places a **critical financial burden** on the healthcare system, costing **€660-€3,286 million** annually across European countries.²⁰⁻²⁴

AF is a new millennium epidemic that affects millions of lives, mostly affecting the middle-aged and elderly.

OVER 11M PEOPLE AFFECTED IN EUROPE

How common is AF?

AF is the most common type of cardiac arrhythmia, affecting over 886,000 new people each year in Europe.²⁵

■ Over **1 Million people suffer with AF** in each of France, Germany, Italy, and the UK.²⁵

■ The number of **new people each year with AF varies by region**, from nearly 78,000 in France to over 116,000 in Germany.²⁵



Prevalence and Incidence of AF & Atrial Flutter in Europe

Total number of people with AF & AFL (Prevalence)

Region	Total number of people with AF & AFL (Prevalence)	Rate* for AF & AFL per 100,000 of the population
EUROPE**	11,062,761	788
FRANCE	1,001,409	814
GERMANY	1,453,541	833
ITALY	1,014,483	753
UNITED KINGDOM	1,232,144	1094

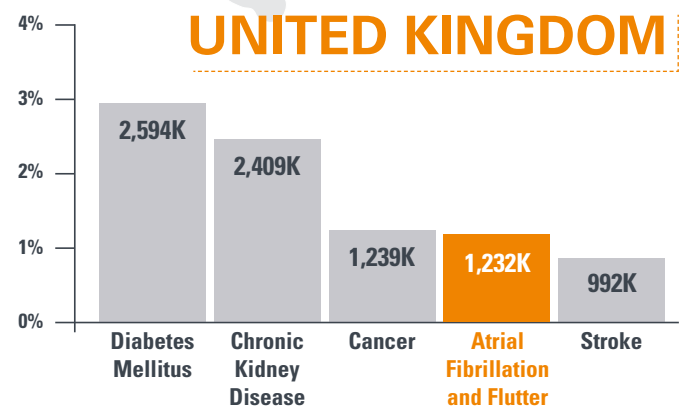
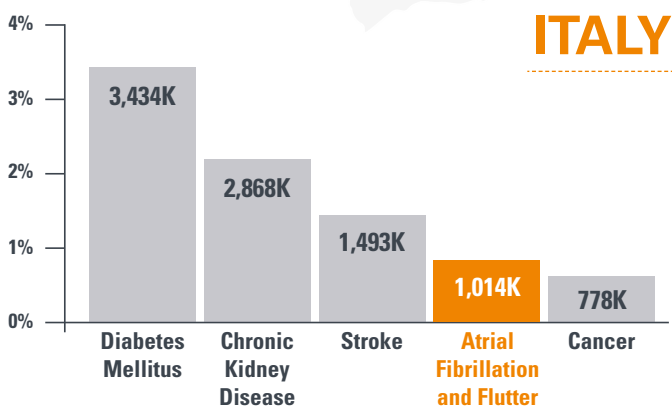
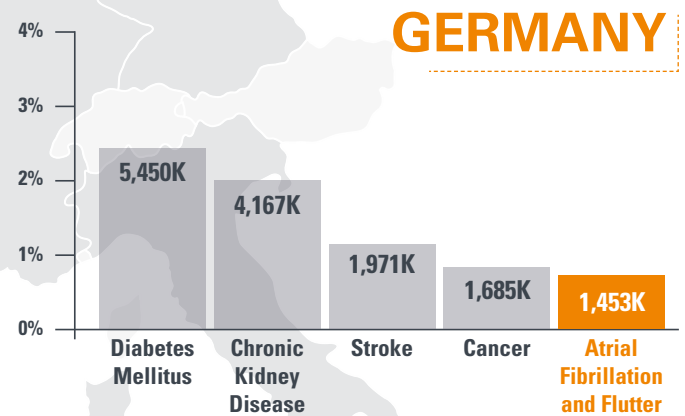
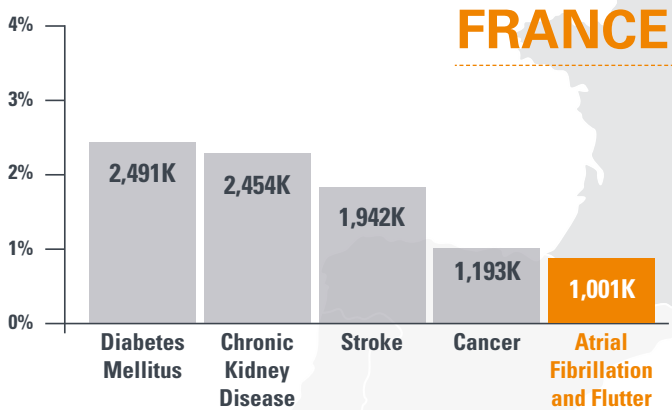
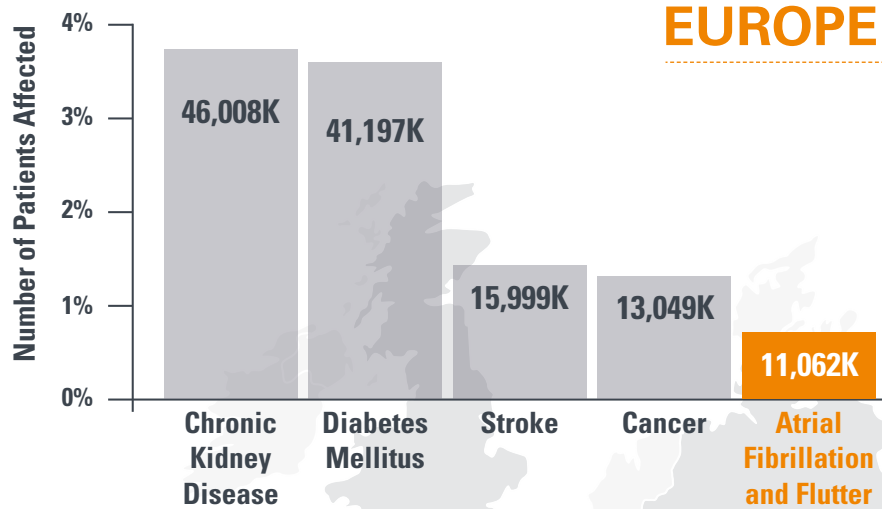
Number of new people diagnosed with AF & AFL per year (Incidence)

Region	Number of new people diagnosed with AF & AFL per year (Incidence)	Rate* for AF & AFL per 100,000 of the population
EUROPE**	886,500	66
FRANCE	77,837	69
GERMANY	116,468	71
ITALY	81,907	68
UNITED KINGDOM	97,555	92

*Age-standardized values.

**Obtained for Europe, part of the Four World Regions category in the Online GBD Tool.
Source: Global Burden of Disease Collaborative Network (2016).

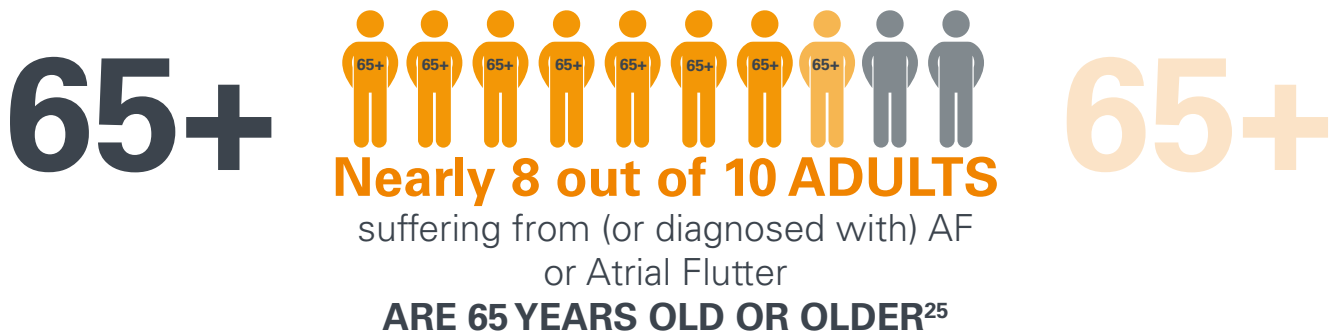
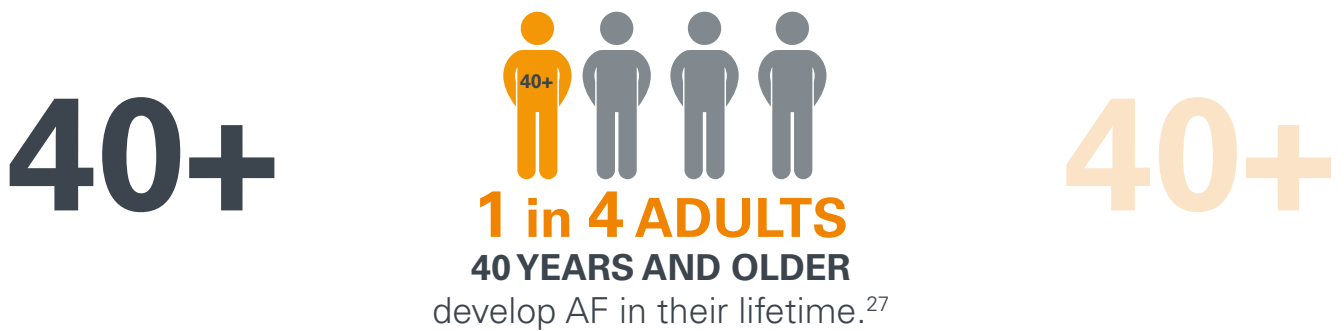
AF is almost as common as stroke and cancer in Europe, France, Germany, Italy, and the United Kingdom.²⁵



DEMOGRAPHICS OF AF

Who is at risk for AF?

AF is a common age-related arrhythmia:^{3; 26; 27} it mostly affects people **40 years old and older** and is more **common in men**.



■ In adults of European descent older than 40 years, men are 13% more likely to develop AF than women during their lifetime.²⁷

TYPES OF AF

Which type of AF is most common?

In Europe, 75% of patients have paroxysmal or persistent AF.

■ PERSISTENT AF IS

2X MORE COMMON

in patients with symptoms than in patients without.²⁸

■ PERMANENT AF IS

3X MORE COMMON

in patients without symptoms than in those with, primarily due to lower use of therapeutic management strategies and treatments.²⁸

Distribution* of AF Types Among European Patients

Type of AF	Patients WITH symptoms	Patients WITHOUT symptoms
PAROXYSMAL	40%	34%
PERSISTENT	46%	24%
PERMANENT**	14%	42%

*Based on reported distribution of AF type in symptomatic patients. proportions were redistributed to include paroxysmal, persistent and permanent.

**Permanent AF reflects a decision regarding the patient's treatment strategy, and does not physiologically differ from other types of AF.

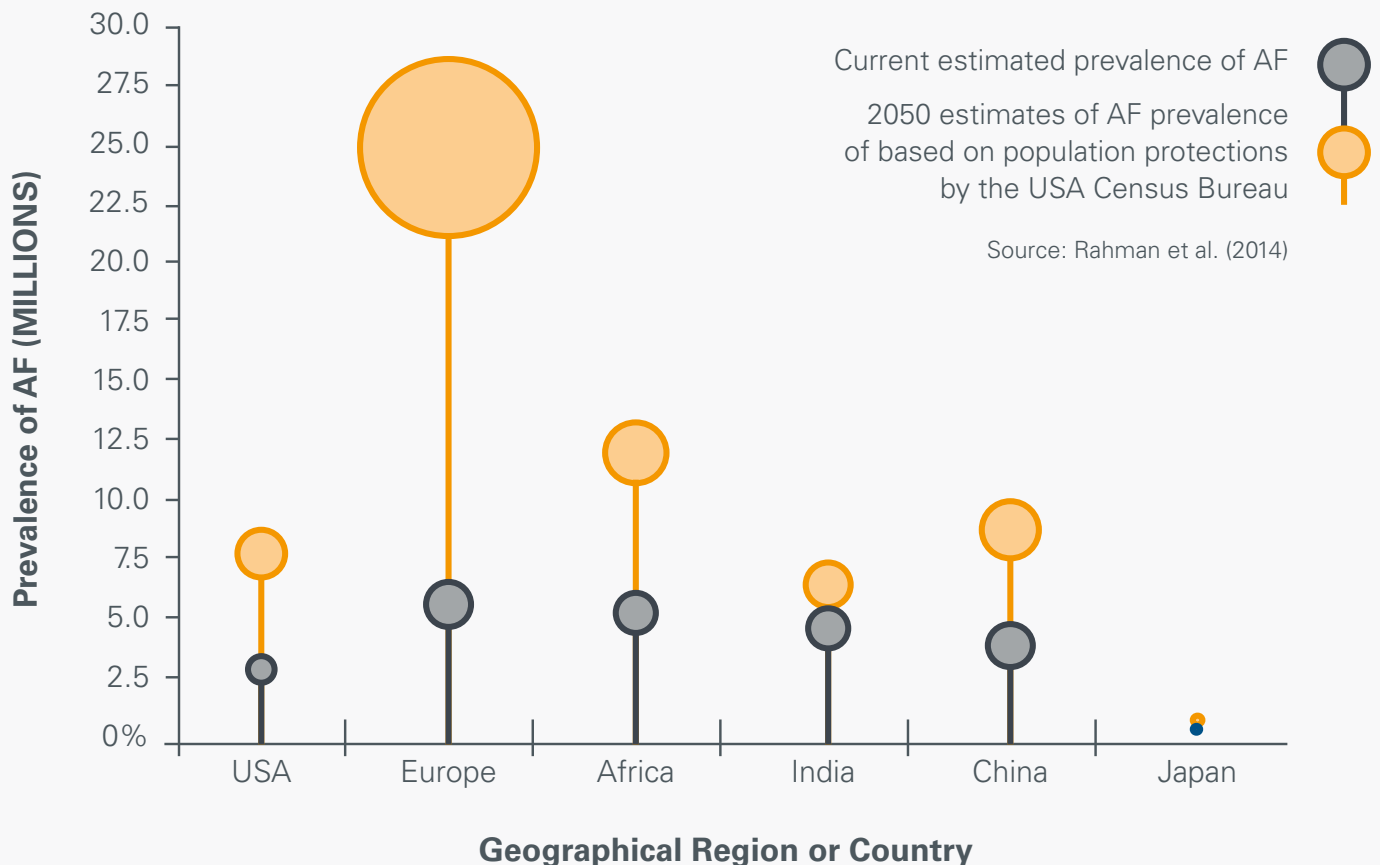
Source: adapted from Boriani et al. (2015)

HOW WILL AF AFFECT EUROPE IN THE FUTURE?

By 2050, Europe is expected to have the most patients with AF compared to other regions.²⁹

BY 2030 THE NUMBER PEOPLE WITH AF IS EXPECTED TO INCREASE UP TO **70%**³¹

- European countries have an aging population that is growing rapidly.³⁰
- By 2030, the number people with AF is expected to increase up to 70%.³¹
- By 2050, Europe is projected to have the **greatest increase in AF** compared to other regions globally.²⁹



With more patients suffering with atrial fibrillation, rate of stroke, hospitalizations, and doctor visits are expected to rise.

- Estimates suggest that over the next 12 years, there will be a 70% increase in the number of people affected by Atrial Fibrillation, **the number of stroke events and medical visits is expected to increase by:**³¹



**280K-
340K**

**ADDITIONAL
ISCHEMIC
STROKES**



**3.5-4
MILLION**

**HOSPITALIZATIONS
FOR AF**



**100-120
MILLION**

**OUTPATIENT
VISITS**

CAUSE AND RISK FACTORS OF AF

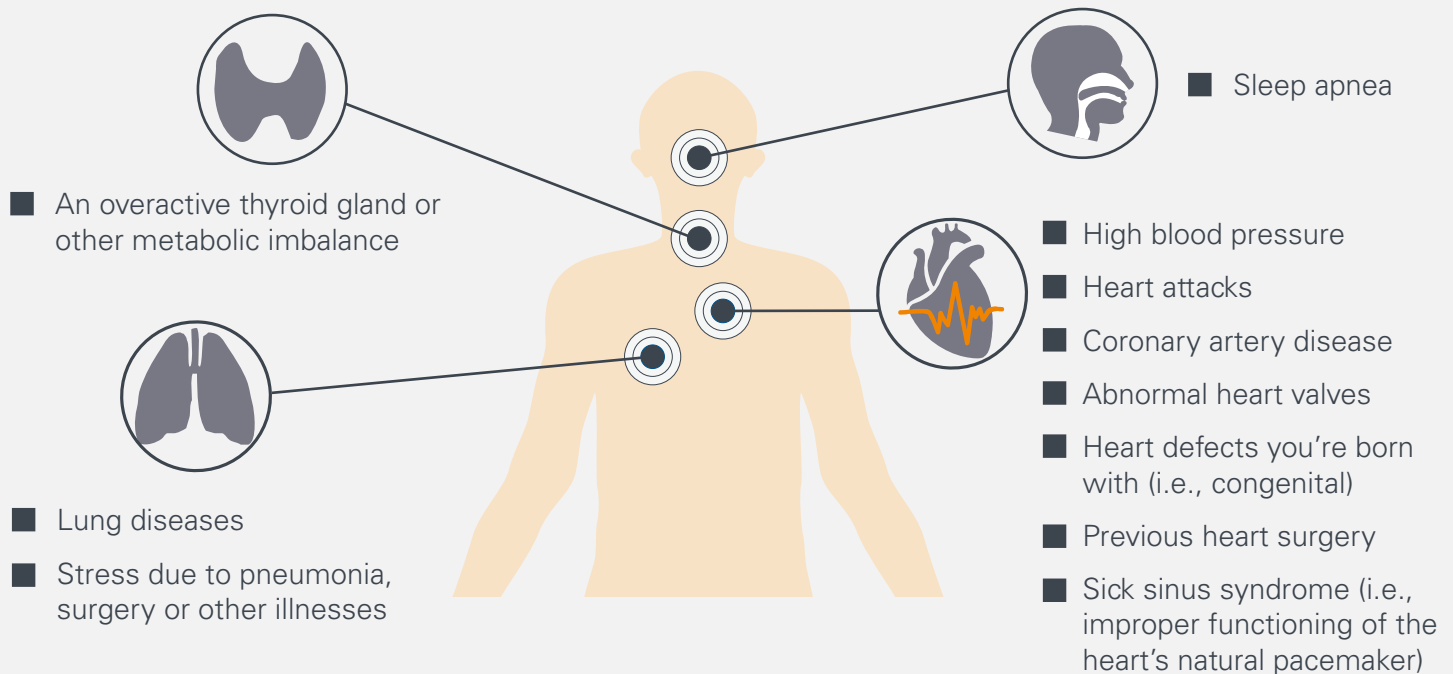
AF develops from structural changes to the heart due to lifestyle, other chronic conditions, and non-modifiable factors.

WHAT CAUSES AF?

- AF is an **irregular and often rapid heartbeat** that occurs when there are extra, uncoordinated electrical signals in the atria.¹

Common causes of AF

Abnormalities or damage to the heart's structure are the most common cause of AF, and this can be caused by:^{2,3,27,32}



Other factors that cause AF:



- Exposure to stimulants, such as medications, caffeine, tobacco or alcohol

WHAT FACTORS LEAD TO AF?

Lifestyle factors, other conditions, and non-modifiable factors increase the risk of developing AF.



LIFESTYLE FACTORS

- Obesity³²⁻³⁵
- Alcohol consumption^{3; 35; 36}
- Risks for cardiovascular disease: smoking, stress, caffeine and other stimulants³
- Activity level^{2; 3; 35}

OTHER CONDITIONS

- High blood pressure³⁵
- Heart failure^{27; 31; 37-40}
- History of heart attack^{27; 41}
- Coronary artery and other heart disease^{27; 33}
- Previous surgery^{42; 43}
- Sleep-disordered breathing (eg, obstructive sleep apnea)^{35; 44}
- Diabetes^{35; 45}

NON-MODIFIABLE FACTORS

- Older age^{3; 46}
- Congenital heart defects⁴⁵
- Family history or other genetic factors^{27; 47; 48}
- Male sex^{3; 27; 46}

The symptoms and clinical consequences of AF negatively impact patient quality of life and increase the risk of mortality.

WHAT ARE THE SYMPTOMS OF AF?

Symptoms of AF disrupt daily life and range from mild to debilitating.^{14; 49-50}
The most common symptoms are:^{8; 31; 51}



65%
PALPITATIONS

50%
FATIGUE

43%
SHORTNESS
OF BREATH

30%
MALAISE



19%
DIZZINESS

12%
ANXIETY

12%
CHEST PAIN

5%
OTHER



OVER
50% of AF PATIENTS
have a reduced ability to exercise⁸

■ The frequency and severity of symptoms varies a lot from patient to patient and, within a patient, symptoms can fluctuate widely over time.⁸

- Patients with AF often experience symptoms that impair functional status, disrupt daily life activities, and impact quality of life.⁴⁹⁻⁵¹



19%
IMPAIRMENT IN
FUNCTIONAL
STATUS^{52*}

25%
DISRUPTION TO
DAILY
ACTIVITIES^{52**}

UP TO 47%
REDUCTION IN
QUALITY
OF LIFE^{52; 53***}

- **Patients who do not** experience symptoms of AF may be at **greater risk** of complications and disease severity due to lack of treatment:



15%-30%
have SILENT AF^{8; 28}



AS MANY AS 1 in 4
PATIENTS are DIAGNOSED
WITH AF AFTER SUFFERING A
STROKE^{3; 8}



PATIENTS WITH SILENT AF
EXPERIENCE **POORER**
general HEALTH and QUALITY OF LIFE
than HEALTHY INDIVIDUALS⁵⁴

With disease progression, patients are more likely to experience:⁵⁵

- **More severe mobility problems**

- **Problems with self-care**

- **Inability to continue regular activities**

- **Increased pain and discomfort**

- **Anxiety and depression**

*Based on functional capacity, as measured using the Goldman Specific Activity Scale, in AF patients (score, 75 [standard deviation (SD) 20]) vs. healthy individuals (score, 93 [SD 11]).

**As measured using the Illness Intrusiveness scale in AF patients (score, 35 [SD 15]) vs. health individuals (score, 28 [SD 19]).

***As measured using the SF-36 QoL scale. Reductions were observed on SF-36 subscales.

HOW DOES AF CHANGE OVER TIME?

AF is typically a progressive disease.



15%-20%
OF PATIENTS WITH
PAROXYSMAL AF

WILL PROGRESS TO

PERSISTENT AF
over 1 year.^{9; 10; 12}

- AF causes remodeling of the heart, making normal heart rhythm more difficult.^{9; 10; 12; 56}
- AF typically progresses from paroxysmal AF, where episodes are intermittent and self-terminating, to long-standing persistent AF, where episodes are continuous and terminate with intervention.³
- At diagnosis, **each decade** of age was associated with **nearly double the risk of disease progression**.⁵⁷
- Patients with silent AF (i.e., without symptoms) may be **more likely to progress or may progress faster** to persistent AF, partly due to a lack of treatment.¹¹
- AF **may also regress** from persistent AF to paroxysmal AF.^{12; 57; 58}

A higher risk of AF progression is associated with:

- | | | |
|--|--|---|
| <ul style="list-style-type: none"> ■ Older age⁹ ■ Heart failure⁹ ■ Valvular heart disease^{9; 12; 36} | <ul style="list-style-type: none"> ■ Larger left atrium⁹ ■ Hyperthyroidism¹² | <ul style="list-style-type: none"> ■ Moderate to high alcohol consumption³⁶ ■ Asymptomatic and untreated AF^{11; 59} |
|--|--|---|

- Compared with patients who did not progress, patients who progress from paroxysmal to persistent AF more often experience:⁹

- | | |
|---|---|
| <ul style="list-style-type: none"> ■ New onset heart failure, or worsening heart failure | <ul style="list-style-type: none"> ■ Thromboembolism |
|---|---|

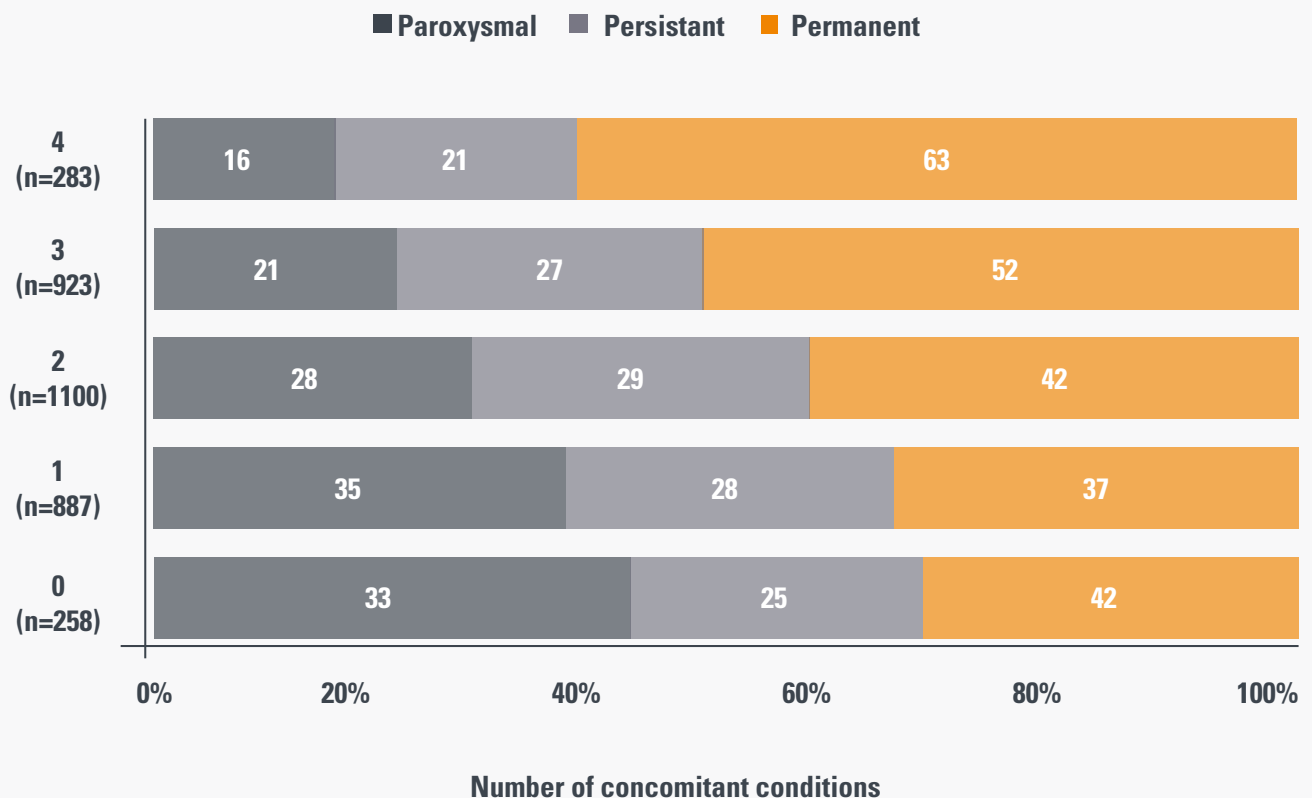
WHAT ARE THE CONSEQUENCES OF AF?

AF increases a patient's risk for life-threatening events and conditions, including stroke, heart failure, and death.



AS MANY AS
80%
OF AF PATIENTS
have **ANOTHER**
condition
or **CARDIAC**
DISEASE.³¹

- The seriousness of AF is critically misunderstood:
 - **45% of patients believe** it is not a life-threatening condition⁶⁰
- Most patients with AF have other serious conditions and complications:
 - **One-third have at least 3 other conditions.**^{31; 61}
 - **63% with 4 other conditions have permanent AF.**⁶¹



Source: Meinertz et al. (2011)

AF increases the risk of:^{31; 41; 44}

- Mortality:**
 AF is independently associated with a significantly greater risk of mortality.
- Stroke:**
 a serious complication of AF that is associated with long-term disability and mortality.
- Heart attack:**
 a serious complication of AF that also significantly increases the risk of stroke and mortality.
- Heart failure and left ventricular dysfunction:**
 a common complication of AF that increases the risk of mortality and lengthens hospital stay.
- Cognitive dysfunction or vascular dementia:**
 a complication of AF that causes a decline in memory and thinking skills, which can interrupt daily life and independent function.
- Obstructive sleep apnea:**
 is common in AF patients and may increase the risk of stroke, heart failure, and AF recurrence.

Increased risk* of morbidity and mortality in patients with AF.^{13; 35; 62}



142%
ANY STROKE

133%
ISCHEMIC STROKE

40%
DEMENTIA OR COGNITIVE IMPAIRMENT



399%
HEART FAILURE

103%
CARDIOVASCULAR MORTALITY

96%
MAJOR CARDIOVASCULAR EVENTS

61%
ISCHEMIC HEART DISEASE



64%
CHRONIC KIDNEY DISEASE



46%
ALL-CAUSE MORTALITY



31%
PERIPHERAL ARTERIAL DISEASE

*Relative increased risk based on the relative risk of morbidity and mortality when compared to patients without AF. Source: Boriani and Proietti (2017), Odotayo et al. (2016), Kalantarian et al. (2013)

WHAT IS THE RISK OF MORTALITY?

AF is independently associated with a significantly greater risk of mortality.



AF PATIENTS HAVE A **46%** GREATER RISK of death than patients WITHOUT AF.^{13; 35}

THE RATE OF MORTALITY IS **40%** in NEW AF PATIENTS after DIAGNOSIS³¹

- Even without the presence of other conditions, patients with AF have a 46% greater risk of mortality than patients without AF, based on pooled estimates from studies conducted in the last 5 years.^{13; 35}
- In a single year, **approximately 6%** of AF patients die.⁵¹
 - About 70% of these deaths were directly related to cardiovascular complications.⁵¹
- The rate of mortality is 40% in new AF patients after diagnosis and 60% within 5-10 years.³¹
- **Lack of symptoms increases the risk of mortality more**, with an added 2x risk compared to patients with symptoms.²⁸

Risk of death in patients with AF is increased by:^{28; 63}

■ Older age

■ Congestive heart failure

■ Chronic kidney disease

■ Diabetes

■ Prior stroke or transient ischemic attack

■ History of bleeding

WHAT IS THE RISK OF STROKE?

Stroke is a serious complication of AF that is associated with long-term disability and mortality.^{64; 65}

■ **What is stroke caused by?**

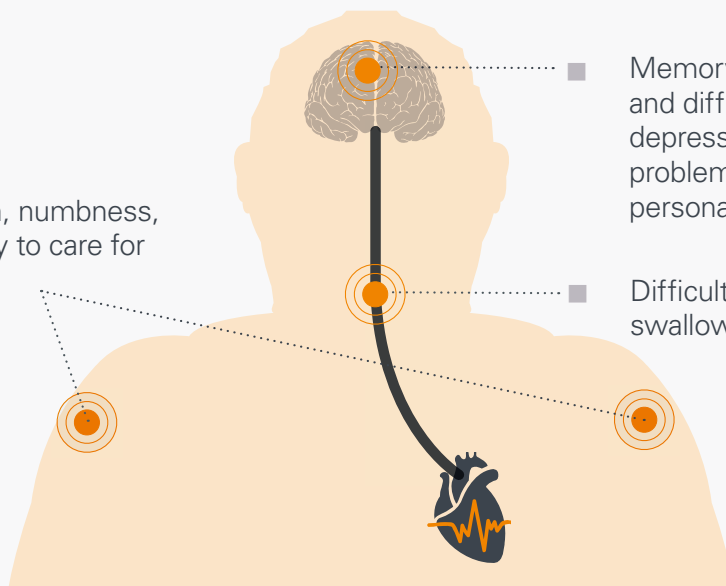
Uncoordinated contractions during AF can lead to clot formation within the heart that, when pumped out of the heart, can block an artery of the brain, resulting in stroke.⁶⁴

■ **What does stroke cause?**^{64; 65}

■ Paralysis, pain, numbness, reduced ability to care for oneself

■ Memory loss; cognitive impairment and difficulty understanding language; depression and other emotional problems; changes in behavior, personality, and independence

■ Difficulty speaking or swallowing



20%-30%
OF ALL STROKES
OCCUR IN
AF PATIENTS^{3; 31}

142%
INCREASED
RISK OF ANY
STROKE¹³

133%
INCREASED
RISK OF ISCHEMIC
STROKE¹³

- Patients with AF have a significantly greater risk of any stroke and ischemic stroke than those without AF, based on pooled estimates from studies conducted in the last 5 years.¹³
- The annual rate of stroke in AF patients is high:

2% for **ISCHEMIC STROKE**³¹

0.2% for **HEMORRHAGIC STROKE**³¹

- Undiagnosed silent AF is a likely cause of some strokes with an undetermined source.^{3; 11}
- Highest level of evidence suggests that patients with persistent AF have a higher risk of stroke than those with paroxysmal AF, whether treated with OACs or not.⁶⁶

In patients with AF, the risk of stroke is increased by:



■ Older age^{3; 67}



■ Chronic kidney disease⁶⁷



■ Prior stroke, transient ischemic attack, or embolism^{3; 67; 68}



■ Vascular disease and high blood pressure^{3; 68}



■ Female sex^{3; 67}



■ Congestive heart failure^{3; 67}



■ Diabetes^{3; 67; 68}

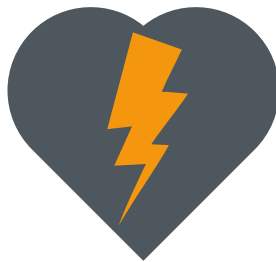


■ Obstructive sleep apnea⁴⁴

- Stroke in patients with AF is more severe and debilitating than in patients who do not have AF.^{69; 70}
 - Immediately after a stroke, patients with AF have **greater neurologic impairment and functional disability** than patients without AF.⁶⁹
 - Up to 3 months after a stroke, patients with AF were **significantly more disabled** than patients without AF.⁶⁹

WHAT IS THE RISK OF A HEART ATTACK?

Heart attack is a serious complication of AF that also significantly increases the risk of stroke and mortality.



THE RATE OF
HEART ATTACKS IS

0.4%-2.5%

PER YEAR IN
AF PATIENTS.^{3; 41}

- Uncoordinated contractions during AF can **lead to clot formation within the heart** that, when pumped out of the heart, can block an artery of the heart, resulting in heart attack.^{1; 41; 64}
- Heart attack is even more common in patients with AF **who also have other cardiovascular diseases** such as coronary artery disease, peripheral vascular disease, and heart failure.⁴¹
- Compared with patients without AF, those with AF who suffer a heart attack have worse medical outcomes.⁷¹
 - AF patients are more likely to have **a subsequent heart attack, ischemic stroke, or die.**⁷¹

WHAT IS THE RISK OF HEART FAILURE?

Heart failure is a common complication of AF that increases the risk of mortality and lengthens hospital stay.



2X
HIGHER RISK
of mortality
IN NEW AF
PATIENTS
WITH HEART
FAILURE.³¹

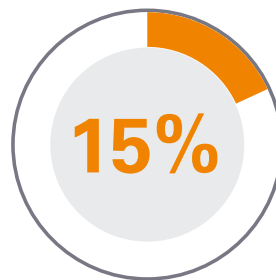
- AF and heart failure are both associated with a greater likelihood of death. New AF patients with heart failure have a 2x higher risk of mortality than with patients without AF.³¹
- Left ventricular (LV) dysfunction is an important risk factor for heart failure that is commonly caused or worsened by AF.^{3;38}

20%-30% OF PATIENTS WITH AF
HAVE LV DYSFUNCTION³

- Heart failure coexists with AF in **22%-42%** of AF patients.³¹



OF HEART FAILURE
PATIENTS WILL
DEVELOP AF
WITHIN 5 YEARS.^{39; 40}



OF AF PATIENTS
WILL DEVELOP
HEART FAILURE
WITHIN 5 YEARS.^{39; 40}

- The risk of developing heart failure for patients with AF varies by patient demographics.

11X  GREATER RISK IN
WOMEN³¹

3X  GREATER RISK IN
MEN³¹

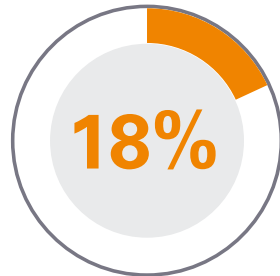
- Patients with AF who also have heart failure tend to have **longer hospital stays** than patients who have only AF or only heart failure.^{37; 38}

WHAT IS THE RISK OF COGNITIVE DYSFUNCTION?

Cognitive dysfunction is a complication of AF that causes a decline in memory and thinking skills, which can interrupt daily life and independent function.

■ Decline in cognitive function and vascular dementia **severely impacts patients' quality of life**, including the ability to learn, function independently, and perform important daily and self-care tasks.^{72; 73}

■ In patients with AF, **cognitive decline and vascular dementia may arise** from poor blood supply to the brain and the equivalent of "mini-strokes" that lack symptoms.^{31; 72; 74}



18% OF AF PATIENTS MAY HAVE COGNITIVE DYSFUNCTION OR DEMENTIA.^{31; 75; 76}



UP TO 40% INCREASED RISK OF COGNITIVE DECLINE, WHICH MAY OCCUR AT A FASTER RATE THAN IN NON-AF PATIENTS^{13; 62; 74; 77}

■ Cognitive dysfunction and vascular dementia **can even develop in AF patients receiving oral anticoagulation therapy.**^{3; 78}

HOW DOES OBSTRUCTIVE SLEEP APNEA IMPACT AF?

Obstructive sleep apnea is common in AF patients and may increase the risk of stroke, heart failure, and AF recurrence.



32%-39%

**OF PATIENTS WITH AF
HAVE OBSTRUCTIVE
SLEEP APNEA²**

- Obstructive sleep apnea **may lead to AF** by causing changes to the size and shape of the heart.⁴⁴
- AF and obstructive sleep apnea **share several risk factors**, including obesity, heart failure, and hypertension.⁴⁴
- The severity of obstructive sleep apnea may be linked to AF prevalence and progression.²
- Obstructive sleep apnea may increase the risk of stroke, heart failure, and AF recurrence, particularly after treatment.^{2; 3; 79-80}

AF worsens the quality of life for patients, placing additional pressure on caregivers.

HOW LONG DO PEOPLE LIVE WITH AF?

AF is a life-long chronic disease and patients are burdened with frequent and repeated episodes over their lifetime.

IN AN ITALIAN REGISTRY OF PATIENTS WITH AF,

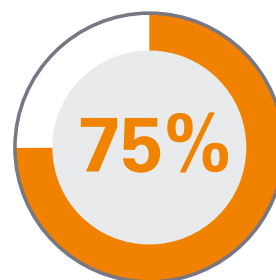


13% had AF for <1 year;
30% for 5-10 years;
and 18% for >10 years.^{31; 75}

■ Recurrence of AF is frequent, with ≥ 2 recurrences occurring in:



OF AF PATIENTS
DURING 1 YEAR³¹



OF PATIENTS
DURING 5 YEARS³¹

WHY DO PEOPLE WITH AF SEEK MEDICAL TREATMENT?

AF symptoms and repeated recurrence increase unplanned medical visits and hospitalizations.



SYMPTOMS OCCUR IN **69%** PATIENTS WITH AF, EVEN IF THEY ARE BEING TREATED^{8; 81}

- Symptoms are a major reason why patients with AF seek medical attention.⁸
- Clinical decision-making can be challenging because symptoms related to AF can differ a lot between patients and within patients at different time points.⁸
- AF and its related symptoms are a major therapeutic challenge and burden to healthcare systems.⁸

2/3 of

EMERGENCY ROOM VISITS
for SYMPTOMS LEADING
to AF DIAGNOSIS result in

**HOSPITAL
ADMISSIONS⁸**

HOW DOES AF IMPACT PATIENT QUALITY OF LIFE?

Quality of life is significantly poorer in patients with AF than patients with other cardiovascular conditions.

■ The Short Form 36 (SF-36) Health Survey is the most common questionnaire used to measure patient quality of life.

■ The questionnaire measures the impact on physical and mental health using 8 subscales:⁸²

PHYSICAL COMPONENT SUBSCALES

PHYSICAL FUNCTION

ROLE PHYSICAL

BODILY PAIN

GENERAL HEALTH

MENTAL COMPONENT SUBSCALES

MENTAL HEALTH

ROLE EMOTIONAL

SOCIAL FUNCTION

VITALITY

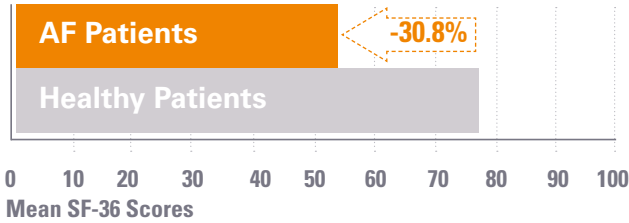
■ Lower total scores on each subscale indicate poorer quality of life.

■ Patients with AF have **significantly poorer quality of life** than the general population in several SF-36 subscales, with reductions of **up to 47%**.^{14-17; 52}

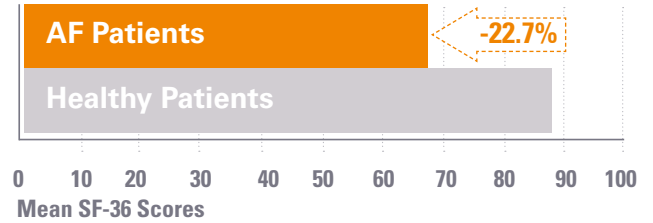
Comparison of Quality of Life between AF Patients and the General Population

SF-36 Quality of Life Subscales

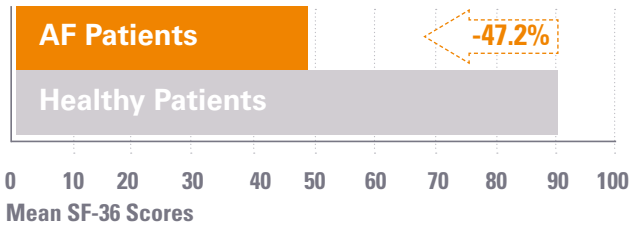
General Health



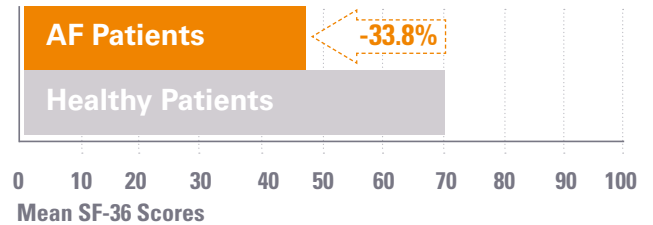
Physical Functioning



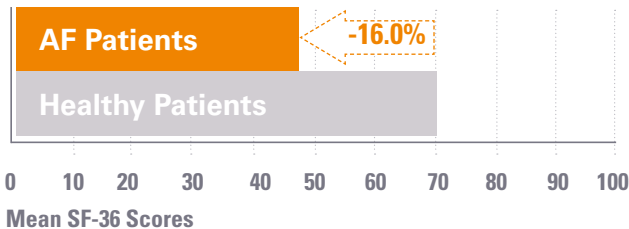
Role Physical



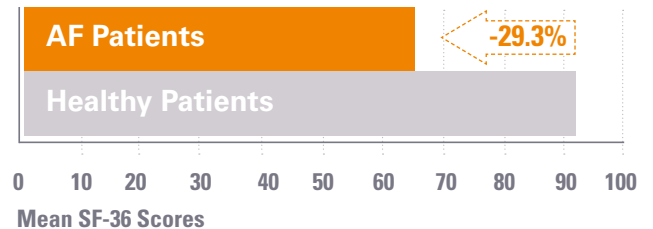
Vitality



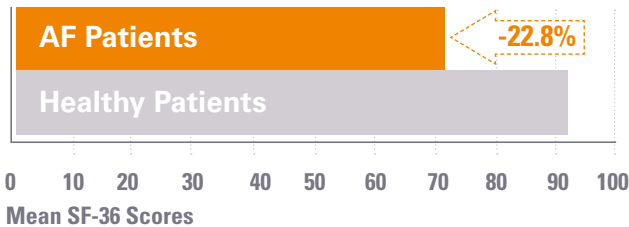
Mental Health



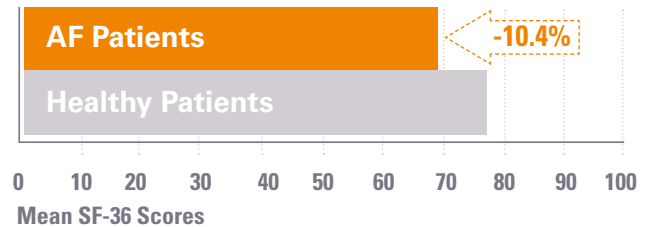
Role Emotional



Social Functioning



Bodily Pain



Abbreviations: AF = atrial fibrillation; SF-36 = Short Form 36 Quality of Life Questionnaire
Source: Dorian et al. (2000)⁵²

Healthy Patients (n=47) AF Patients (n=152)

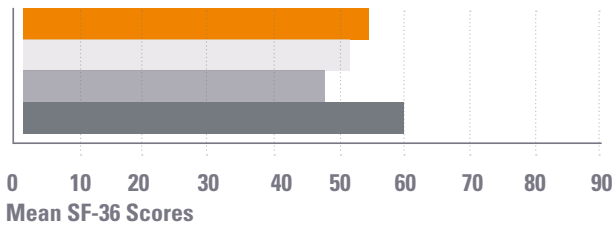
Patients with AF or other cardiovascular diseases such as coronary artery disease, congestive heart failure, and history of heart attack have **similar reductions in quality of life.**^{15; 52}

Comparison of Quality of Life between Patients with AF and other Cardiovascular Conditions

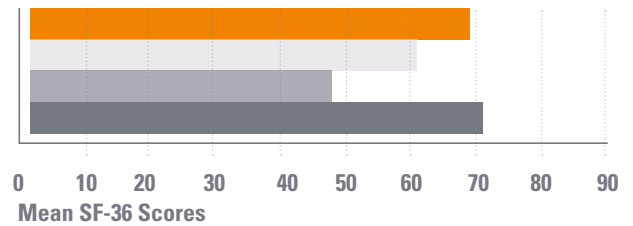
SF-36 Quality of Life Subscales

■ AF Patients (n=152)
 ■ PTCA Patients (n=69)
 ■ CHF Patients (n=216)
 ■ Post-Heart Attack Patients (n=69)

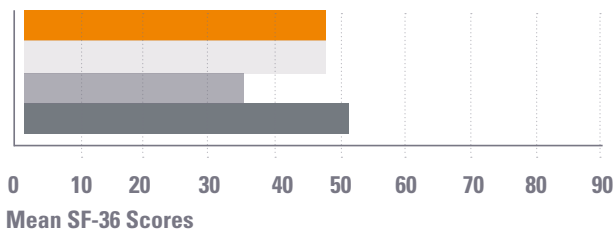
General Health



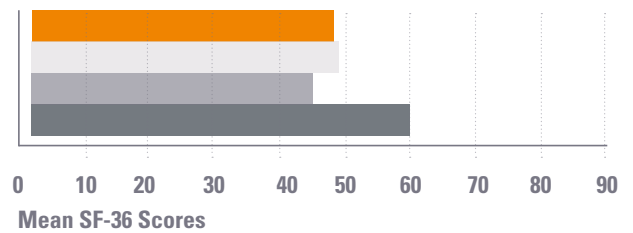
Physical Functioning



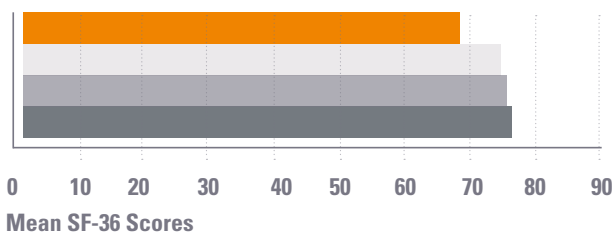
Role Physical



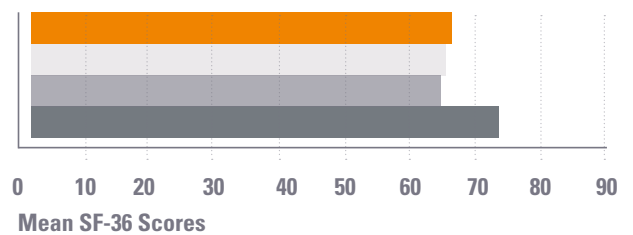
Vitality



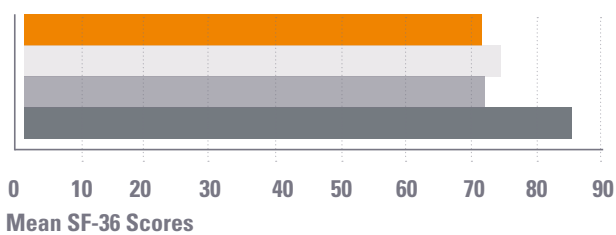
Mental Health



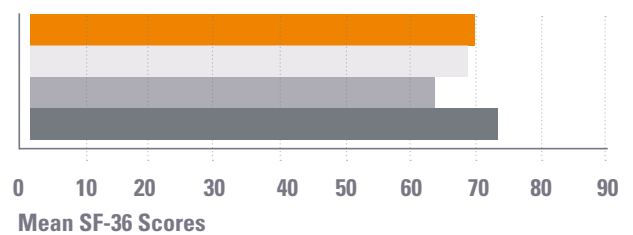
Role Emotional



Social Functioning



Bodily Pain



Abbreviations: AF = atrial fibrillation; CHF = congestive heart failure; PTCA = percutaneous transluminal coronary angioplasty in patients with coronary artery disease
 Source: Dorian et al. (2000)¹²

AF type has been associated with perceived symptom severity and reductions in quality of life.¹⁴

- Patients with intermittent AF (paroxysmal and early persistent AF) **had worse impairment of quality of life** than those with chronic AF (persistent and permanent AF).¹⁴

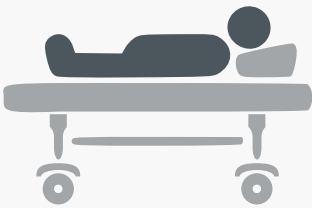
In patients with AF, factors that may impair quality of life include:



■ **Greater disability**⁸³



■ **High number of prescribed drugs (7 or more)**⁸³



■ **Greater number of visits to emergency department**⁵⁶



■ **Greater number of symptomatic episodes**⁵⁶



■ **Increased anxiety and the perception of more severe palpitations**^{14; 56; 84}



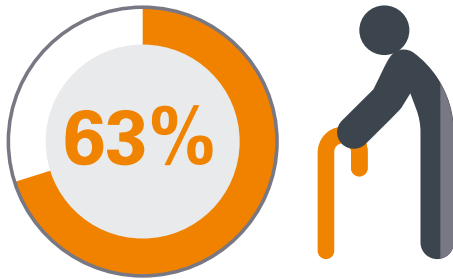
■ **Disease progression**⁵⁵



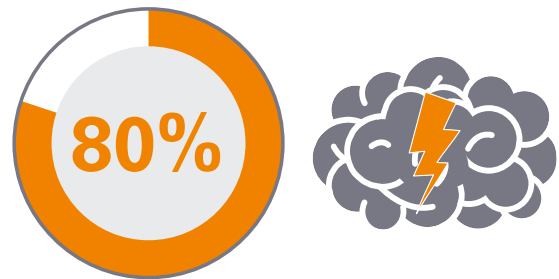
■ **Major complications and other conditions** such as stroke, heart failure, obstructive sleep apnea, chronic obstructive pulmonary disease, and coronary artery disease^{55; 85}

HOW DOES AF IMPACT FAMILY MEMBERS?

Caring for family members with AF can be burdensome. Some form of caregiver assistance is required in:^{19; 86}



OF ELDERLY AF PATIENTS⁸⁶



OF PATIENTS RECOVERING FROM STROKE¹⁹

■ AF patients require caregiver assistance for several activities of daily living, including:⁸⁷

- **Opening** medication packaging
- **Assisting** with activities of daily living due to tiredness experienced due to AF
- **Assisting or confirming** correct dosage of medication
- **Monitoring** for signs of bleeding
- **Driving** to the primary care physician or anticoagulation clinic for regular monitoring
- **Ensuring adherence** to any dietary restrictions

- Caregivers of AF patients experience considerable changes to their daily lives, including:¹⁸



**Disrupted
schedules**



**Financial
burden**



**Lack of
family support**



**Health
problems**

- Caregivers experience considerable disruption to their schedules and are at high risk of burnout when:^{18; 19}

- Patients are **frail, sick, or disabled**¹⁸

- Patients have low **quality of life**¹⁹

- Patients have had or are at **high risk of stroke**^{18; 19}

- Patients have low level of **independence**¹⁹

- Provide care for **long hours** (e.g., >4 hrs/week)^{18; 19}

**>40% OF STROKE PATIENTS
RECEIVING CARE**

**NEED ANOTHER caregiver by the
THIRD MONTH of
RECOVERY.**¹⁹

- Burden to caregivers may lead to less adequate patient support, physical and emotional stress, caregiver burnout, and suboptimal patient outcomes.⁸⁷

HOW DOES STROKE IMPACT QUALITY OF LIFE?

The occurrence of stroke can have a devastating impact on patient quality of life and the ability to perform daily activities.

- Stroke can cause significant impairment in physical, psychological, and social function, and can reduce a patient's ability to carry out routine activities.⁸⁸
- Limitations after a stroke include:⁸⁸

- Paralysis
- Depression
- Personality changes
- Problems with communication
- Anxiety
- Memory loss
- Cognitive impairment



STROKE in patients with AF IS MORE SEVERE AND DEVASTATING than in patients who do not have AF⁶⁹⁻⁷⁰

30% OF STROKE PATIENTS WILL HAVE A SECOND STROKE⁸⁹

- Patients who experience a stroke are at risk of suffering a second stroke.⁸⁹
 - In stroke patients, the risk of a second stroke is nearly 9x higher than the risk of stroke in the general population.⁸⁹

HOW DOES STROKE TREATMENT AFFECT QUALITY OF LIFE?

Oral anticoagulant therapy is a psychological, logistical, and therapeutic challenge for patients and their physicians.

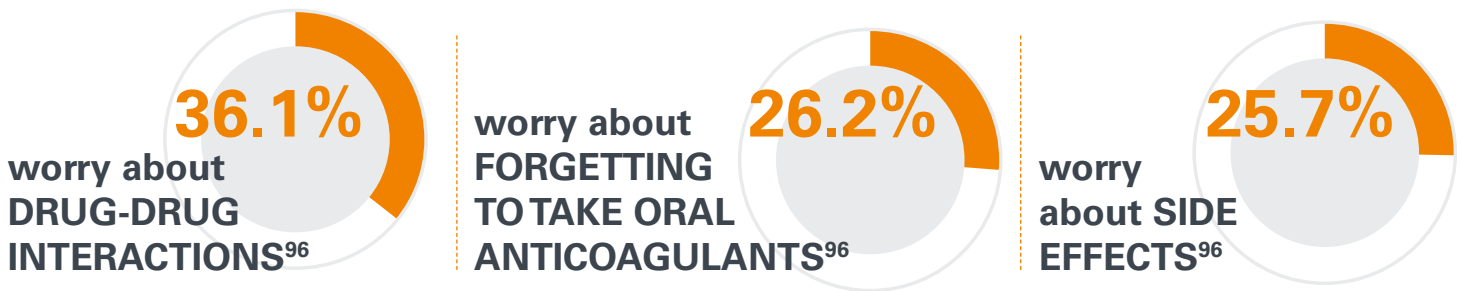
■ Oral anticoagulation therapy reduces the risk of stroke and prolongs life, **but increases the risk of bleeding** in patients with AF.⁹⁰⁻⁹³

■ Oral anticoagulation therapy can be **burdensome** to patients, as it requires:

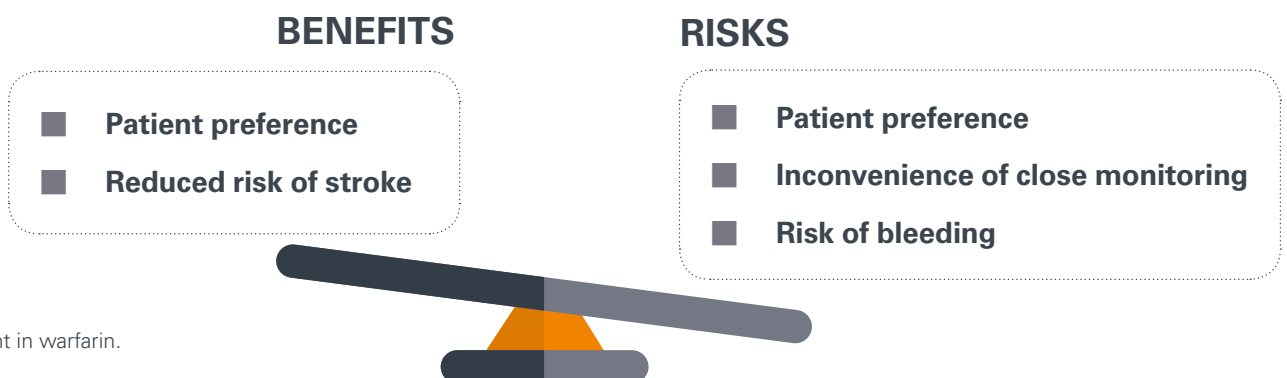
■ **FREQUENT AND REGULAR VISITS**
to monitor and optimize dosage^{*72; 94; 95}

■ **CHANGES TO PATIENT BEHAVIOR AND LIFESTYLE**
that disrupt daily activities and negatively impact quality of life.⁹⁴⁻⁹⁵

■ Common concerns for AF patients on oral anticoagulants such as warfarin:



■ Prescription of oral anticoagulants requires physicians to weigh the **benefit of stroke prevention** against the **risk of bleeding**, as well as consider the **inconvenience of close monitoring and patient preference**.⁹⁷⁻⁹⁸



*For patient in warfarin.

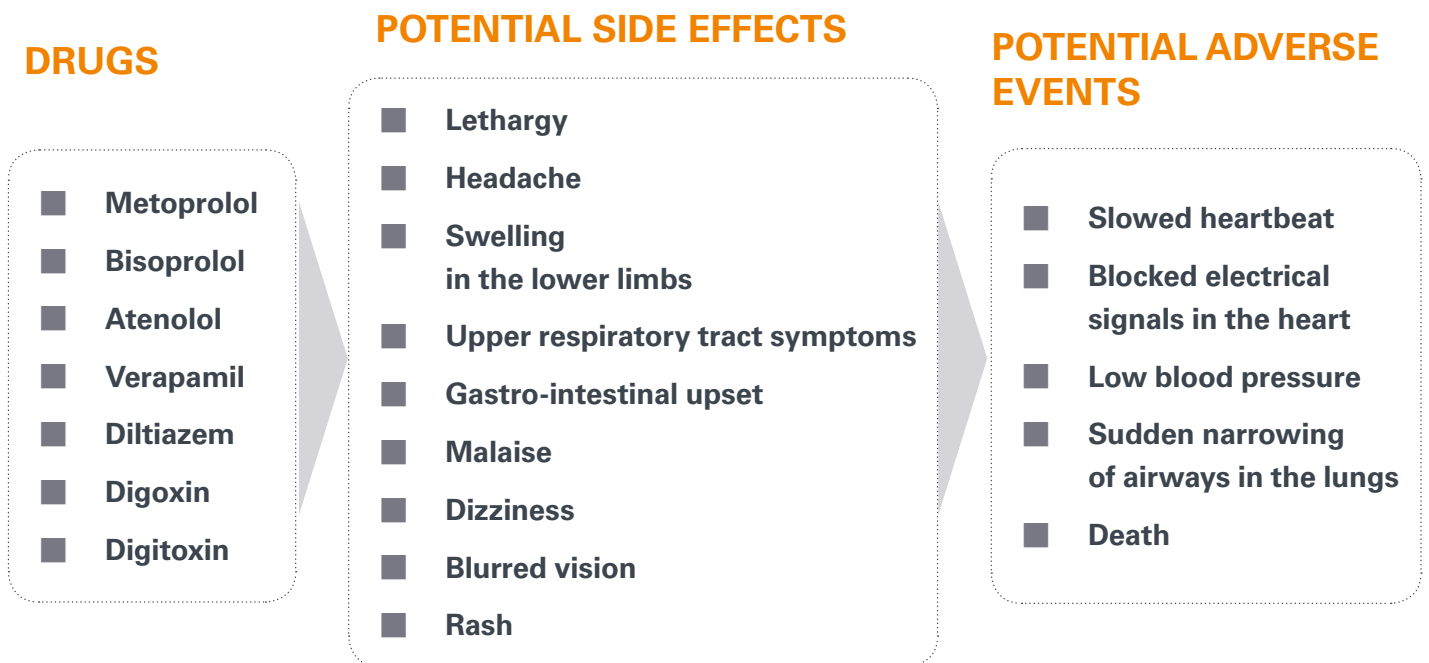
HOW DOES AF TREATMENT AFFECT QUALITY OF LIFE?

Pharmaceutical treatment for AF carries risks of serious side effects and may increase patient anxiety and worsen quality of life.

■ Antiarrhythmic drugs for managing AF have many side effects, including **drug-drug interactions and irregular heartbeats** that cannot be distinguished from AF.^{3; 99}

■ Concern over side effects may contribute to **patient anxiety**, which reduces quality of life.^{14; 56; 84; 96}

Safety Risks Associated with Pharmaceutical Treatment of AF – Rate Control Drugs



Safety Risks Associated with Pharmaceutical Treatment of AF – Rhythm Control Drugs



AF increasingly places a critical financial burden on healthcare systems.

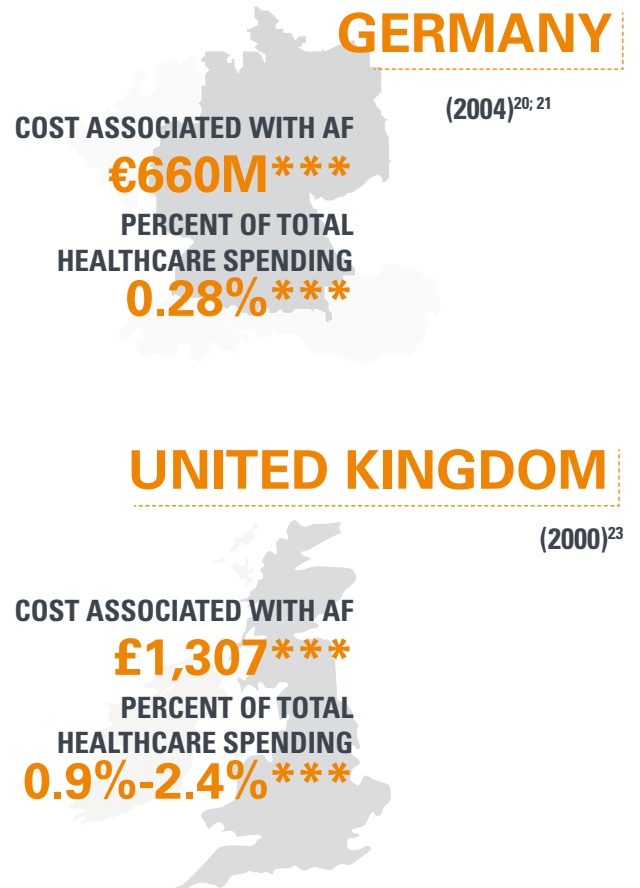
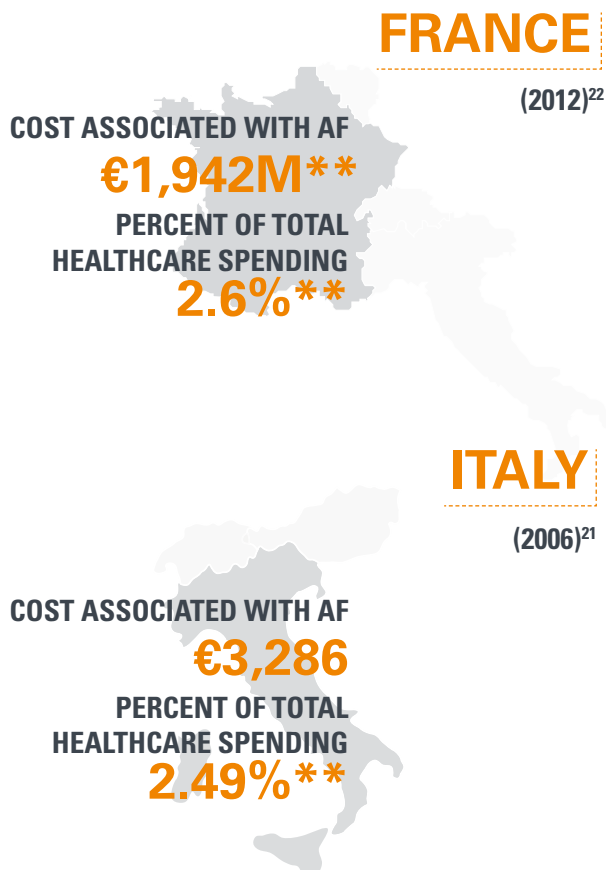
WHAT IS THE TOTAL COST OF AF TO NATIONAL HEALTHCARE SYSTEMS?

It is estimated that up to 2.6% of total annual health care expenditure is associated with AF in European countries.

■ The national economic burden of AF is high and varies across European countries.^{21; 100; 101}

■ The total healthcare costs of AF account for 0.28% to 2.6% of total healthcare spending in European countries.^{3; 21-23; 100*}

Annual National Healthcare Costs of AF



*Based on limited country data reporting.

**Based on in-patient and rehabilitation costs to hospitals for AF patients hospitalized for cardiovascular reasons. The study noted exclusion of minor cardiovascular complications, community consultation, and prescription; as such, these costs do not represent the total cost in France.

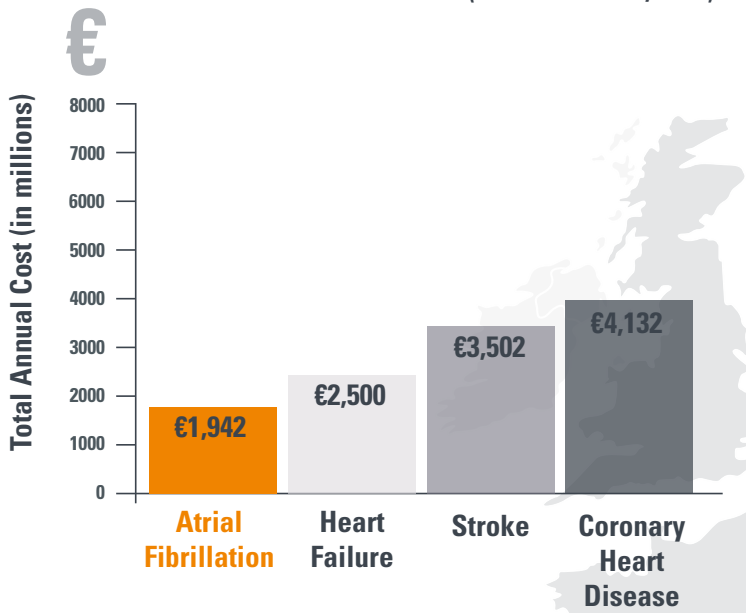
***Based on direct costs.

ECONOMIC BURDEN

- The high cost of AF is largely due to **hospitalizations and complications** such as stroke.^{21; 23}
- **National healthcare costs for AF are similar** to those for other cardiovascular diseases.^{20; 22; 23; 102-106}

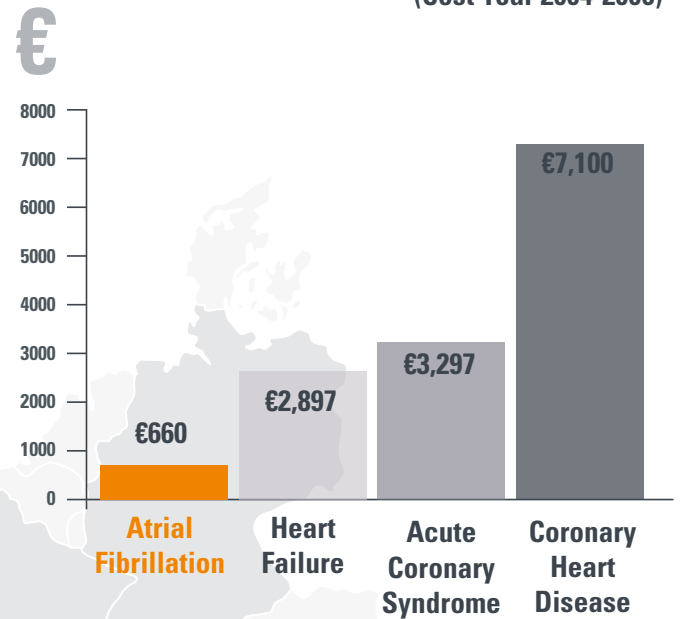
FRANCE

(Cost Year 2012/2013)



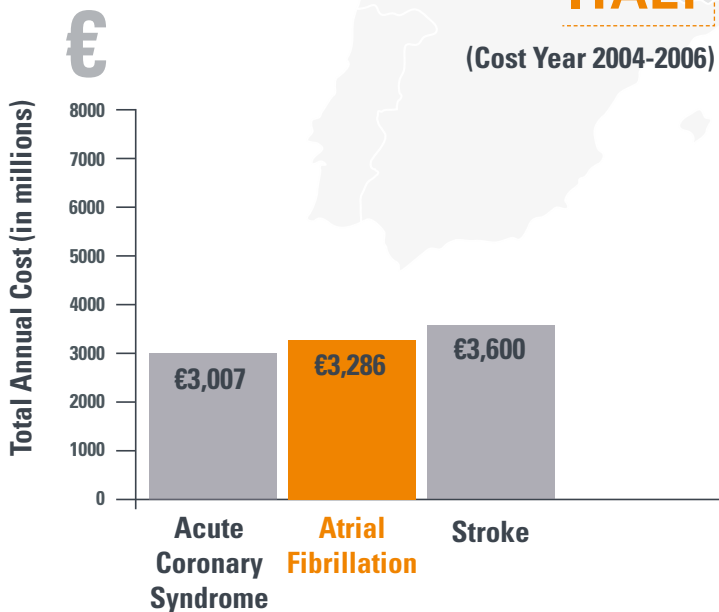
GERMANY

(Cost Year 2004-2006)



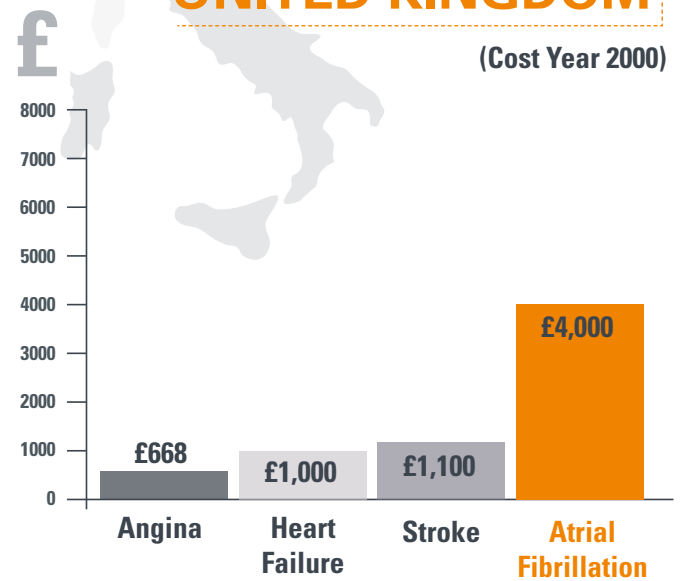
ITALY

(Cost Year 2004-2006)



UNITED KINGDOM

(Cost Year 2000)



WHAT ARE THE DIRECT AND INDIRECT COSTS OF AF?

Direct and indirect costs for the management of AF are highly variable across European countries.

■ Costs for AF management can be divided into 2 groups:

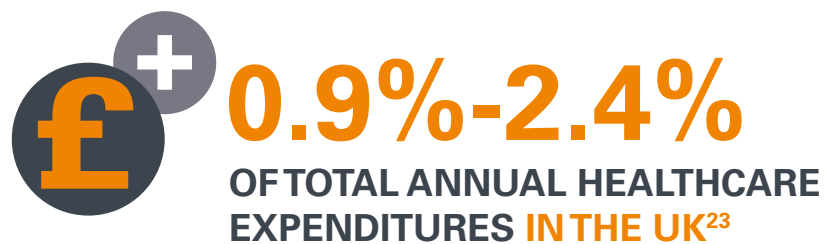
DIRECT COSTS

- Hospitalization
- Outpatient and Physicians Visits
- Prescriptions
- Laboratory Testing
- Long-term Care

INDIRECT COSTS

- Work Productivity Losses
- Support Provided By Caregivers

■ Direct costs of AF are high, accounting for*:



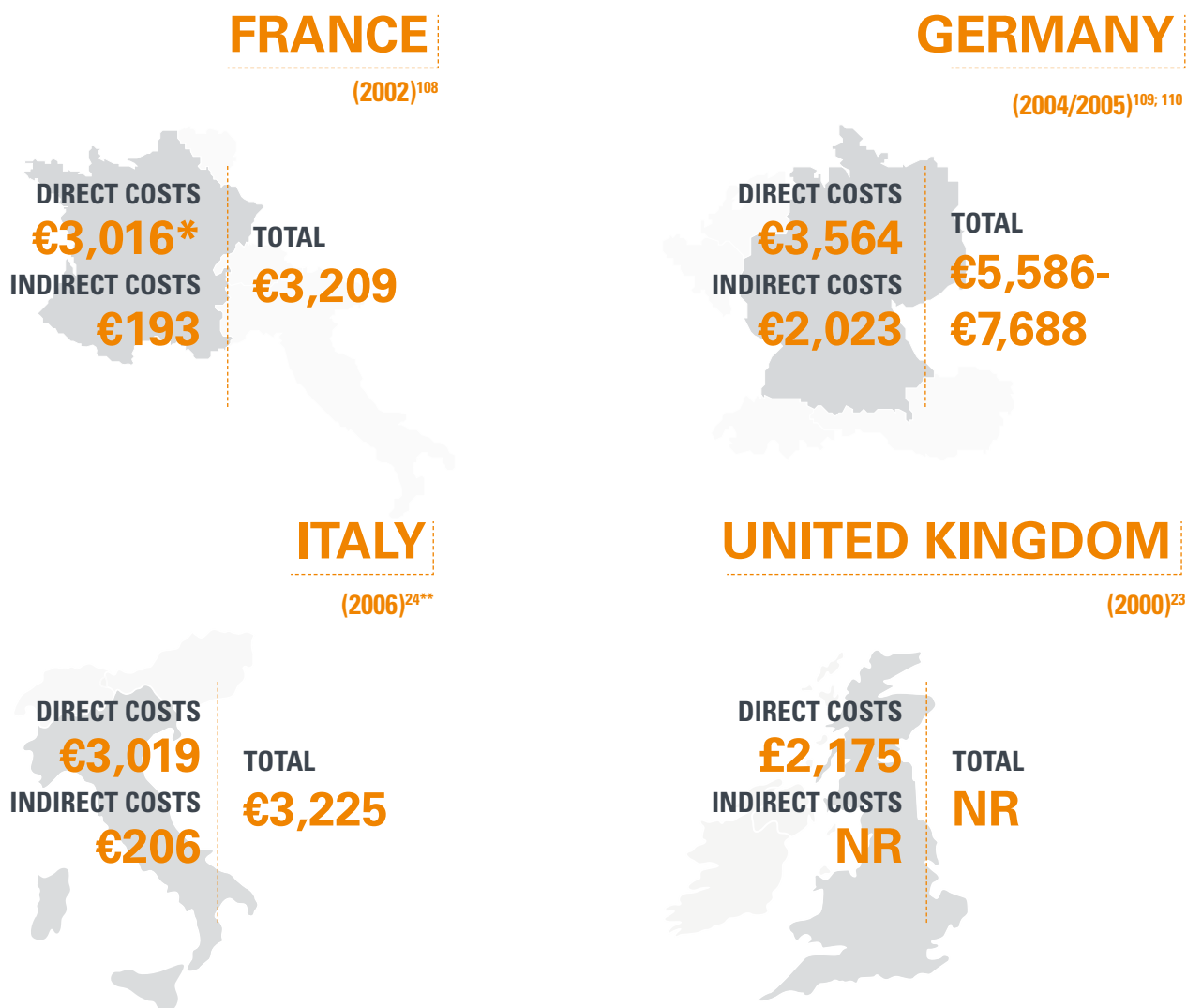
■ Annual direct per-patient costs of AF are **similar in France, Germany, Italy, and the UK.**^{23; 24; 107-109}

■ Indirect costs reported are **highly variable by country, with highest costs in Germany.**^{24; 108; 109}

- Indirect costs related to AF were higher for paroxysmal and persistent AF, whereas those not related to AF were higher for permanent AF.¹⁰⁸

*Based on limited country data reporting.

Annual Direct and Indirect Cost of AF per Patient



- Persistent AF can **cost significantly more to treat** than paroxysmal or permanent AF in some countries.¹⁰⁸
 - In Germany, **costs were lowest** for permanent AF and highest for persistent AF.¹⁰⁸
 - In Sweden, **costs were equally high** for paroxysmal and persistent AF.¹⁰⁸

*Direct cost was calculated by excluding costs for loss of work from the total per-patient cost reported for the societal perspective in Le Heuzey et al. (2004). Drug costs contained out-of-pocket costs, however, the authors noted that these costs were not statistically different from the those in the healthcare payer perspective; as such, drug costs were assumed to be direct costs.

**Based 1-year follow-up costs after index admission.

Abbreviations: NR = not reported.

WHAT FACTORS INFLUENCE DIRECT COSTS OF AF?



HOSPITALIZATIONS
AT 44%-78%
OF AF MANAGEMENT COSTS^{20; 21; 23; 24; 109*}



ANTIARRHYTHMIC DRUGS
AT 15%-20%
OF AF MANAGEMENT COSTS^{20; 21; 23; 109*}

Hospital costs represent the largest expense in AF management.

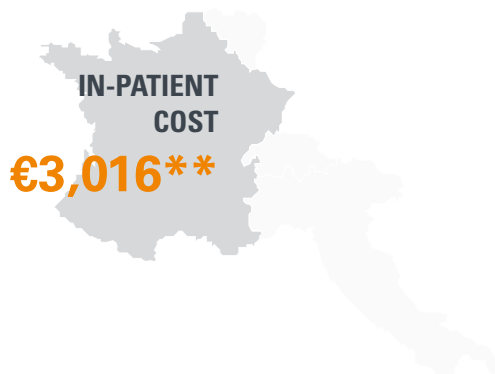
IN-PATIENT COSTS
ACCOUNT FOR **50%-70%** OF ANNUAL DIRECT
COSTS¹⁰⁰

- Healthcare resource use in AF patients is high, with **up to 40%** of AF patients hospitalized each year primarily due to heart failure and arrhythmia recurrence.^{3; 110}
- **Hospitalization costs can be 2x higher** for persistent AF than paroxysmal AF.¹⁰⁷
- Other factors associated with a high hospital cost include stroke and bleeding events, high stroke risk, high bleeding risk, and presence of other conditions.¹¹¹

Mean Annual Cost of In-patient Care per Patient*

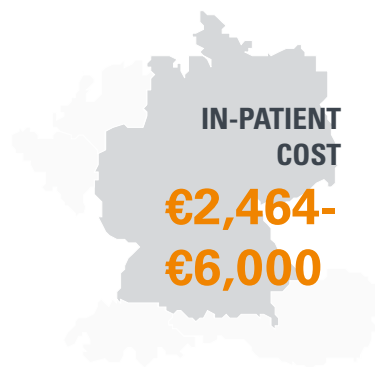
FRANCE

(2002)¹⁰⁷



GERMANY

(2004/2005)¹⁰⁸⁻¹⁰⁹



ITALY

(2006)²⁴



UNITED KINGDOM

(2000)²³



*Data is based on limited countries reporting.

**Based on direct costs that were calculated by excluding costs for loss of work from the total per-patient cost reported for the societal perspective in Le Heuzey et al. (2004).

WHY ARE AF PATIENTS ADMITTED TO HOSPITAL?

AF represents a significant portion of admissions for cardiac arrhythmias.



■ Main reasons for AF admissions include:^{22; 107; 113}



■ Atrial fibrillation



■ Heart Failure



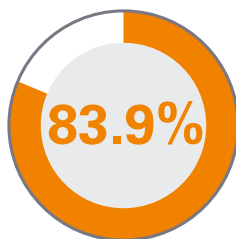
■ Vascular and ischemic diseases



■ Stroke, transient ischemic attack, or systemic emboli

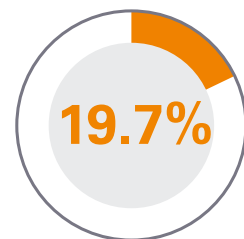
■ Reasons for admission or consultation differ by AF type:

AF WAS THE MOST COMMON REASON



IN PERSISTENT AF PATIENTS WHEN COMPARED TO OTHER AF TYPES¹¹³

HEART FAILURE WAS MOST COMMON REASON



IN PERMANENT AF PATIENTS WHEN COMPARED TO OTHER AF TYPES¹¹³

HOW DOES STROKE AFFECT THE COST OF AF?

The cost for the treatment and prevention of stroke in AF is high, contributing substantially to the total cost of AF management.

- In Europe, the cost of stroke in patients with AF is **7% to nearly 60% higher** than in patients without AF.^{70; 114-120}

In 2015, stroke was estimated to cost **€45 billion** a year in the European Union:¹²¹



Higher costs are due to:^{100; 120}



■ Hospitalizations

■ Longer hospital stays

■ Greater use of nursing care

■ In-patient rehabilitation

■ Hospital readmissions

Cost of Stroke in AF (Annual Per-patient Cost)

FRANCE

(2002)²²

OVERALL

€10,094

HEMORRHAGIC STROKE

€12,748

ISCHEMIC STROKE

€11,243

SYSTEMIC EMBOLISM

€9,087

UNSPECIFIED STROKE

€8,108

TRANSIENT ISCHEMIC ATTACK

€3,734

GERMANY

(2001)¹²⁰

HOSPITAL ADMISSION FOR STROKE

€5,447

DIRECT COST OF STROKE WITH AF

€11,799

ITALY

(2015)¹²²

TOTAL HEALTHCARE COSTS FOR STROKE SURVIVORS WITH AF:

€13,054

UNITED KINGDOM

(2008-2009)¹¹⁵

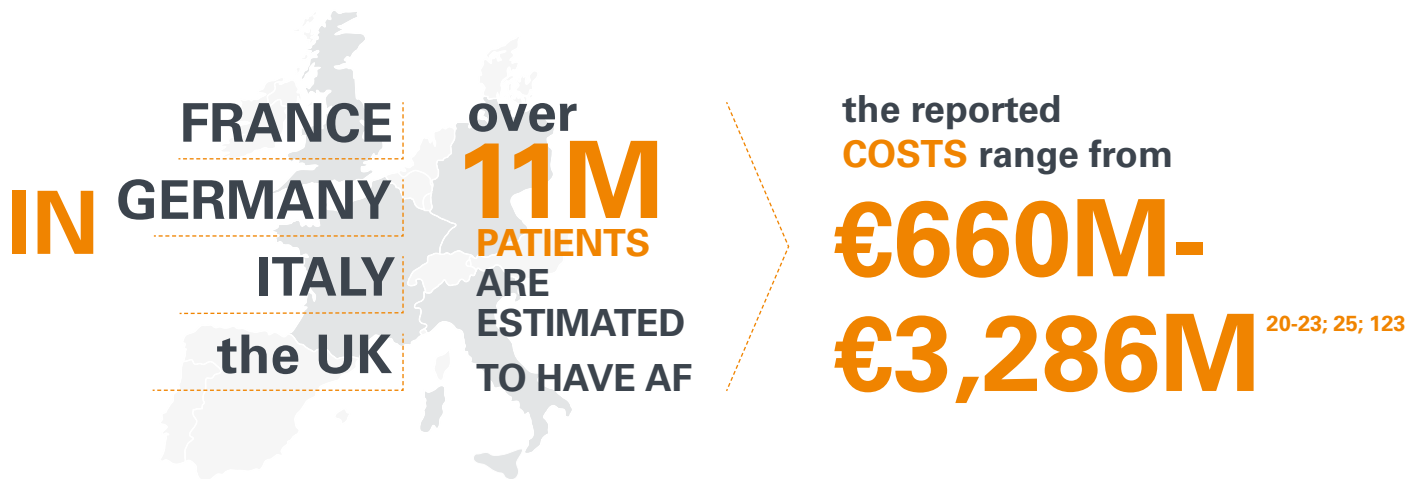
MEAN HOSPITAL AND 5-YEAR CARE COSTS - ISCHEMIC STROKE

£22,423 - £23,345

MEAN HOSPITAL AND 5-YEAR CARE COSTS - SYSTEMIC EMBOLISM

£13,634 - £13,720

The burden of AF is high and places a critical financial burden on healthcare systems in Europe.



BY 2050 Europe is projected to have **the greatest number of AF patients** compared to other regions globally.²⁹ This is expected to increase the number of stroke events, hospitalizations, and doctor visits, **ultimately raising the cost to national healthcare systems.**³¹

- The 2016 European Society of Cardiology’s Guidelines for the Management of AF and the 2017 HRS/EHRA/ECAS/APHS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation highlight several gaps in the evidence, where evidence is currently being developed or requires more recent and/or better studies.^{2;3} **Key areas for future research include the following:**

■ National and regional burden of AF

Most of the evidence on the national or regional burden of AF in Europe, particularly future projections on the total number of patients affected, number of new patients, and cost of AF, are based on data collected over 10 years ago, and are therefore outdated. **Recent data from methodologically robust studies are needed to understand the current epidemiologic and cost burden of AF for Europe and individual European countries.**

Risk of stroke in specific AF populations

Several specific AF groups should be studied to better characterize their risk for AF, stroke, and other AF-related comorbidities (e.g., patients with one stroke risk factor, non-Caucasian patients, women patients).³

Differences in overall patient management (e.g., different treatment for concomitant cardiovascular diseases) **may help explain** the variability in the reported rates of new (incident) AF cases, all (prevalent) AF cases, and AF complications.

Major health modifiers that cause AF

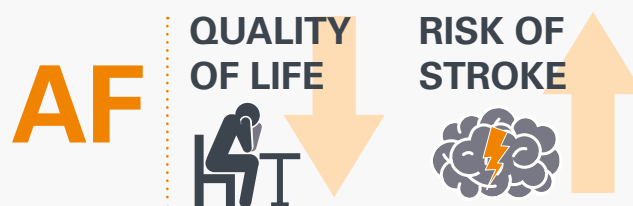
THE CAUSES
OF AF
DIFFER BY
PATIENT



The major causes of AF require **better characterization** by patient group, and should consider the key comorbidities associated with AF and pathophysiologically distinct types of AF.³ In the different patient subgroups, **how many patients have AF, what is the impact on disease progression, and what are the management costs?**

Treatment outcomes and quality of life and risk of stroke

The totality of evidence on AF underscores its role in reducing quality of life and in increasing the risk of stroke.



If treatments for AF aim to reduce or eliminate AF, **how do different treatment outcomes relate to quality of life and stroke risk?**

AF patient pathway

Will a **full pathway approach achieve better outcomes** for patients and Health Care Services (HCSs) **than a siloed approach?**

1. Iuzzo PA (2015). *Handbook of Cardiac Anatomy, Physiology, and DeviceS*. Springer Science+Business Media, LLC: Switzerland.
2. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB et al. (2017) 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 14 (10): e275-e444.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D et al. (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 37 (38): 2893-2962.
4. Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P et al. (2015) Five-Year Outcome of Catheter Ablation of Persistent Atrial Fibrillation Using Termination of Atrial Fibrillation as a Procedural Endpoint.
5. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R et al. (2014) Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 64 (21): 2222-2231.
6. Matsuo S, Lellouche N, Wright M, Bevilacqua M, Knecht S et al. (2009) Clinical predictors of termination and clinical outcome of catheter ablation for persistent atrial fibrillation. *J Am Coll Cardiol* 54 (9): 788-795.
7. Takigawa M, Takahashi A, Kuwahara T, Okubo K, Takahashi Y et al. (2014) Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation: the incidence of recurrence and progression of atrial fibrillation. *Circ Arrhythm Electrophysiol* 7 (2): 267-273.
8. Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD et al. (2012) Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation* 125 (23): 2933-2943.
9. Nieuwlaat R, Prins MH, Le Heuzey JY, Vardas PE, Aliot E et al. (2008) Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. *Eur Heart J* 29 (9): 1181-1189.
10. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG et al. (2010) Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 55 (8): 725-731.
11. Dilaveris PE, Kennedy HL (2017) Silent atrial fibrillation: epidemiology, diagnosis, and clinical impact. *Clin Cardiol* 40 (6): 413-418.
12. Schnabel R, Pecen L, Engler D, Lucerna M, Sellal JM et al. (2018) Atrial fibrillation patterns are associated with arrhythmia progression and clinical outcomes. *Heart*
13. Odotayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG et al. (2016) Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *Bmj* 354 i4482.
14. Nazli C, Kahya Eren N, Yakar Tuluçe S, Kocagra Yagiz IG, Kilicaslan B et al. (2016) Impaired quality of life in patients with intermittent atrial fibrillation. *Anatol J Cardiol* 16 (4): 250-255.
15. Thrall G, Lane D, Carroll D, Lip GY (2006) Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med* 119 (5): 448.e441-419.
16. Hagens VE, Ranchor AV, Van Sonderen E, Bosker HA, Kamp O et al. (2004) Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol* 43 (2): 241-247.
17. Hoehg V, Lundbye-Christensen S, Delmar C, Frederiksen K, Riahi S et al. (2016) Association between the diagnosis of atrial fibrillation and aspects of health status: a Danish cross-sectional study. *Scand J Caring Sci* 30 (3): 507-517.
18. Coleman CI, Coleman SM, Vanderpoel J, Nelson W, Colby JA et al. (2012) Factors associated with 'caregiver burden' for atrial fibrillation patients. *Int J Clin Pract* 66 (10): 984-990.
19. Oliva-Moreno J, Pena-Longobardo LM, Mar J, Masjuan J, Soulard S et al. (2018) Determinants of Informal Care, Burden, and Risk of Burnout in Caregivers of Stroke Survivors: The CONOCES Study. *Stroke* 49 (1): 140-146.
20. McBride D, Mattenklotz AM, Willich SN, Bruggenjurgen B (2009) The costs of care in atrial fibrillation and the effect of treatment modalities in Germany. *Value Health* 12 (2): 293-301.
21. Ball J, Carrington MJ, McMurray JJ, Stewart S (2013) Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 167 (5): 1807-1824.
22. Cotte FE, Chaize G, Gaudin AF, Samson A, Vainchtock A et al. (2016) Burden of stroke and other cardiovascular complications in patients with atrial fibrillation hospitalized in France. *Europace* 18 (4): 501-507.
23. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ (2004) Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 90 (3): 286-292.
24. Ringborg A, Nieuwlaat R, Lindgren P, Jonsson B, Fidan D et al. (2008) Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. *Europace* 10 (4): 403-411.
25. Global Burden of Disease Collaborative Network (2016) Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017. Accessed 2018-04-20. Available from <http://ghdx.healthdata.org/gbd-results-tool>.
26. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G et al. (2006) Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 27 (8): 949-953.
27. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D et al. (2004) Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 110 (9): 1042-1046.
28. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI et al. (2015) Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF Pilot General Registry. *Am J Med* 128 (5): 509-518 e502.
29. Rahman F, Kwan GF, Benjamin EJ (2014) Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 11 (11): 639-654.
30. United Nations DoEaSA, Population Division (2017). *World Population Prospects: The 2017 Revision, Key Findings and Advance Tables*. Working Paper No. ESA/P/WP/248, Available online at: https://esa.un.org/unpd/wpp/publications/Files/WPP2017_KeyFindings.pdf. Accessed:
31. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S (2014) Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 6 213-220.
32. Naser N, Dilic M, Durak A, Kulic M, Pepic E et al. (2017) The Impact of Risk Factors and Comorbidities on The Incidence of Atrial Fibrillation. *Mater Sociomed* 29 (4): 231-236.
33. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R et al. (2017) Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemost* 117 (5): 837-850.
34. Nystrom PK, Carlsson AC, Leander K, de Faire U, Hellenius ML et al. (2015) Obesity, metabolic syndrome and risk of atrial fibrillation: a Swedish, prospective cohort study. *PLoS One* 10 (5): e0127111.
35. Boriani G, Proietti M (2017) Atrial fibrillation prevention: an appraisal of current evidence. *Heart* (0):1-6
36. Ruigomez A, Johansson S, Wallander MA, Garcia Rodriguez LA (2005) Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. *BMC Cardiovasc Disord* 5 20.
37. Ziff OJ, Carter PR, McGowan J, Uppal H, Chandran S et al. (2018) The interplay between atrial fibrillation and heart failure on long-term mortality and length of stay: Insights from the, United Kingdom ACALM registry. *Int J Cardiol* 252 117-121.
38. Batul SA, Gopinathannair R (2017) Atrial Fibrillation in Heart Failure: a Therapeutic Challenge of Our Times. *Korean Circ J* 47 (5): 644-662.
39. Masarone D, Limongelli G, Rubino M, Valente F, Vastarella R et al. (2017) Management of Arrhythmias in Heart Failure. *J Cardiovasc Dev Dis* 4 (1):
40. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP et al. (2003) Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 107 (23): 2920-2925.
41. Violi F, Soliman EZ, Pignatelli P, Pastori D (2016) Atrial Fibrillation and Myocardial Infarction: A Systematic Review and Appraisal of Pathophysiologic Mechanisms. *J Am Heart Assoc* 5 (5):
42. Omae T, Inada E (2018) New-onset atrial fibrillation: an update. *J Anesth*
43. Chebbout R, Heywood EG, Drake TM, Wild JRL, Lee J et al. (2018) A systematic review of the incidence of and risk factors for postoperative atrial fibrillation following general surgery. *Anaesthesia* 73 (4): 490-498.
44. Marulanda-Londono E, Chaturvedi S (2017) The Interplay between Obstructive Sleep Apnea and Atrial Fibrillation. *Front Neurol* 8 668.
45. Andrade J, Khairy P, Dobrev D, Nattel S (2014) The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 114 (9): 1453-1468.
46. Zulkifly H, Lip GYH, Lane DA (2018) Epidemiology of atrial fibrillation. *Int J Clin Pract* e13070

47. Paludan-Muller C, Svendsen JH, Olesen MS (2016) The role of common genetic variants in atrial fibrillation. *J Electrocardiol* 49 (6): 864-870.
48. Gundlund A, Fosbol EL, Kim S, Fonarow GC, Gersh BJ et al. (2016) Family history of atrial fibrillation is associated with earlier-onset and more symptomatic atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J* 175 28-35.
49. Rho RW, Page RL (2005) Asymptomatic atrial fibrillation. *Prog Cardiovasc Dis* 48 (2): 79-87.
50. Guerra F, Brambatti M, Nieuwlaet R, Marcucci M, Dudink E et al. (2017) Symptomatic atrial fibrillation and risk of cardiovascular events: data from the Euro Heart Survey. *Europace* 19 (12): 1922-1929.
51. Lip GY, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L et al. (2014) Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J* 35 (47): 3365-3376.
52. Dorian P, Jung W, Newman D, Paquette M, Wood K et al. (2000) The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol* 36 (4): 1303-1309.
53. van den Berg MP, Hassink RJ, Tuinenburg AE, van Sonderen EF, Lefrandt JD et al. (2001) Quality of life in patients with paroxysmal atrial fibrillation and its predictors: importance of the autonomic nervous system. *Eur Heart J* 22 (3): 247-253.
54. Savelieva I, Paquette M, Dorian P, Luderitz B, Camm AJ (2001) Quality of life in patients with silent atrial fibrillation. *Heart* 85 (2): 216-217.
55. Dudink E, Erkuner O, Berg J, Nieuwlaet R, de Vos CB et al. (2017) The influence of progression of atrial fibrillation on quality of life: a report from the Euro Heart Survey. *Europace*
56. Aliot E, Botto GL, Crijns HJ, Kirchhof P (2014) Quality of life in patients with atrial fibrillation: how to assess it and how to improve it. *Europace* 16 (6): 787-796.
57. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO et al. (2007) Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation* 115 (24): 3050-3056.
58. Potpara TS, Stankovic GR, Beleslin BD, Polovina MM, Marinkovic JM et al. (2012) A 12-year follow-up study of patients with newly diagnosed lone atrial fibrillation: implications of arrhythmia progression on prognosis: the Belgrade Atrial Fibrillation study. *Chest* 141 (2): 339-347.
59. Senoo K, Suzuki S, Otsuka T, Sagara K, Matsuno S et al. (2014) Progression to the persistent form in asymptomatic paroxysmal atrial fibrillation. *Circ J* 78 (5): 1121-1126.
60. Aliot E, Breithardt G, Brugada J, Camm J, Lip GY et al. (2010) An international survey of physician and patient understanding, perception, and attitudes to atrial fibrillation and its contribution to cardiovascular disease morbidity and mortality. *Europace* 12 (5): 626-633.
61. Meinertz T, Kirch W, Rosin L, Pittrow D, Willich SN et al. (2011) Management of atrial fibrillation by primary care physicians in Germany: baseline results of the ATRIUM registry. *Clin Res Cardiol* 100 (10): 897-905.
62. Kalantarian S, Stern TA, Mansour M, Ruskin JN (2013) Cognitive Impairment Associated With Atrial Fibrillation: A Meta-analysis. *Annals of Internal Medicine* 158 (5_Part_1): 338-346.
63. Diemberger I, Fantecchi E, Reggiani MLB, Martignani C, Angeletti A et al. (2018) Atrial fibrillation and prediction of mortality by conventional clinical score systems according to the setting of care. *Int J Cardiol* 261 73-77.
64. Menke J, Luthje L, Kastrup A, Larsen J (2010) Thromboembolism in atrial fibrillation. *Am J Cardiol* 105 (4): 502-510.
65. Hillis AE, Tippet DC (2014) Stroke Recovery: Surprising Influences and Residual Consequences. *Advances in Medicine* 2014 1-10.
66. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL et al. (2018) Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity: A Scientific Statement From the American Heart Association. *Circulation*
67. Bassand JP, Accetta G, Al Mahmeed W, Corbalan R, Eikelboom J et al. (2018) Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: Rationale for comprehensive management of atrial fibrillation. *PLoS One* 13 (1): e0191592.
68. Hughes M, Lip GY (2008) Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemostasis* 99 (2): 295-304.
69. Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A et al. (2010) Stroke associated with atrial fibrillation—incidence and early outcomes in the north Dublin population stroke study. *Cerebrovasc Dis* 29 (1): 43-49.
70. Andrew NE, Thrift AG, Cadilhac DA (2013) The prevalence, impact and economic implications of atrial fibrillation in stroke: what progress has been made? *Neuroepidemiology* 40 (4): 227-239.
71. Batra G, Svennblad B, Held C, Jernberg T, Johanson P et al. (2016) All types of atrial fibrillation in the setting of myocardial infarction are associated with impaired outcome. *Heart* 102 (12): 926-933.
72. Lane DA, Aguinaga L, Blomstrom-Lundqvist C, Boriani G, Dan GA et al. (2015) Cardiac tachyarrhythmias and patient values and preferences for their management: the European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 17 (12): 1747-1769.
73. Bostrom JA, Saczynski JS, Hajduk A, Donahue K, Rosenthal LS et al. (2017) Burden of Psychosocial and Cognitive Impairment in Patients With Atrial Fibrillation. *Crit Pathw Cardiol* 16 (2): 71-75.
74. Alonso A, Arenas de Larriva AP (2016) Atrial Fibrillation, Cognitive Decline And Dementia. *Eur Cardiol* 11 (1): 49-53.
75. Zoni-Berisso M, Filippi A, Landolina M, Brignoli O, D'Ambrosio G et al. (2013) Frequency, patient characteristics, treatment strategies, and resource usage of atrial fibrillation (from the Italian Survey of Atrial Fibrillation Management [ISAF] study). *Am J Cardiol* 111 (5): 705-711.
76. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE et al. (1997) Atrial fibrillation and dementia in a population-based study. *The Rotterdam Study*. *Stroke* 28 (2): 316-321.
77. Singh-Manoux A, Inserm UCfRiE, Population Health UP-SHPBBAPVCVCF, Department of E, Public Health UCLTLWCETUK et al. (2018) Atrial fibrillation as a risk factor for cognitive decline and dementia. *Eur Heart J* 38 (34): 2612-2618.
78. Ball J, Carrington MJ, Stewart S, investigators S (2013) Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? *Heart* 99 (8): 542-547.
79. Yaranov DM, Smyrlis A, Usatii N, Butler A, Petrini JR et al. (2015) Effect of obstructive sleep apnea on frequency of stroke in patients with atrial fibrillation. *Am J Cardiol* 115 (4): 461-465.
80. Oza N, Baveja S, Khayat R, Houmsse M (2014) Obstructive sleep apnea and atrial fibrillation: understanding the connection. *Expert Rev Cardiovasc Ther* 12 (5): 613-621.
81. Nieuwlaet R, Capucci A, Camm AJ, Olsson SB, Andresen D et al. (2005) Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 26 (22): 2422-2434.
82. Ware J, Jr., Snow K, Kosinski M, Gandek B (1993). SF-36 health survey manual and interpretation guide. The Health Institute, New England Medical Center: Boston, MA.
83. Roalfe AK, Bryant TL, Davies MH, Hackett TG, Saba S et al. (2012) A cross-sectional study of quality of life in an elderly population (75 years and over) with atrial fibrillation: secondary analysis of data from the Birmingham Atrial Fibrillation Treatment of the Aged study. *Europace* 14 (10): 1420-1427.
84. Serpytis R, Navickaite A, Serpytiene E, Barysiene J, Marinskis G et al. (2018) Impact of Atrial Fibrillation on Cognitive Function, Psychological Distress, Quality of Life, and Impulsiveness. *Am J Med*
85. Randolph TC, Simon DN, Thomas L, Allen LA, Fonarow GC et al. (2016) Patient factors associated with quality of life in atrial fibrillation. *Am Heart J* 182 135-143.
86. Chen SY, Vanderpoel J, Mody S, Nelson WW, Schein J et al. (2012) Caregiver assistance among Medicare beneficiaries with atrial fibrillation and factors associated with anticoagulant treatment. *Am J Geriatr Pharmacother* 10 (5): 273-283.
87. Ferguson C, Inglis SC, Newton PJ, Middleton S, Macdonald PS et al. (2015) The caregiver role in thromboprophylaxis management in atrial fibrillation: a literature review. *Eur J Cardiovasc Nurs* 14 (2): 98-107.
88. Lo Buono V, Corallo F, Bramanti P, Marino S (2017) Coping strategies and health-related quality of life after stroke. *J Health Psychol* 22 (1): 16-28.

89. Burn J, Dennis M, Bamford J, Sandercock P, Wade D et al. (1994) Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke* 25 (2): 333-337.
90. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361 (12): 1139-1151.
91. Rocket AF Study Investigators (2010) Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* 159 (3): 340-347 e341.
92. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD et al. (2013) Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 369 (22): 2093-2104.
93. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM et al. (2011) Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 365 (11): 981-992.
94. Suarez Fernandez C, Castilla-Guerra L, Cantero Hinojosa J, Surinach JM, Acosta de Bilbao F et al. (2018) Satisfaction with oral anticoagulants in patients with atrial fibrillation. *Patient Prefer Adherence* 12 267-274.
95. Ynsaurriaga FA, Peinado RP, Ormaetxe Merodio JM (2014) Atrial fibrillation and quality of life related to disease and treatment: focus on anticoagulation. *Future Cardiol* 10 (3): 381-393.
96. Wang Y, Kong MC, Lee LH, Ng HJ, Ko Y (2014) Knowledge, satisfaction, and concerns regarding warfarin therapy and their association with warfarin adherence and anticoagulation control. *Thromb Res* 133 (4): 550-554.
97. McCrory DC, Matchar DB, Samsa G, Sanders LL, Pritchett EL (1995) Physician attitudes about anticoagulation for nonvalvular atrial fibrillation in the elderly. *Arch Intern Med* 155 (3): 277-281.
98. Induruwa I, Amis E, Hannon N, Khadjooi K (2017) The increasing burden of atrial fibrillation in acute medical admissions, an opportunity to optimise stroke prevention. *J R Coll Physicians Edinb* 47 (4): 331-335.
99. Dan GA, Martinez-Rubio A, Agewall S, Boriani G, Borggreffe M et al. (2018) Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Europace*
100. Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC (2011) The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace* 13 (10): 1375-1385.
101. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB et al. (2011) 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol* 57 (11): e101-198.
102. Tuppin P, Riviere S, Rigault A, Tala S, Drouin J et al. (2016) Prevalence and economic burden of cardiovascular diseases in France in 2013 according to the national health insurance scheme database. *Arch Cardiovasc Dis* 109 (6-7): 399-411.
103. Neumann T, Biermann J, Erbel R, Neumann A, Wasem J et al. (2009) Heart failure: the commonest reason for hospital admission in Germany: medical and economic perspectives. *Dtsch Arztebl Int* 106 (16): 269-275.
104. Piscitelli P, Iolascon G, Argentiero A, Chitano G, Neglia C et al. (2012) Incidence and costs of hip fractures vs strokes and acute myocardial infarction in Italy: comparative analysis based on national hospitalization records. *Clin Interv Aging* 7 575-583.
105. Taylor MJ, Scuffham PA, McCollam PL, Newby DE (2007) Acute coronary syndromes in Europe: 1-year costs and outcomes. *Curr Med Res Opin* 23 (3): 495-503.
106. Kolominsky-Rabas PL, Heuschmann PU, Marschall D, Emmert M, Baltzer N et al. (2006) Lifetime cost of ischemic stroke in Germany: results and national projections from a population-based stroke registry: the Erlangen Stroke Project. *Stroke* 37 (5): 1179-1183.
107. Le Heuzey JY, Paziud O, Piot O, Said MA, Copie X et al. (2004) Cost of care distribution in atrial fibrillation patients: the COCAF study. *Am Heart J* 147 (1): 121-126.
108. Jonsson L, Eliasson A, Kindblom J, Almgren O, Edvardsson N (2010) Cost of illness and drivers of cost in atrial fibrillation in Sweden and Germany. *Appl Health Econ Health Policy* 8 (5): 317-325.
109. Reinhold T, Lindig C, Willich SN, Bruggenjürgen B (2011) The costs of atrial fibrillation in patients with cardiovascular comorbidities—a longitudinal analysis of German health insurance data. *Europace* 13 (9): 1275-1280.
110. Kirchhof P, Schmalowsky J, Pittrow D, Rosin L, Kirch W et al. (2014) Management of patients with atrial fibrillation by primary-care physicians in Germany: 1-year results of the ATRIUM registry. *Clin Cardiol* 37 (5): 277-284.
111. Casajuana M, Giner-Soriano M, Roso-Llorach A, Vedia C, Violan C et al. (2018) Annual costs attributed to atrial fibrillation management: cross-sectional study of primary healthcare electronic records. *Eur J Health Econ*
112. Anter E, Jessup M, Callans DJ (2009) Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation* 119 (18): 2516-2525.
113. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F et al. (2018) Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace* 20 (5): 747-757.
114. Cotte FE, Chaize G, Kachaner I, Gaudin AF, Vainchtock A et al. (2014) Incidence and cost of stroke and hemorrhage in patients diagnosed with atrial fibrillation in France. *J Stroke Cerebrovasc Dis* 23 (2): e73-83.
115. Yiin GS, Howard DP, Paul NL, Li L, Luengo-Fernandez R et al. (2014) Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. *Circulation* 130 (15): 1236-1244.
116. Ali AN, Howe J, Abdel-Hafiz A (2015) Cost of acute stroke care for patients with atrial fibrillation compared with those in sinus rhythm. *Pharmacoeconomics* 33 (5): 511-520.
117. Ali AN, Abdelhafiz A (2016) Clinical and Economic Implications of AF Related Stroke. *J Atr Fibrillation* 8 (5): 1279.
118. Ghatnekar O, Glader EL (2008) The effect of atrial fibrillation on stroke-related inpatient costs in Sweden: a 3-year analysis of registry incidence data from 2001. *Value Health* 11 (5): 862-868.
119. Hannon N, Daly L, Murphy S, Smith S, Hayden D et al. (2014) Acute hospital, community, and indirect costs of stroke associated with atrial fibrillation: population-based study. *Stroke* 45 (12): 3670-3674.
120. Bruggenjürgen B, Rosnagel K, Roll S, Andersson FL, Selim D et al. (2007) The impact of atrial fibrillation on the cost of stroke: the berlin acute stroke study. *Value Health* 10 (2): 137-143.
121. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J et al. (2017). European Heart Network, European Cardiovascular Disease Statistics 2017. Brussels. Available online at: <https://www.bhf.org.uk/-/media/files/research/heart-statistics/european-cardiovascular-disease-statistics-2017.pdf>. Accessed: 2018-05-25.
122. Fattore G, Torbica A, Susi A, Giovanni A, Benelli G et al. (2012) The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study. *BMC Neurol* 12 137.
123. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 390 (10100): 1211-1259.

EC Representative | Biosense Webster
A Division of Johnson & Johnson Medical NV/SA
Leonardo da Vincilaan 15 | 1831 Diegem, Belgium
Tel: +32-2-7463-401 | Fax: +32-2-7463-403

Manufacturer | Biosense Webster
33 Technology Drive, Irvine | California 92618, USA
Tel: +1-909-839-8500 | Tel: +1-800-729-9010 | Fax: +1-909-468-2905
www.biosensewebster.com

