



# **ATRIAL FIBRILLATION MANAGEMENT**

---

2021 FULL REPORT

**Overview of Atrial Fibrillation Management  
and Treatment Outcomes**

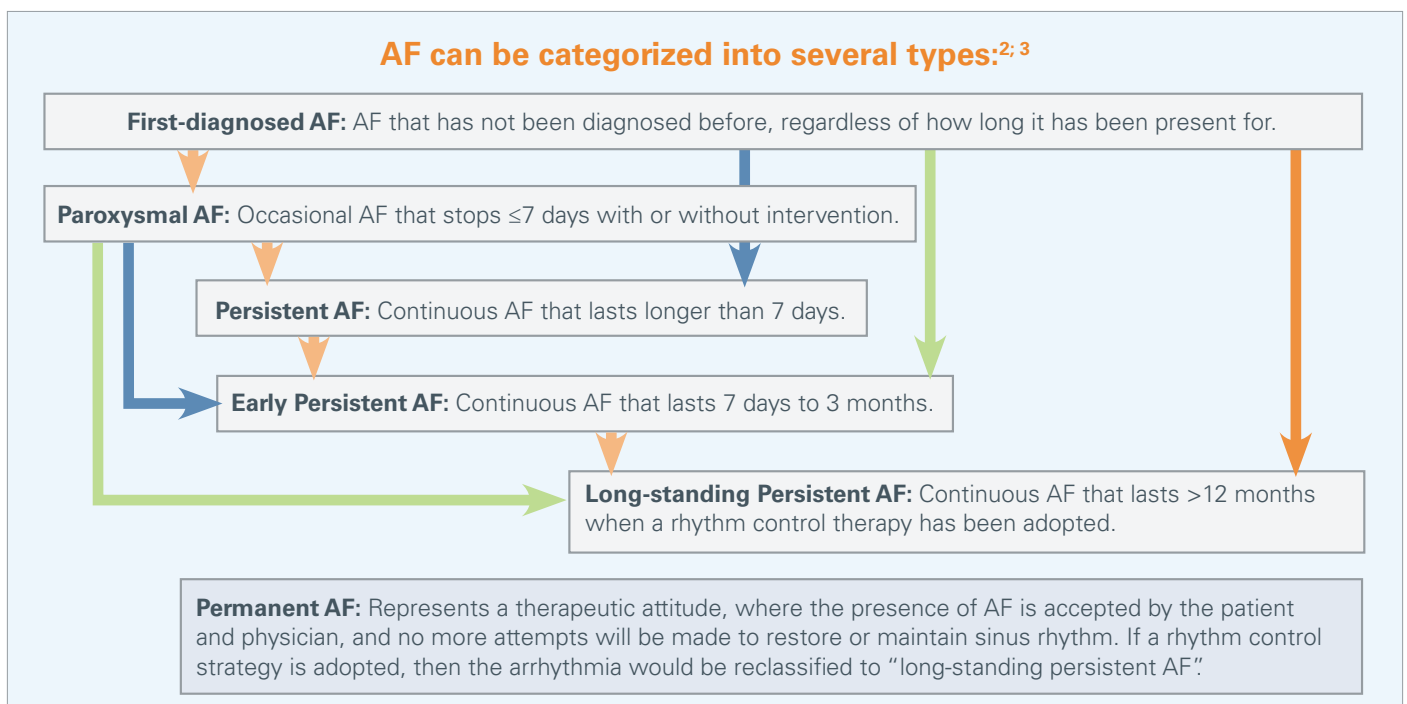


<b>OVERVIEW .....</b>	<b>3</b>
What is Atrial Fibrillation and why is it important .....	3
<b>MANAGEMENT OF AF PATIENTS.....</b>	<b>7</b>
What is the goal of AF management? .....	7
How is the patient with AF treated? .....	8
What are the recommendations for managing a patient with AF? .....	10
<b>DRUG THERAPY .....</b>	<b>15</b>
How to choose an AAD for managing AF? .....	15
What is the clinical impact of AAD therapy? .....	16
What is the patient impact of AAD therapy? .....	18
What is the economic impact of AAD therapy? .....	20
<b>CATHETER ABLATION .....</b>	<b>22</b>
How is catheter ablation used in the management of AF? .....	22
What is the clinical impact of catheter ablation? .....	22
What is the patient impact of catheter ablation? .....	26
What is the economic impact of catheter ablation? .....	28
<b>COMPARISON OF TREATMENTS.....</b>	<b>31</b>
What is the impact of catheter ablation compared to drug therapy in managing AF? .....	31
What is the clinical impact of catheter ablation as compared to AADs? .....	32
What is the impact of catheter ablation on patients as compared to AAD treatment? .....	36
What is the economic impact of catheter ablation compared to AAD therapy? ...	38
<b>CONCLUSION .....</b>	<b>40</b>
<b>REFERENCES .....</b>	<b>44</b>

The management of atrial fibrillation focuses on effectively and safely controlling the irregular heart rhythm, improving symptoms, and reducing key complications based on shared decision-making between healthcare professionals and patients.

## WHAT IS ATRIAL FIBRILLATION AND WHY IS IT IMPORTANT?

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 (ie, atria).<sup>1</sup>



■ Risk factors for AF include:



### LIFESTYLE FACTORS

Obesity<sup>4-7</sup>, smoking<sup>3</sup>, alcohol consumption<sup>3, 7-8</sup>



### OTHER CONDITIONS

High blood pressure<sup>7</sup>, heart failure<sup>9-14</sup>, history of heart attack<sup>9,15</sup>, coronary artery or other heart disease<sup>5,9</sup>



### NON-MODIFIABLE FACTORS

Older age<sup>3,16</sup>, family history or other genetic factors<sup>9, 17-18</sup>, male sex<sup>3, 9, 16</sup>

Early detection and diagnosis of AF may help improve patient outcomes, since a long history and duration of AF have been associated with recurrence.<sup>19-22</sup>



**15%-30%**

OF PATIENTS EXPERIENCE  
**NO SYMPTOMS** (i.e. silent AF)<sup>23</sup>



**1 in 5**  
PATIENTS PROGRESS  
**IN 1 YEAR**<sup>24-27</sup>



PAROXYSMAL  
AF

PERSISTENT  
AF

Patients with AF have an increased risk for life-threatening complications and other diseases:<sup>28</sup>

**5x**

Increase heart  
failure



**2.4x**

Increase stroke



**2x**

Increase cardiovascular  
mortality



- AF worsens quality of life for patients and caregivers.<sup>29-34</sup>
- AF increasingly places **a critical financial burden** on the healthcare system, costing **€660-€3,286 million annually across European countries**.<sup>35-39</sup>

The 2020 (ESC)/ (EACTS) guidelines on the management of AF and the 2017(HRS)/ (EHRA)/(ECAS)/ (APHRS)/ (SOLAECE) expert consensus statement on catheter and surgical ablation of AF recommend an integrated management strategy to reduce mortality, tailor management to patient preferences, and reduce hospitalizations.

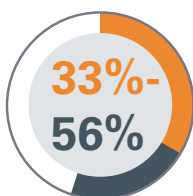
The ABC pathway for integrated AF patient management includes:<sup>3</sup>

- A** – Anticoagulation/Avoid stroke
- B** – Better symptom control
- C** – Comorbidities/Cardiovascular risk factor management

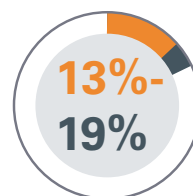
- Education and screening programs aimed at **increasing awareness and diagnosis of AF are critical to reducing the risk of stroke and death** in patients with undiagnosed AF.<sup>40, 41</sup>
  - Ideally, patients will recognize AF symptoms and contact their clinicians when symptoms arise.<sup>42</sup>
- **Early treatment of AF is important**, as it may improve patient life expectancy and quality of life.<sup>92, 93</sup>

Antiarrhythmic drug (AAD) therapy is moderately effective. It is commonly associated with treatment withdrawals, however, it has been shown to improve quality of life, and is affordable in the short term.

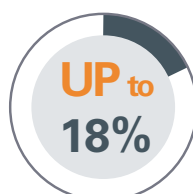
With drug therapy treatment:



of patients are in  
**NORMAL SINUS  
RHYTHM  
AT 1 YEAR<sup>43</sup>**



of patients  
**WITHDRAW FROM  
TREATMENT DUE TO  
ADVERSE EVENTS<sup>43</sup>**



of patients  
**UP to  
18%  
IMPROVEMENT  
IN QUALITY OF  
LIFE<sup>44</sup>**

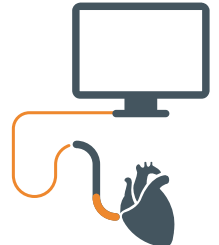
Catheter ablation is highly effective, associated with a low rate of ablation-related adverse events, and has been shown to reduce the rate of AF-related complications. It has also been shown to improve quality of life, and reduce resource utilization.

With catheter ablation treatment:



**94%**  
of patients are **FREE FROM ARRHYTHMIA RECURRENCE**  
**AT 1 YEAR**<sup>45-54</sup>

**1.8%** of patients experience  
**AN ABLATION-RELATED ADVERSE EVENT**<sup>55</sup>



**IMPROVEMENT IN QUALITY OF LIFE**<sup>56</sup>



Catheter ablation is more effective than drug therapy, has a low chance of AF-related complications, has significantly greater improvement in quality of life, and is less costly over the long term:



more patients  
**FREE FROM ATRIAL ARRHYTHMIA**  
over **4 years** after  
ablation<sup>55</sup>



**PAROXYSMAL AF**



**PERSISTENT AF**



Patients with **paroxysmal AF** are almost **10 TIMES LESS LIKELY TO PROGRESS TO PERSISTENT AF** than **those on AADs**<sup>\*59</sup>

Similarly  
**LOW**

**RATES OF AF-RELATED COMPLICATIONS**<sup>55, 57-58</sup>



Death



Stroke



Cardiac arrest



Cardiovascular hospitalization

\*(HR 0.11; 95% CI 0.025-0.483; p=0.0034.)

## ■ MANAGEMENT OF AF PATIENTS

Therapeutic goals of the ABC pathway for integrated care of patients with AF are to reduce the risk of stroke, reduce symptoms of AF, and manage cardiovascular risk factors and comorbidities.<sup>3</sup>

### WHAT IS THE GOAL OF AF MANAGEMENT?

- AF is associated with an **increased risk of stroke** compared to patients in sinus rhythm.<sup>11</sup>
- The presence of cardiovascular risk factors **significantly impact the lifetime risk** of developing AF.<sup>3</sup>
- The ABC pathway has been shown **to significantly lower the risk** of all-cause death, composite outcome of stroke/major bleeding/cardiovascular death and first hospitalization, rates of cardiovascular events, and health-related costs than usual care.<sup>3</sup>

### TREAT AF: THE ABC PATHWAY

The Atrial fibrillation Better Care (ABC) pathway streamlines integrated care for patients with AF and involves **anticoagulation/avoidance of stroke (A), better symptom management (B), and cardiovascular and comorbidity optimization (C).**



**NEW**  
ESC 2020<sup>3</sup>



## HOW IS THE PATIENT WITH AF TREATED?

AF patient care pathway management includes rhythm control therapy to restore sinus rhythm during an episode of AF and rate and rhythm control therapies in over the long-term.

Current treatment options recommended for managing AF include:

### RATE CONTROL THERAPIES



#### PHARMACOLOGICAL

Beta blockers or non-dihydropyridine calcium channel antagonists, digitalis glycosides, or amiodarone



#### SURGICAL

AV node ablation with pacemaker implantation

### RHYTHM CONTROL THERAPIES

#### RHYTHM CONTROL THERAPIES FOR AN EPISODE OF AF

Electrical and pharmacological cardioversion

#### LONG-TERM RHYTHM CONTROL THERAPIES



#### PHARMACOLOGICAL



#### CATHETER ABLATION



#### SURGICAL



## ■ MANAGEMENT OF AF PATIENTS

Several therapies previously used to treat AF are **no longer recommended** or are only recommended for use in select patient populations:<sup>3</sup>



IMPLANTABLE CARDIOVERTER **DEFIBRILLATORS** (ICDS) **ARE NOT** indicated for rhythm control of AF

**NEW**  
ESC 2020<sup>3</sup>



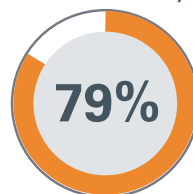
**PACEMAKERS** are **CONSIDERED** for use in patients with AF-related bradycardia, symptomatic pre-automaticity pause after AF conversion, atrioventricular conduction abnormalities and/or sinus node dysfunction

- Electrical and pharmacological cardioversion is recommended in patients experiencing an episode of AF, and the type of cardioversion chosen is dependent on **haemodynamic stability, presence and type of structural heart disease, management of stroke risk, and patient choice**.<sup>3</sup>

### **RATE CONTROL THERAPIES**

are effective at lowering and controlling heart rate in patients with AF,

with as many as



of patients in the target heart rate range of **60-100 BEATS PER MINUTES**.<sup>60</sup>

### **OVER THE LONG-TERM:**

#### **RHYTHM CONTROL THERAPIES**

that include AADs and catheter ablation are

the most common methods for **CONTROLLING AF**, effectively preventing recurrence in



as many as **94%** of patients **OVER 1-YEAR** <sup>3, 45-50</sup>

Guidance on the delivery of good care to patients with AF are available from the 2020 ESC/EACTS guidelines and 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement.

## WHAT ARE THE RECOMMENDATIONS FOR MANAGING A PATIENT WITH AF?

The 2020 ESC/EACTS Guidelines recommend a structured approach to the diagnosis, characterization, and treatment of AF, known as the Confirm and Characterise To Atrial fibrillation Better Care (CCTo ABC) pathway.<sup>3</sup>

### CCTO ABC

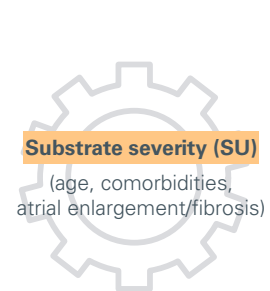
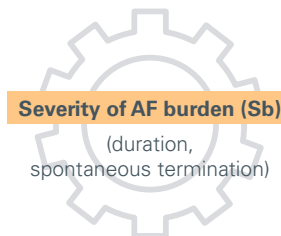
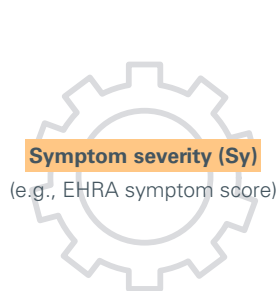
#### Confirm AF

**NEW**  
ESC 2020<sup>3</sup>



A 12-lead ECG or a rhythm strip showing AF pattern for ≥ 30s.

#### Characterise AF (the 4S-AF scheme)



#### Treat AF: The ABC pathway



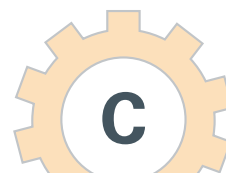
Anticoagulation/  
Avoid stroke

1. Identify low risk patients CHA<sub>2</sub>DS<sub>2</sub>-VASc 0(m), 1(f)
2. Offer stroke prevention if CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥ 1(m), 2(f)  
Assess bleeding risk, address modifiable bleeding risk factors
3. Choose OAC (NOAC or VKA with well-managed TTR)



Better symptom  
control

Assess symptoms, QoL and patient's preferences  
Optimize rate control  
Consider a rhythm control strategy (CV, AADs, ablation)



Comorbidities/  
Cardiovascular risk factor  
management

Comorbidities and cardiovascular risk factors  
Lifestyle changes (obesity reduction, regular exercise, reduction of alcohol use, etc.)

# ■ MANAGEMENT OF AF PATIENTS

## 1 Integrated Management of AF & Collaborative Decision Making

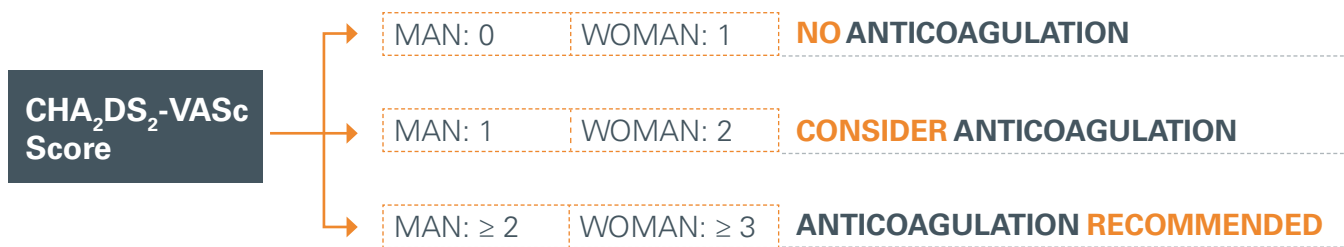
**NEW**  
ESC 2020<sup>3</sup>

Following the diagnosis of AF, guidelines recommend an integrated and structured approach to patient care and AF management that involves multidisciplinary teams of cardiologists and electrophysiologists, non-specialist healthcare professionals, and allied health professionals, and places patients and their carers in a central role in decision-making.<sup>3</sup>

**Physicians are recommended to optimize shared decision making about specific AF treatment option(s) in consideration by:<sup>3</sup>**

- Informing patient about advantages/ limitations and benefits/risks associated with options being considered
- Discussing potential burden of treatment with patient and include patient's perspective of treatment burden in the treatment decision

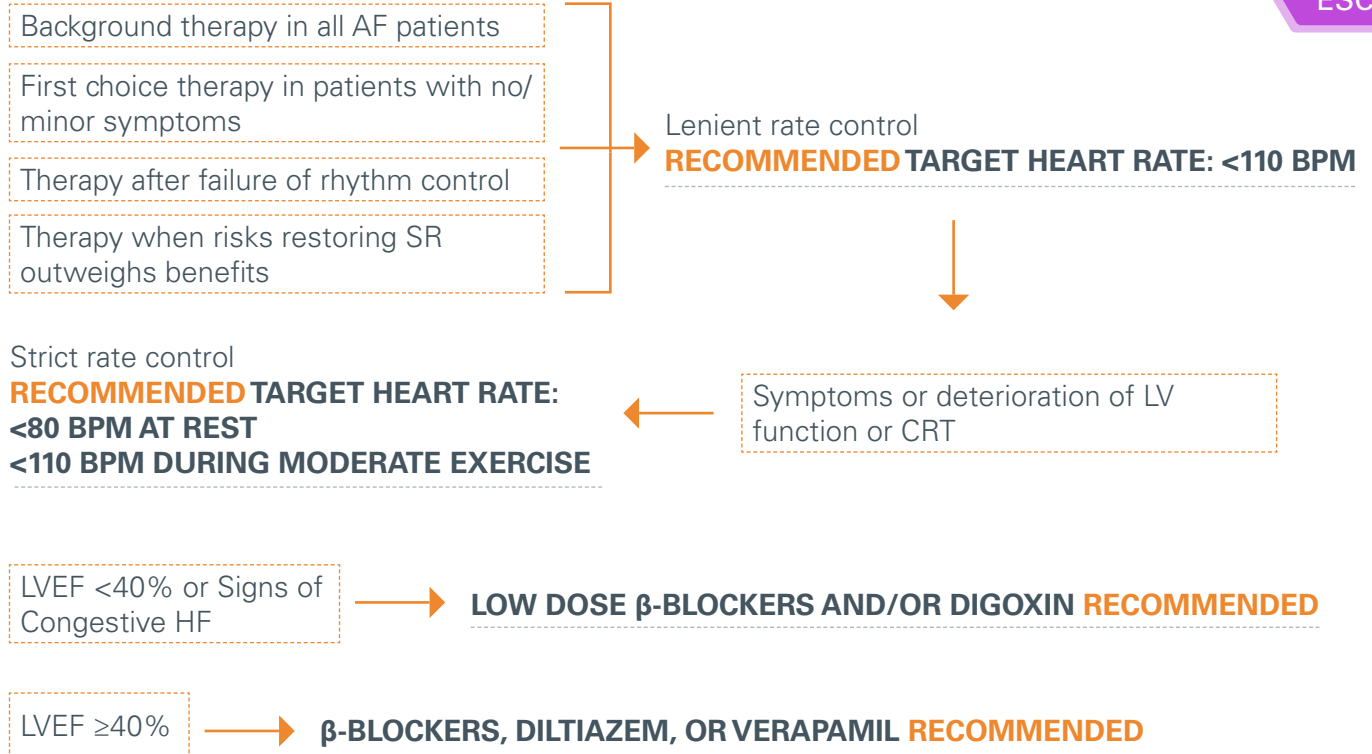
## 2 Oral Anticoagulation Therapy for Stroke Prevention in Patients with AF<sup>3</sup>



## ■ MANAGEMENT OF AF PATIENTS

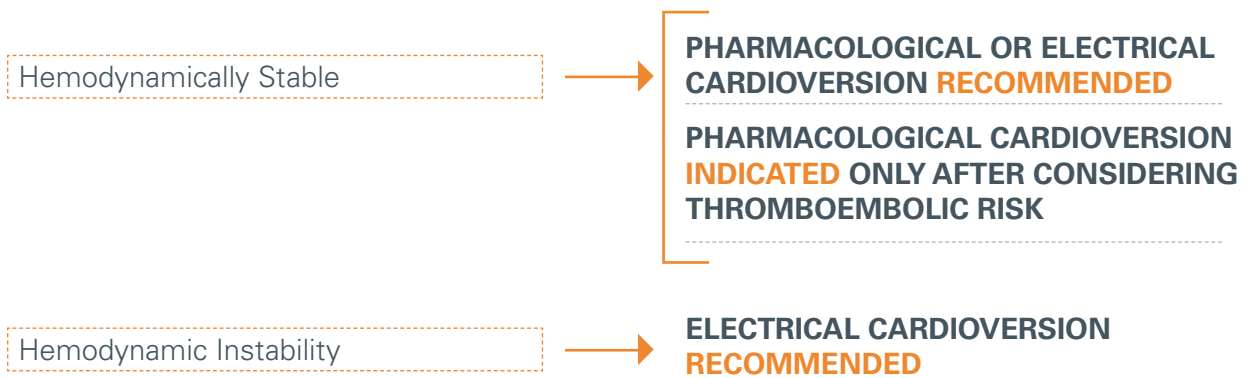
### 3 Rate Control Therapy to Lower and Control Heart Rate and Improve Symptoms of AF<sup>3</sup>

**NEW**  
ESC 2020<sup>3</sup>



### 4 Acute Rhythm Control Therapy to Restore Normal Sinus Rhythm<sup>3</sup>

**NEW**  
ESC 2020<sup>3</sup>

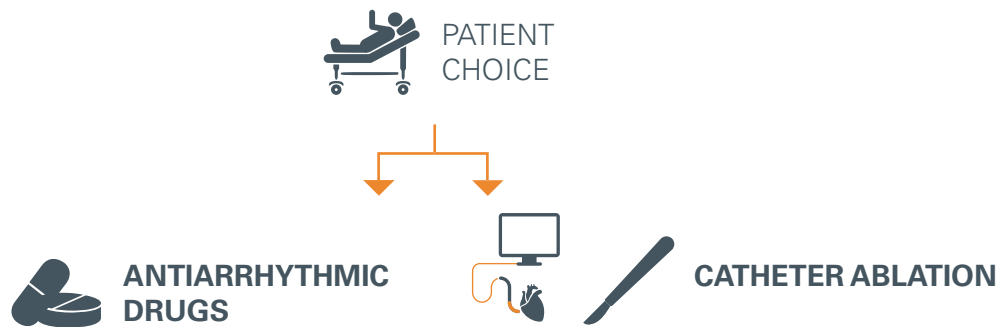


## ■ MANAGEMENT OF AF PATIENTS

### 5 Rhythm Control Therapy for Reducing AF-related Symptoms and Improving Quality of Life<sup>3</sup>

**NEW**  
ESC 2020<sup>3</sup>

- Guidelines recommend that decision to treat with AADs, catheter ablation, and/or surgical ablation include patient choice.<sup>2,3</sup>
- The choice of AADs needs to consider the presence of comorbidities, cardiovascular risk, potential for proarrhythmia, toxic effects, symptom burden, and patient preference.<sup>2</sup>



**NEW**  
ESC 2020<sup>3</sup>

#### Symptomatic AF

Paroxysmal

Persistent without  
recurrence risk factors

Persistent with  
recurrence risk factors

**First line therapy**  
(Before AADs - Class I  
or III)

**CONSIDER CATHETER ABLATION\***

**Refractory/intolerant**  
to  $\geq 1$  AADs  
(Class I or III)

**CATHETER ABLATION RECOMMENDED**

**Refractory/intolerant**  
to  $\geq 1$   $\beta$ -blocker

**CONSIDER CATHETER ABLATION**

\*In rare individual circumstances, catheter ablation may be carefully considered as first-line therapy for persistent with recurrent risk factors

## Special populations

All AF - First-line

LV dysfunction when  
tachycardia-induced  
cardiomyopathy is  
highly probable

**CATHETER ABLATION RECOMMENDED**

HF with reduced LVEF

**CONSIDER CATHETER ABLATION**

## Surgical ablation of AF

**CONSIDER CONCOMITANT AF ABLATION IN PATIENTS UNDERGOING CARDIAC SURGERY, BALANCING THE BENEFITS OF FREEDOM FROM ATRIAL ARRHYTHMIAS AND THE RISK FACTORS FOR RECURRENCE (LEFT ATRIAL DILATATION, YEARS IN AF, AGE, RENAL DYSFUNCTION, AND OTHER CV RISK FACTORS).**

## AF recurrence after catheter ablation

**CONSIDER SHORT-TERM AAD THERAPY TO PREVENT EARLY RECURRENCE AFTER CATHETER ABLATION**

**CONSIDER CATHETER ABLATION WHEN FIRST CATHETER ABLATION IMPROVED SYMPTOMS**

Implementation of guideline recommendations for the management of individual patients with AF is **needed to improve patient outcomes and reduced healthcare costs**; however, **adherence to guidelines is modest worldwide**.<sup>3</sup>

Abbreviations: AAD = antiarrhythmic drug; AF = atrial fibrillation; AVR = aortic valve replacement; CABG = coronary artery bypass graft; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); HF = heart failure; LVEF = left ventricular ejection fraction.

Source: 2020 ESC Guidelines<sup>3</sup>, and 2017 HRS/EHRA Consensus Statement<sup>2</sup>

## Antiarrhythmic drug therapy is an integral part of maintaining sinus rhythm after cardioversion<sup>2</sup>

### HOW TO CHOOSE AN AAD FOR MANAGING AF?

Antiarrhythmic drugs act to suppress the firing of or depress the transmission of abnormal electrical signals.

#### AADs Available for Rhythm Control

CLASS	DRUGS
<b>Class I: Sodium Channel Blockers</b> IA AC	Disopyramide, <b>Flecainide, Propafenone</b>
<b>Class III: Potassium Channel Blockers</b>	<b>Amiodarone, Dronedarone,</b> Sotalol

- Principles of AAD therapy:<sup>3</sup>
  - AAD therapy aims to reduce AF-related symptoms
  - Efficacy of AADs to maintain sinus rhythm is modest
  - Clinically successful AADs therapy may reduce rather than eliminate AF recurrences
  - If one AAD “fails”, a clinically acceptable response may be achieved by another drug
  - Drug-induced proarrhythmia or extracardiac side-effects are frequent
  - Safety rather than efficacy consideration should primarily guide the choice of AAD
- Choice of AAD is primarily guided by safety considerations, namely the risk of proarrhythmia and organ toxicity:<sup>3</sup>

**As patients are ultimately responsible for taking their medication, placing patients in a central role in the decision-making process is recommended to improve patient compliance and reduce the risk of the clinical consequences of AF.<sup>3</sup>**

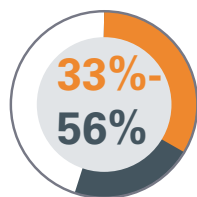
NB: Bolded AADs represent those with Class IA recommendations for preventing recurrent symptomatic patients with AF per the 2020 ESC Guidelines.<sup>3</sup>  
 Abbreviations: AAD = antiarrhythmic drugs, AE = adverse event  
 Source: Valembois et al. (2019)



## WHAT IS THE CLINICAL IMPACT OF AAD THERAPY?

Antiarrhythmic drug therapy is fairly safe and moderately effective at maintaining normal sinus rhythm; its impact on consequences such as stroke, heart failure and mortality have been demonstrated in a limited number of studies.

**AAD THERAPY  
IS MODERATELY  
EFFECTIVE:**



rate for **maintaining normal sinus rhythm** at 1 year.<sup>43</sup>

**48%** of patients with AF are not well managed on AADs.<sup>62</sup>

- Recurrence of AF can be asymptomatic and symptomatic.<sup>61</sup>
- Reported event rates for stroke, heart failure, and mortality are **low** depending on the AAD and the potential **benefits** of AADs in reducing these events **have yet to be established**.<sup>3, 43, 63</sup>

**1%-2%**



**STROKE**

**1%-3%**



**HEART FAILURE**

**0%-5.1%**



**MORTALITY**

- The toxicity profile of AADs is varied with adverse events leading to **treatment discontinuation in 13%-19% of patients**.<sup>43</sup>

## COMMON ADVERSE EVENTS


### CLASS IA




Urinary  
retention



Diarrhea



Dry mouth



Nausea/  
vomiting

**19%** TREATMENT WITHDRAWALS DUE TO AES (%)


### CLASS IC




Congestive  
heart failure



Dizziness



Nausea/  
vomiting




Visual  
disturbances

**13%** TREATMENT WITHDRAWALS DUE TO AES (%)

### CLASS III




Dyspnea



Diarrhea



Headache



Nausea/  
vomiting

**13%** TREATMENT WITHDRAWALS DUE TO AES (%)

## WHAT IS THE PATIENT IMPACT OF AAD THERAPY?

**Antiarrhythmic drug therapy is effective at controlling symptoms of AF and significantly improves patient quality of life.**

■ Symptoms and quality of life of AF patients on AADs were measured using:

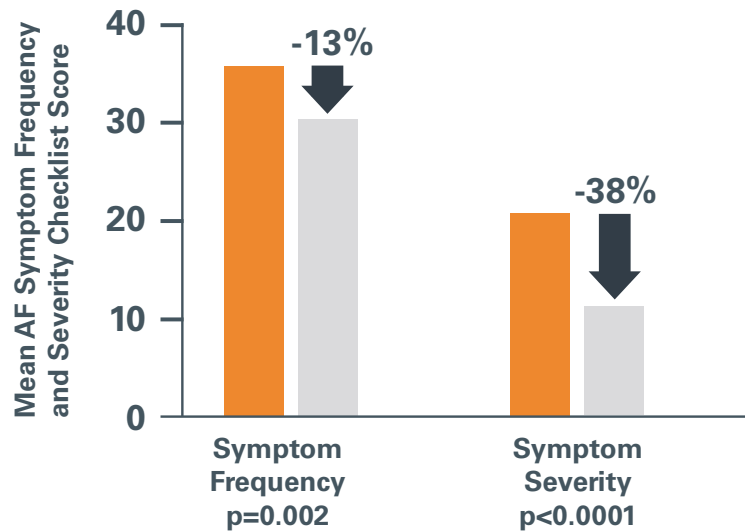
	AF SYMPTOM FREQUENCY AND SEVERITY CHECKLIST	SF-36
<b>OUTCOMES MEASURED</b>	AF-related symptom frequency and severity	QoL
<b>ITEMS/ SUBSCALES</b>	16 items	8 subscales, including physical, mental, and general health
<b>SCORE RANGE</b>	Symptom frequency: 0-64 Symptom severity: 0-48	0-100
<b>SCORE INTERPRETATION</b>	Lower scores indicate reduced symptom frequency and severity	Higher scores represent better QoL
<b>CLINICALLY MEANINGFUL DIFFERENCE</b>	Not demonstrated	≥5 points



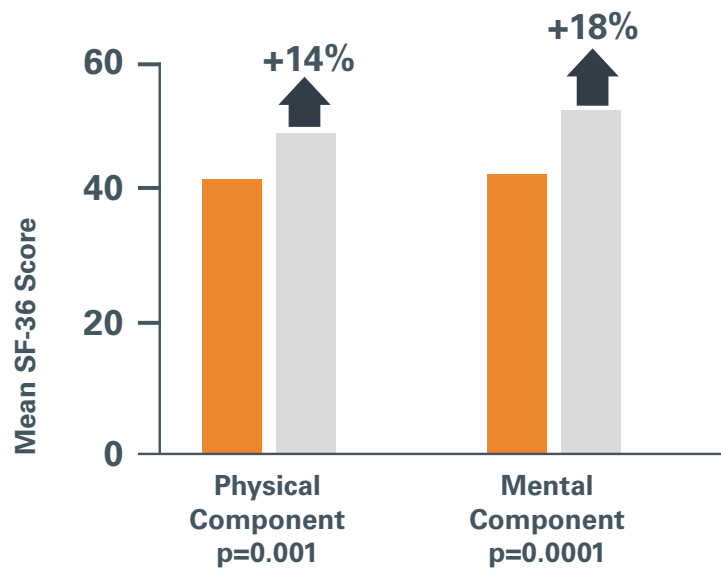
**IMPROVEMENT  
IN QUALITY OF LIFE  
WITH AAD THERAPY <sup>44</sup>**



## REDUCED SYMPTOMS WITH AAD THERAPY <sup>44</sup>



## IMPROVED QUALITY OF LIFE WITH AAD THERAPY <sup>44</sup>



■ Before AAD Initiation

■ 1 Year After AAD Initiation

## WHAT IS THE ECONOMIC IMPACT OF AAD THERAPY?

**Antiarrhythmic drug therapy is cost effective and affordable in the short term, but can be costly over the long term.**

- Several studies show that AADs are cost effective, with key drivers including **reduced adverse events, stroke, and mortality.**<sup>65-67</sup>

Initial cost of AAD treatment is **LOW**

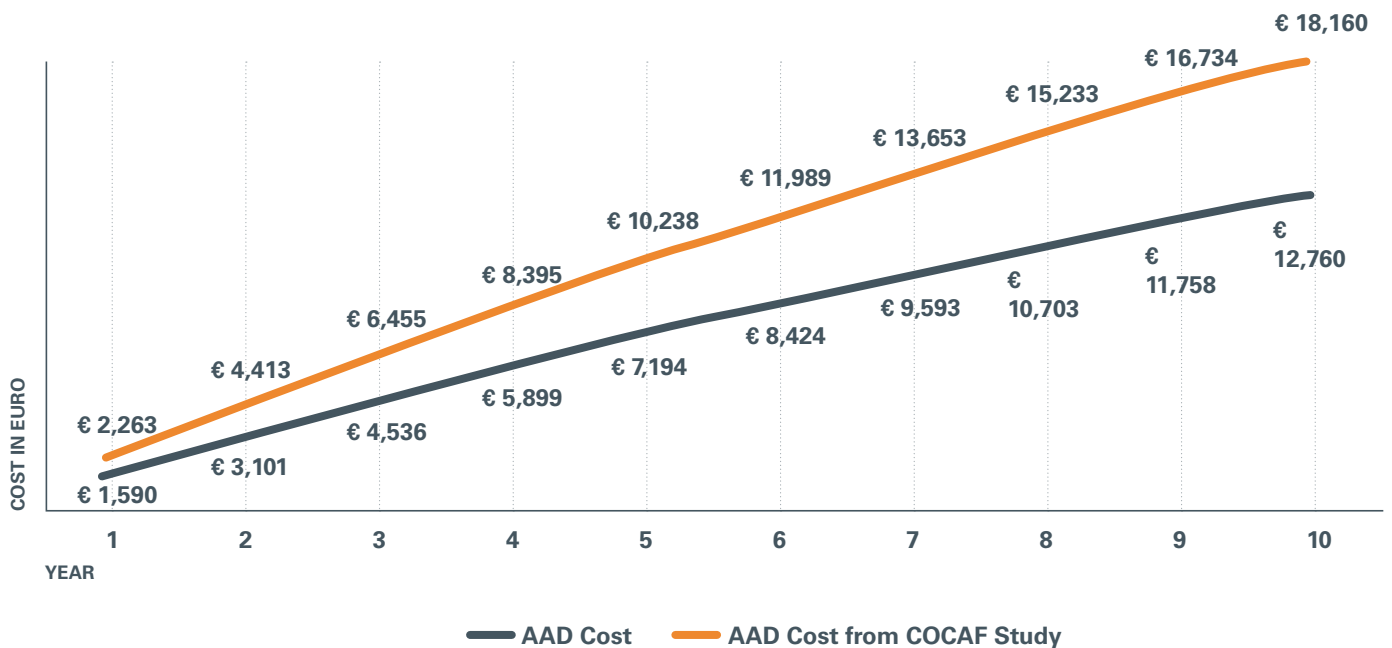


however

**LENGTH** of treatment is **INDEFINITE** and the **cumulative cost** of AADs

**INCREASES 28% ANNUALLY** over 9 years<sup>\*68</sup>

**CUMULATIVE COST OF AADS OVER 10 YEARS IN PAROXYSMAL AF UNSUCCESSFULLY TREATED WITH 2 AADS**

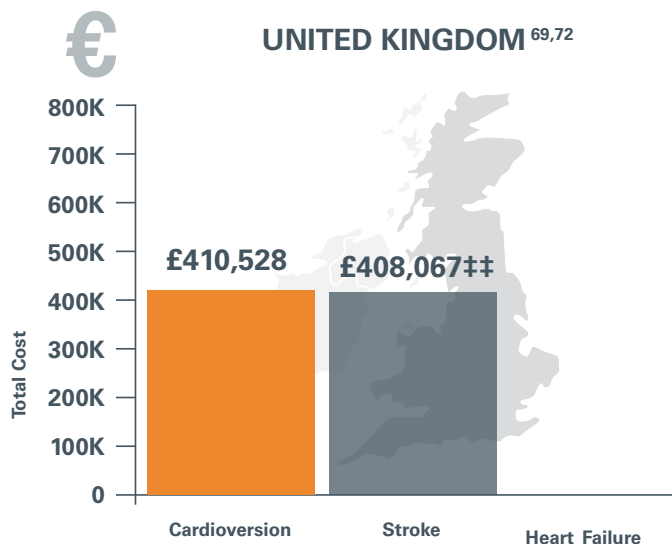
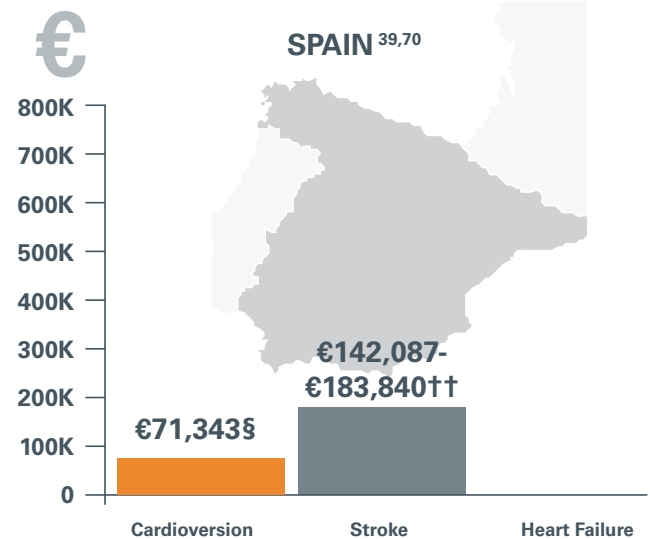
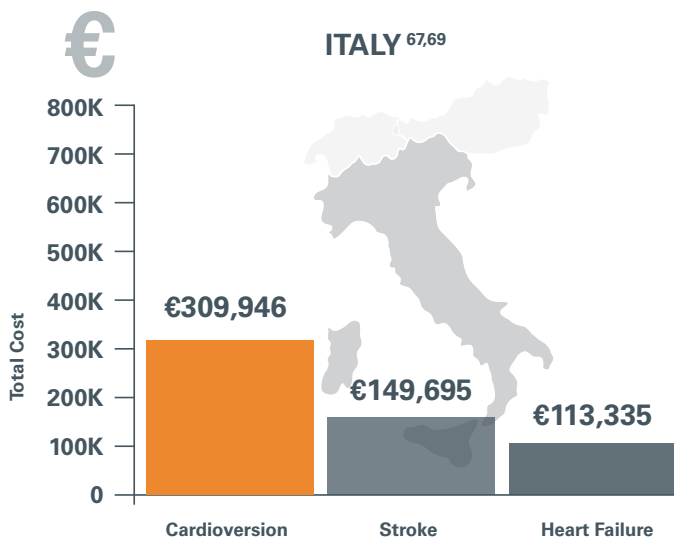
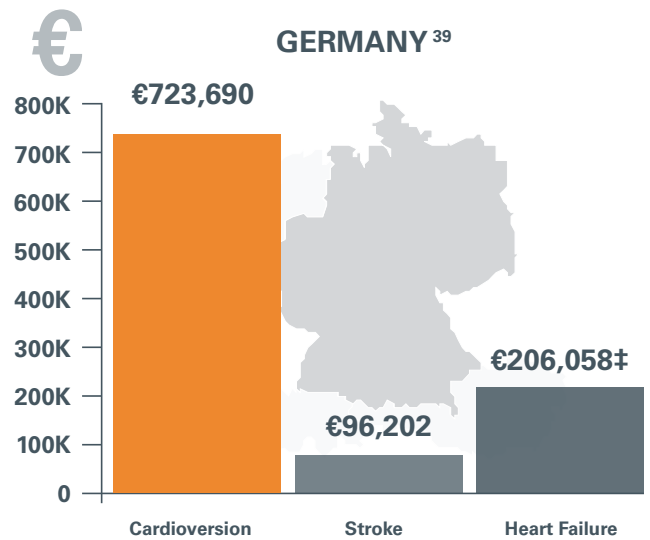
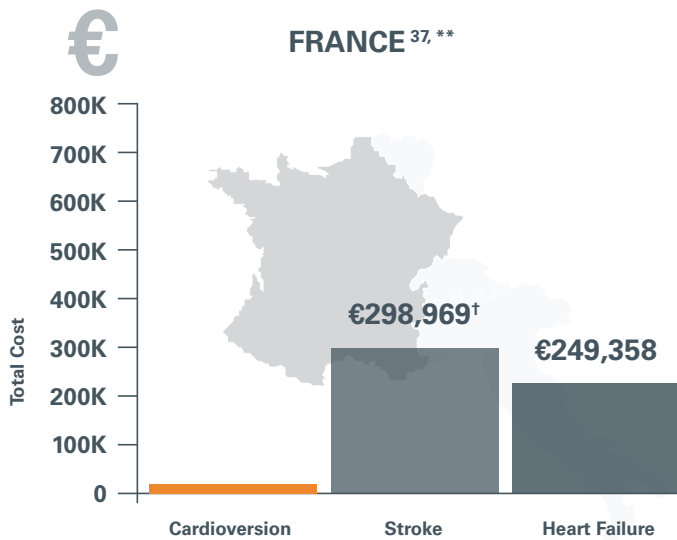


- Cost of AAD therapy is influenced by its **toxicity level** and **effectiveness in restoring sinus rhythm** and **reducing the risk of AF-related consequences.**<sup>35,37,39,67,69-71</sup>

\*From one study performed in France; data were limited for other European countries.

Abbreviations: AAD = antiarrhythmic drug; AF = atrial fibrillation; COCAF = Cost of Care in Atrial Fibrillation  
Source: adapted from Weerasooriya et al. (2003)

## POTENTIAL TREATMENT COSTS\* FOR PATIENTS WITH AAD THERAPY



\* Costs are estimates for 1000 patients, based on efficacy and event rates for AADs reported earlier and unit costs reported in the literature. Unit costs were inflated to 2019 Euros<sup>61</sup>;  
 \*\* Based on mean per patient per event costs in AF patients;  
 † Cost reported is a mean per patient per event of stroke, transient ischemic attack, and systemic embolism;  
 ‡ Assumes costs for hospital admissions for pacer implantation represents heart failure hospitalization;  
 § Electrical cardioversion only;  
 †† Includes fatal ischemic stroke, and mild, moderate, and severe ischemic stroke events;  
 ‡‡ Includes intracranial haemorrhage, haemorrhagic stroke, and ischaemic stroke.  
 Abbreviations: AAD = antiarrhythmic drug; AF = atrial fibrillation

**Catheter ablation is a well-established treatment for the prevention of AF recurrence that is used to create small scars on targeted parts of heart tissue that block the abnormal electrical signals causing the arrhythmia.<sup>2, 3</sup>**

### HOW IS CATHETER ABLATION USED IN THE MANAGEMENT OF AF?

**Catheter ablation is well-established for the prevention of AF recurrence and is indicated for the treatment of symptomatic paroxysmal and persistent AF in patients with or without major risk factors for AF recurrence.<sup>3</sup>**

Common ablation strategies include isolation of the pulmonary veins and the creation of specific lines of lesions within the left atrium.<sup>3</sup>

Upon deciding that rhythm control is required for long-term management of AF, it is important to discuss the efficacy and complication rates of AF catheter ablation and AADs with patients.<sup>3</sup>

### WHAT IS THE CLINICAL IMPACT OF CATHETER ABLATION?

**Catheter ablation is highly effective at maintaining sinus rhythm, is associated with a low rate of adverse events and reduced patient risk of AF-related complications, including stroke, dementia, heart failure, and mortality.**

Catheter ablation is effective in eligible patients with AF, with recent studies reporting high rates of freedom from atrial arrhythmias at one year after a single procedure with advanced catheter ablation technology:

#### FREEDOM FROM ATRIAL ARRHYTHMIAS AT ONE YEAR



UP TO  
**94%**

**PAROXYSMAL  
AF**<sup>45-50</sup>



UP TO  
**83%**

**PERSISTENT  
AF**<sup>45, 48, 51-54</sup>



Similarly, a single catheter ablation procedure effectively maintains sinus rhythm in eligible **patients with AF and heart failure and the elderly**:

### **PATIENT** with **AF AND HEART FAILURE**<sup>73-75</sup>



**37%-75%**

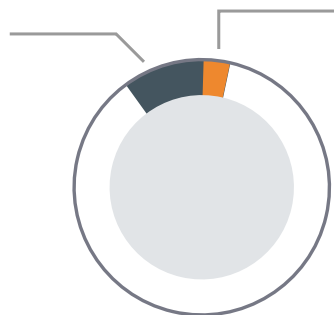
### **PATIENT** with **AF ≥75 YEARS** of age<sup>76</sup>








**78%**

■ Catheter ablation is associated with a low risk of adverse events:

**UP to 14%**  
of patients **MAY**  
**EXPERIENCE A**  
**COMPLICATION**<sup>3</sup>







**2%-3%**  
of patients **MAY EXPERIENCE**  
**POTENTIALLY LIFE-**  
**THREATENING**, but  
manageable, complications<sup>2, 3</sup>

	COMMON ADVERSE EVENTS <sup>3</sup>	INCIDENCE (%)
<b>LIFE-THREATENING COMPLICATION</b>	<ul style="list-style-type: none"> <li>■ Periprocedural death </li> <li>■ Esophageal perforation or fistula</li> <li>■ Periprocedural stroke* </li> <li>■ Cardiac tamponade</li> </ul>	≤1%
<b>SEVERE COMPLICATIONS</b>	<ul style="list-style-type: none"> <li>■ Pulmonary vein stenosis </li> <li>■ Persistent phrenic nerve palsy</li> <li>■ Vascular complications </li> </ul>	≤4%
	<b>OTHER MODERATE OR MINOR COMPLICATIONS</b>	1%-2%
<b>UNKNOWN SIGNIFICANCE</b>	<ul style="list-style-type: none"> <li>■ Asymptomatic cerebral embolism (silent stroke) </li> </ul>	5%-15%

The relative safety of catheter ablation was reaffirmed in the CABANA trial, which reported **0.8% incidence of cardiac tamponade** and **no incidence of atrial esophageal fistula** in over 1,000 patients.<sup>55</sup>

\*Includes transient ischemic attack or air embolism.  
Abbreviations: AE = adverse event  
Source: 2020 ESC Guidelines

**Incidence of AF-related consequences at 3-year follow-up in patients with AF who received catheter ablation compared to those without AF**

AF-RELATED EVENTS		CATHETER ABLATION (N = 4,212)	NO AF (N = 16,848)
	<b>MORTALITY</b>	<b>6%</b>	<b>9%</b>
	<b>STROKE</b>	<b>2%</b>	<b>2%</b>
	<b>ALZHEIMER'S DEMENTIA</b>	<b>0.2%</b>	<b>0.5%</b>
	<b>NON-ALZHEIMER'S DEMENTIA</b>	<b>0.4%</b>	<b>0.7%</b>

**The rates of mortality, stroke and dementia were similar in patients with AF that received ablation when compared to individuals without a history of AF.<sup>77</sup>**

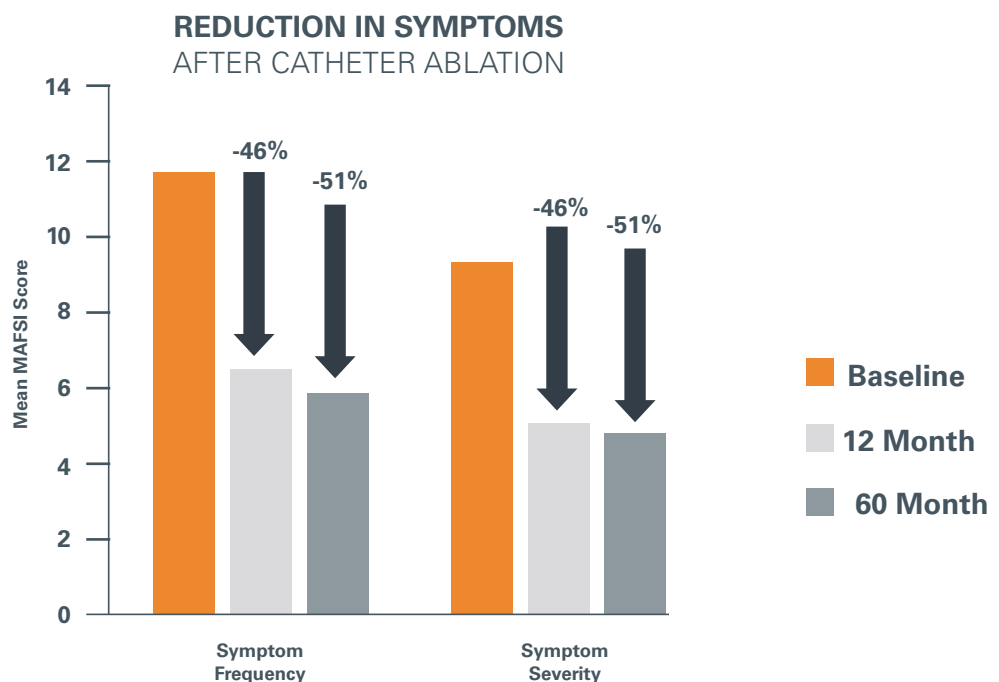
## WHAT IS THE PATIENT IMPACT OF CATHETER ABLATION?

Catheter ablation is highly effective at controlling symptoms of AF and significantly improves patient quality of life.

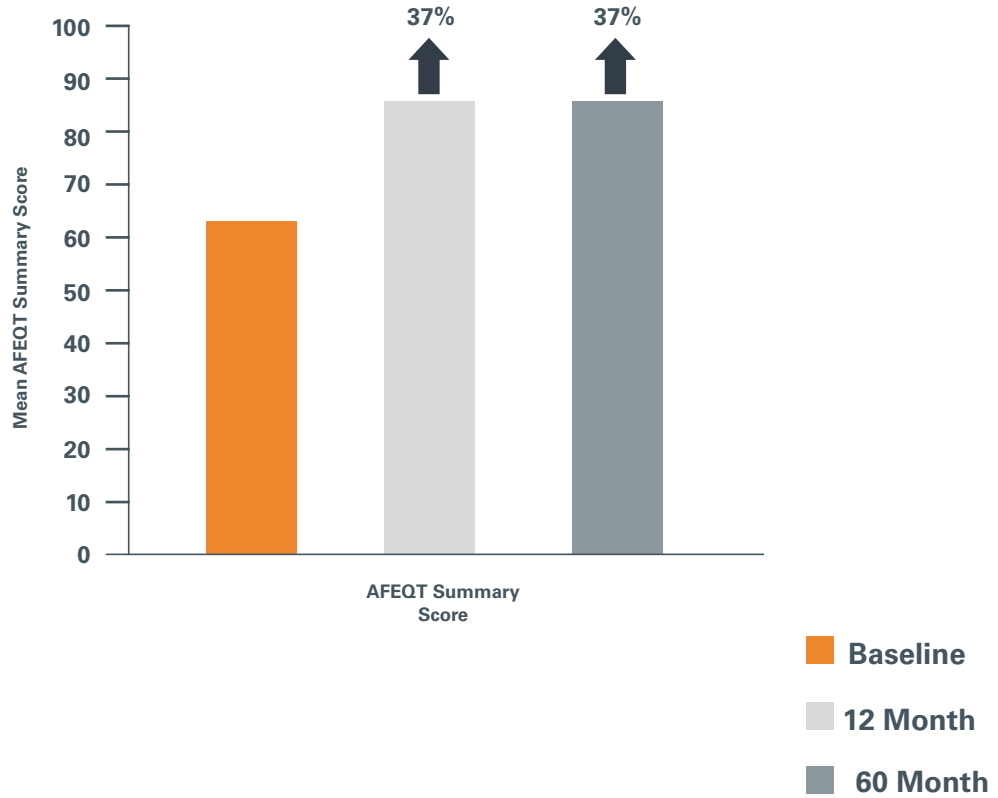
- **Reductions** in symptom severity and improvements in quality of life after catheter ablation of AF are **maintained over long-term follow-up**.<sup>56</sup>



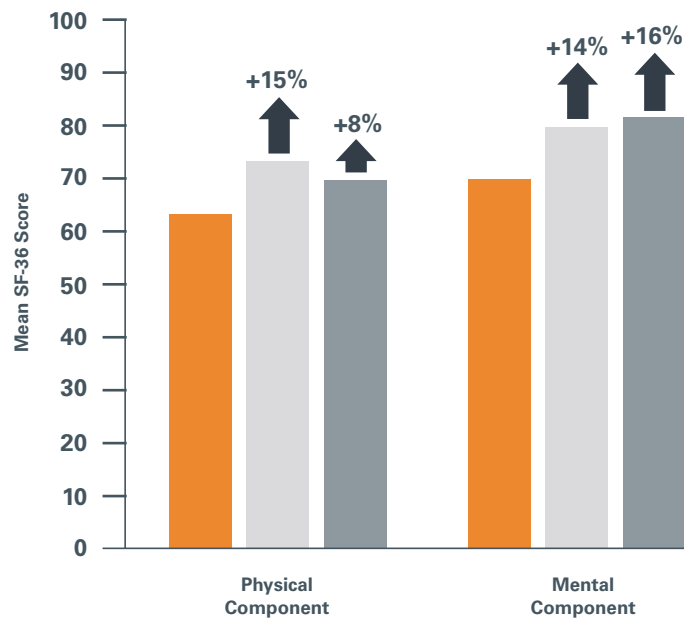
**IMPROVEMENT  
IN QUALITY OF LIFE<sup>56</sup>**



## IMPROVED QUALITY OF LIFE AFTER CATHETER ABLATION



## IMPROVED QUALITY OF LIFE AFTER CATHETER ABLATION



# WHAT IS THE ECONOMIC IMPACT OF CATHETER ABLATION?

Catheter ablation is cost effective; it reduces the need for unplanned medical visits, additional treatments to control AF, and subsequent treatment for long-term consequences of AF, turn, reducing overall healthcare cost.

Several studies show that  
**CATHETER ABLATION OF AF** is **COST EFFECTIVE**

when **BENEFITS ARE MAINTAINED**  
**OVER THE MEDIUM TO LONG-TERM** <sup>68,78-83</sup>

Key drivers include:



**IMPROVED** QUALITY OF LIFE

**REDUCED** COST OF FOLLOW-UP TREATMENT\*

**CATHETER ABLATION** reduces the need for **unplanned medical visits**

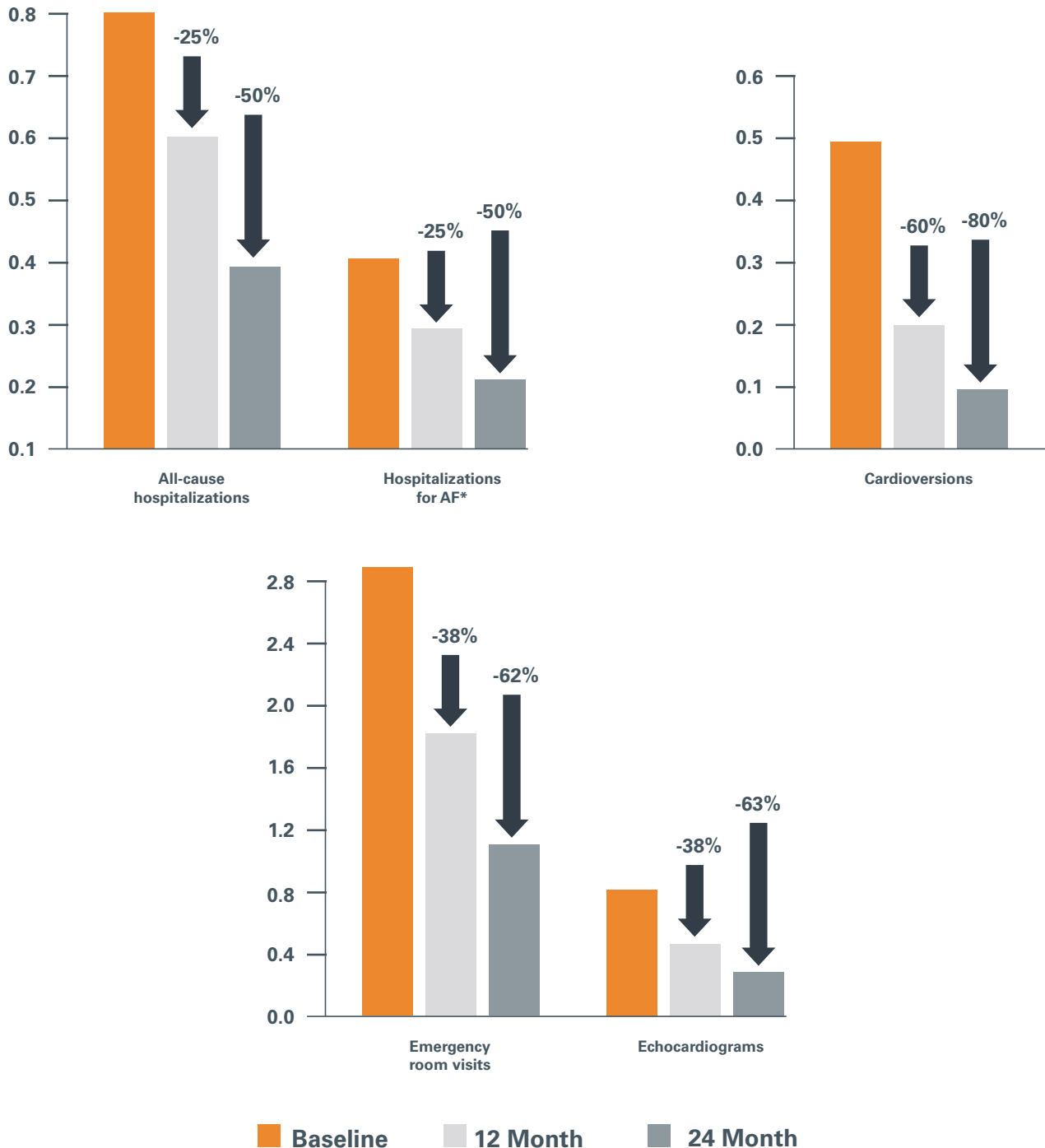
by up to  
**80%**

as compared to before ablation\* \*\*<sup>84</sup>

\*Cost of follow-up treatment included AADs, subsequent ablation for patients initially on AADs, or cardiac events.  
\*\*at 2 years based on evidence outside of Europe

Significant reductions in event rates 1 and 2 years after catheter ablation compared to 1 year before ablation (per patient per year) <sup>84</sup>

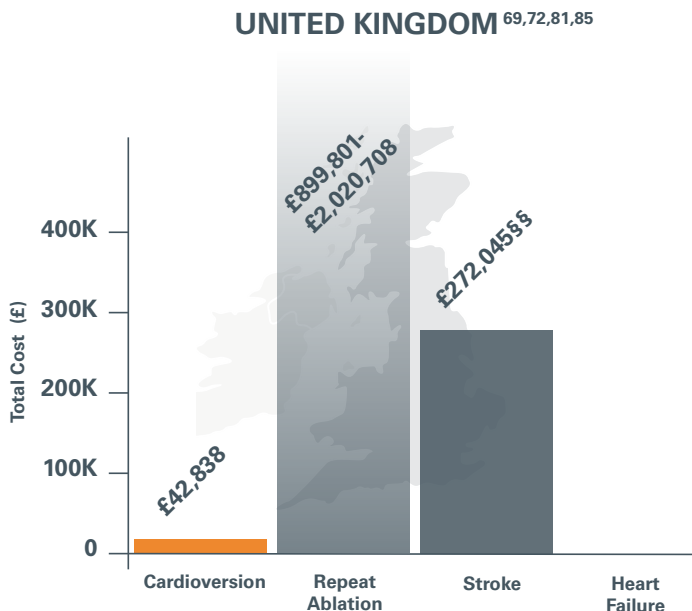
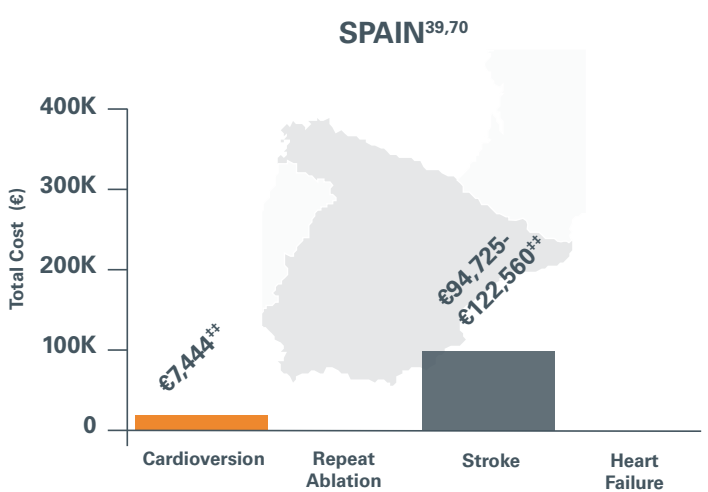
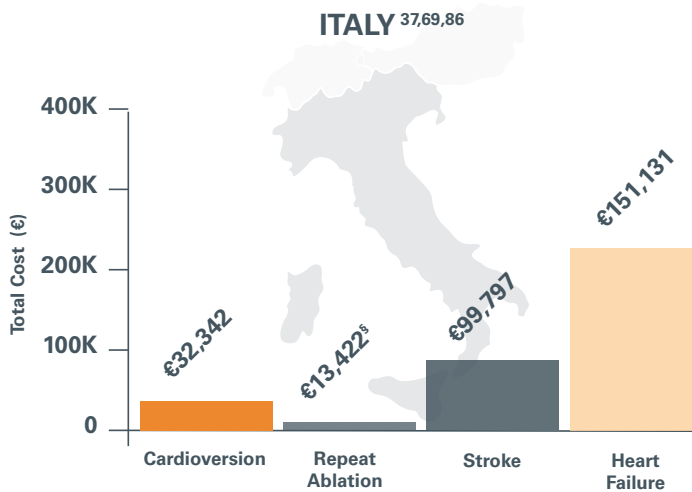
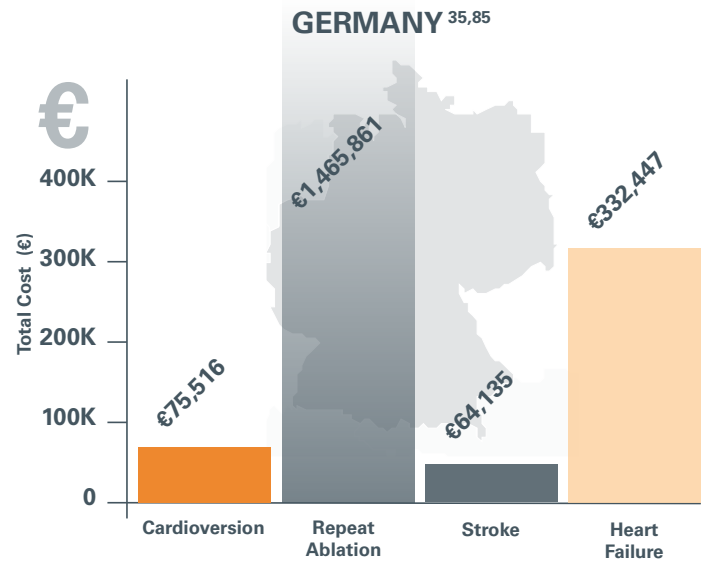
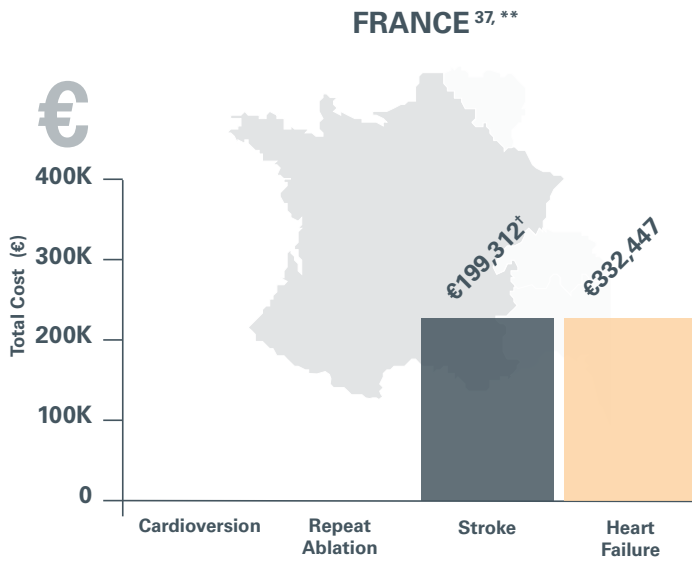
(REDUCED EVENT RATES AFTER CATHETER ABLATION)



Improved efficacy and reductions in unplanned medical visits after catheter ablation can lead to **reduced costs** for managing AF. <sup>67,84</sup>



## Potential Treatment Costs\* for Managing Patients with AF



\* Costs are estimates for 1000 patients, based on efficacy and event rates for AADs reported earlier and unit costs reported in the literature. Unit costs were inflated to 2019 Euros<sup>61</sup>;  
 \*\* Based on mean per patient per event costs in AF patients;  
 † Cost reported is a mean per patient per event of stroke, transient ischemic attack, and systemic embolism;  
 ‡ Assumes costs for hospital admissions for pacer implantation represents heart failure hospitalization; §Based on mean per patient per year costs in AF patients;  
 †† Electrical cardioversion only;  
 †† Includes fatal ischemic stroke, and mild, moderate, and severe ischemic stroke events;  
 §§ Includes intracranial haemorrhage, haemorrhagic stroke, and ischaemic stroke. Abbreviations: AF = atrial fibrillation

## ■ COMPARISON OF TREATMENTS

Recent studies have examined the comparative clinical and cost effectiveness of catheter ablation and drug therapy over long-term follow-up.

### WHAT IS THE IMPACT OF CATHETER ABLATION COMPARED TO DRUG THERAPY IN MANAGING AF?

Several studies have shown that catheter ablation is significantly more effective than AADs at preventing recurrence of atrial arrhythmias with a similar rate of complications.

Several studies have shown that **CATHETER ABLATION** is **SIGNIFICANTLY**



**MORE EFFECTIVE**



than **AADs** at **PREVENTING RECURRENCE** of atrial arrhythmias, with a similar rate of complications.

Economic evaluations have concluded that **CATHETER ABLATION IS**

**COST EFFECTIVE**



**6**   
**RECENT STUDIES**

including the landmark **CABANA** and **CASTLE-AF** trials, **COMPARING CATHETER ABLATION TO DRUG THERAPY** (including rate control therapy and AADs) have been published.

The following sections **summarize the latest comparative clinical and economic evidence** of catheter ablation and drug therapy in the treatment of patients with AF.

# WHAT IS THE CLINICAL IMPACT OF CATHETER ABLATION AS COMPARED TO AADS?

**Catheter ablation is more effective in preventing recurrence, complications, and progression of AF than drug therapy, with a similar rate of adverse events.**

The 2020 ESC Guideline state:<sup>3</sup>

- **Catheter ablation is a safe and superior alternative to AADs** for maintaining sinus rhythm and symptom improvement when performed by appropriately trained operators.
- **AADs are less effective** than AF catheter ablation, but previously ineffective AADs can be continued after ablation to reduce recurrence of AF.
- Key recent trials that compare the clinical efficacy of catheter ablation to drug therapy, including rate and rhythm control, are as follow:

STUDIES OR PUBLICATIONS	CABANA <sup>55</sup>	NOSEWORTHY ET AL. <sup>89</sup>	CASTLE-AF <sup>57</sup>	ATTEST <sup>59</sup>
REGION	Global	US	Global	Global
STUDY DESIGN	Multi-Centre RCT	Database* analysis	Multi-Centre RCT	Multi-Centre RCT
NUMBER OF PATIENTS	2,204	183,760	363	255
DISEASE STATE OF PATIENTS	Symptomatic AF	AF	AF & Heart Failure	Symptomatic paroxysmal AF
REQUIREMENT THAT PATIENT FAILED DRUG THERAPY	No	No	Yes	Yes
FOLLOW-UP DURATION	5 years	Up to 7 years	5 years	3 years

\*Records identified in the OptumLabs Data Warehouse database and were propensity-score weighted, 74% of patients were CABANA trial eligible, 4% did not meet the inclusion criteria, and 22% met at least one exclusion criteria.

Abbreviations: AF = atrial fibrillation; ATTEST = Atrial Fibrillation Progression Trial; CABANA = Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation; CASTLE-AF = Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; N = number; RCT = randomized controlled trial; US = United States

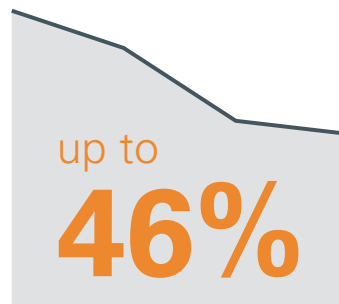
## ■ COMPARISON OF TREATMENTS

The **CABANA** trial found that **CATHETER ABLATION** was more **EFFECTIVE** at preventing recurrence of AF with



more patients  
**FREE FROM ATRIAL ARRHYTHMIA**  
over **4 years** compared to drug therapy<sup>55</sup>

**CATHETER ABLATION** was also associated with



**reduction** in the probability of **AF-RELATED complications\*\***



**Death**



**Stroke**



**Cardiac arrest**



**Cardiovascular  
hospitalization**

compared to drug therapy over 7-years follow-up.<sup>55,89</sup>

\* (hazard ratio [HR] 0.52; 95% confidence interval [CI] 0.45-0.60; p<0.001)

\*\* 46% cardiac arrest, 41% stroke, 33% death, 17% Cardiovascular hospitalization

## ■ COMPARISON OF TREATMENTS

In the **CASTLE-AF** trial:



**OF PATIENTS WITH HEART FAILURE AND AF WHO UNDERWENT CATHETER ABLATION MAINTAINED SINUS RHYTHM,**

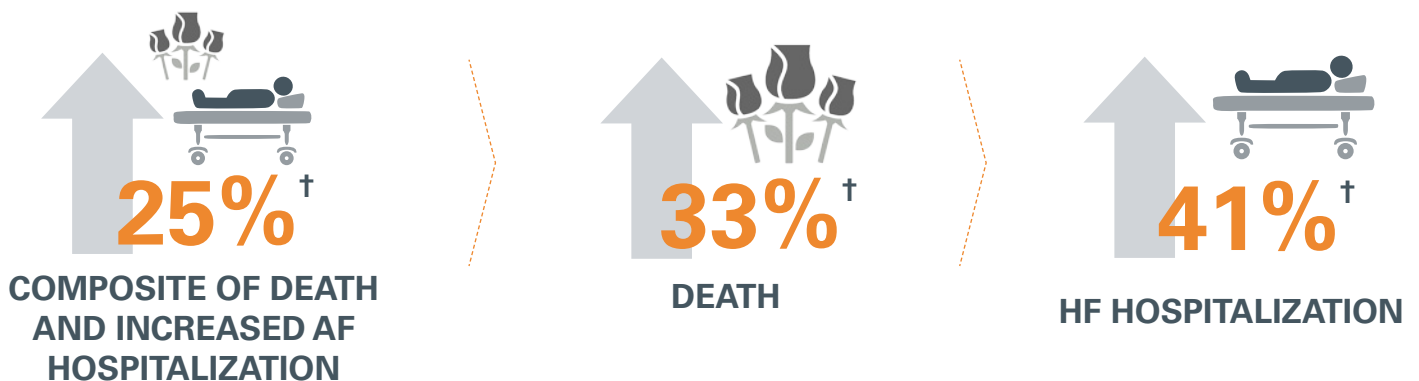
compared to ~25% of patients on drug therapy at 1 year follow-up ( $p > 0.001$ ).<sup>57</sup>



**GREATER IMPROVEMENT IN SURVIVAL OR REDUCTION IN HEART FAILURE HOSPITALIZATION IN PATIENTS**

as compared to drug therapy over a 5 year follow-up.<sup>57</sup>

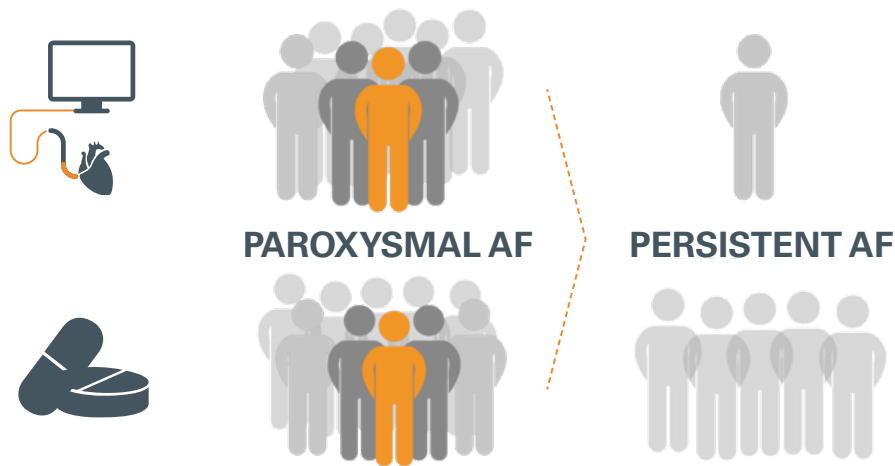
**Catheter ablation provides improvement in the probability of survival free from AF-related complications compared to drug therapy in patients with AF and heart failure.**



\*Modified intention-to-treat analysis which excluded the following: patients who had died or withdrew during the trial run-in period; end-point events occurring during the run-in period; events other than death during the 3-month blanking period after ablation; \*\* $p=0.007$ ; † $p=0.01$ ; ‡ $p=0.004$ .

Abbreviations: AF = atrial fibrillation; HF = heart failure  
Source: Marrouche et al. (2018)

The **ATTEST** randomized controlled trial found that patients receiving ablation, with **paroxysmal AF** are almost  
**10 TIMES LESS LIKELY**  
**TO PROGRESS TO PERSISTENT AF**  
than **those on AADs**\*<sup>59</sup>



The **FREQUENCY OF ADVERSE EVENTS** when treating patients with **CATHETER ABLATION** or **drug therapy**

**IS SIMILAR**

however, the **TYPES OF EVENTS** are **SPECIFIC**  
to the **TREATMENT STRATEGY**.<sup>55,57,58</sup>

\* (HR 0.11; 95% CI 0.02-0.48; p=0.0034)n

# WHAT IS THE IMPACT OF CATHETER ABLATION ON PATIENTS AS COMPARED TO AAD TREATMENT?

**Catheter ablation of AF results in a significantly greater improvement in patient quality of life than drug therapy.**

- Key recent trials that investigated the impact of catheter ablation compared to drug therapy on patient quality of life were:

TRIAL	CABANA <sup>55</sup>	CAPTAF <sup>58</sup>
REGION	Global	Europe
STUDY DESIGN	Multi-Centre RCT	Multi-Centre RCT
NUMBER OF PATIENTS	2,204	155
DISEASE STATE OF PATIENTS	Symptomatic AF	Symptomatic AF
REQUIREMENT THAT PATIENT FAILED DRUG THERAPY	Not required	Not required
FOLLOW-UP DURATION	5 years	4 years

The **CABANA trial** reported significantly **GREATER IMPROVEMENT** from baseline in quality of life **WITH CATHETER ABLATION** than with drug therapy at 1 year.

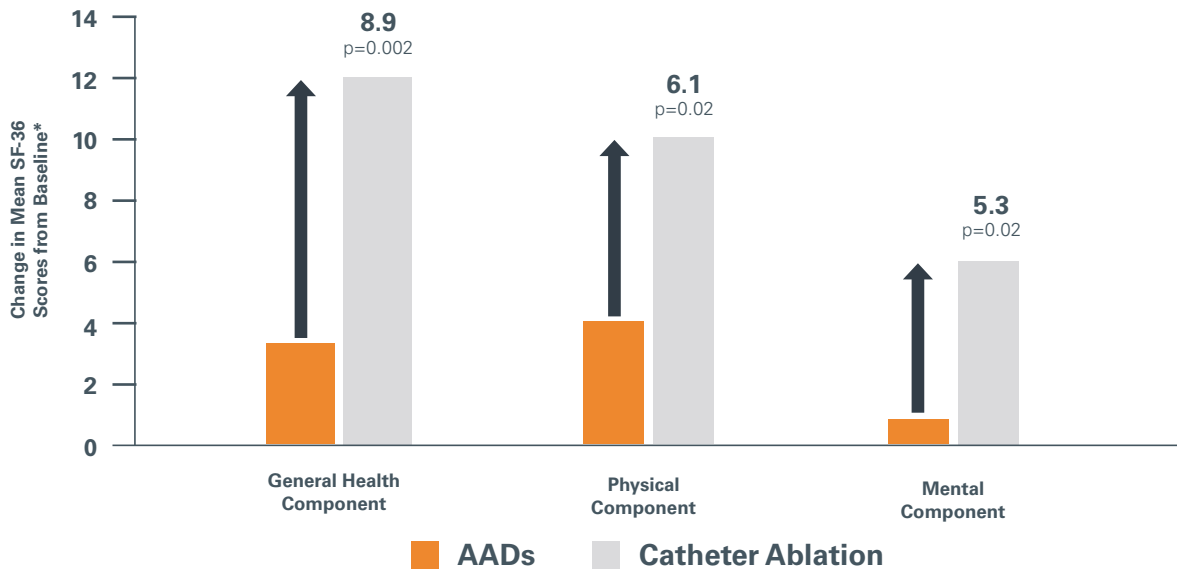


Greater improvement in quality of life from baseline was **MAINTAINED OVER 5 YEARS**.<sup>56</sup>

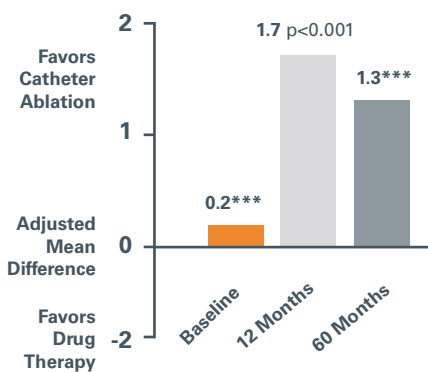


## COMPARISON OF TREATMENTS

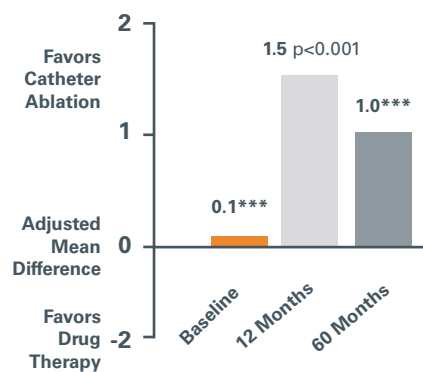
- The CAPTAF trial reported a **significantly** and **clinically** relevant **improvement** from baseline in patient-reported quality of life with catheter ablation than AADs at 1 year.<sup>58</sup>



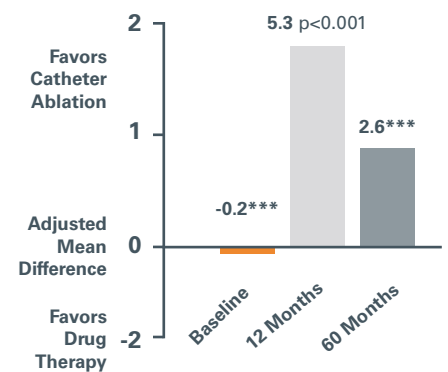
MAFSI\*\* SYMPTOM FREQUENCY SCORES



MAFSI\*\* SYMPTOM SEVERITY SCORES



AFEQT\*\* SUMMARY SCORES



\*As measured by the SF-36 described in Section 4C.

Abbreviations: AAD = antiarrhythmic drug; CAPTAF = Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation; SF-36 = Short Form 36 questionnaire. Source: Blomstrom-Lundqvist et al. (2019)

\*\*As measured by the MAFSI and AFEQT questionnaires as described in Section 5C;

\*\*\*Statistical significance not reported.

Abbreviations: AFEQT = Atrial Fibrillation Effect on Quality of Life; MAFSI = Mayo Atrial Fibrillation-Specific Symptom Inventory  
Source: Mark et al. (2019)

# WHAT IS THE ECONOMIC IMPACT OF CATHETER ABLATION COMPARED TO AAD THERAPY?

**Catheter ablation is cost effective compared to antiarrhythmic drugs for the management of AF.**

- An important recent study compared one-year resource utilization after catheter ablation to antiarrhythmic drug use<sup>90</sup>

TRIAL	JARMAN et al. (2018)
REGION	UK
STUDY DESIGN	Retrospective database analysis*
NUMBER OF PATIENTS	2,428
PATIENT DISEASE STATE	AF
REQUIREMENT THAT PATIENTS FAILED DRUG THERAPY	No
FOLLOW-UP DURATION	1 year

- A UK database analysis found that catheter ablation treatment was associated with reduced resource utilization compared to drugs over 1 year.\*\*<sup>90</sup>



**51% REDUCTION**  
IN CARDIOVASCULAR-RELATED OUTPATIENT VISITS  
( $p < 0.001$ )



**38% REDUCTION**  
IN INPATIENT ADMISSIONS FOR HEART FAILURE  
( $p = 0.0318$ )

\*Records identified in Clinical Practice Research Data-Hospital Episodes Statistics linkage data were propensity-score matched.  
Abbreviations: AF = atrial fibrillation; N = number; UK = United Kingdom

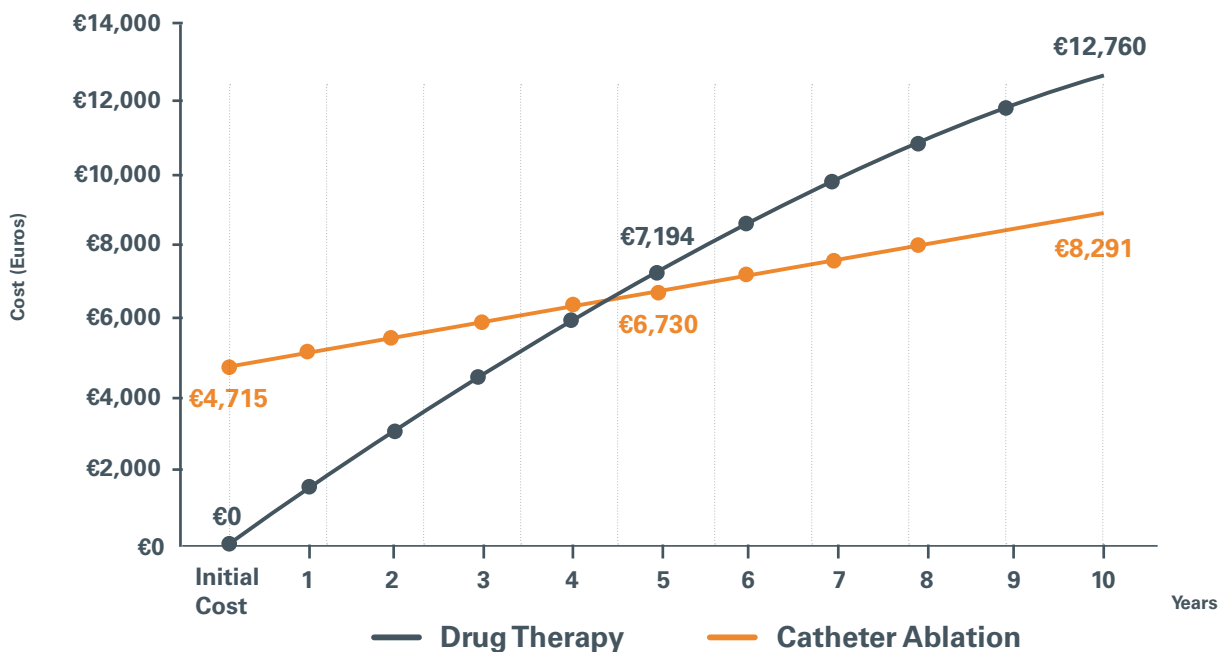
\*\*1 year time frame excludes resource use during the 3 month post-ablation blanking period

## ■ COMPARISON OF TREATMENTS

Several economic analyses show that RF ablation is **cost effective compared to antiarrhythmic drugs** due to improved clinical effectiveness over long term follow.<sup>68,78-83</sup>

Despite the initial investment, **costs become favorable for catheter ablation** at 5 years after the initial ablation procedure when compared to antiarrhythmic drugs.<sup>68</sup>

French study highlights the cumulative costs of PAROXYSMAL AF treatment over 10 Year <sup>66</sup>



PROJECTING COSTS TO 10 YEARS AFTER ABLATION\*



catheter ablation was associated with a

**35% SAVINGS**

**IN COSTS COMPARED TO DRUG THERAPY <sup>68</sup>**

Catheter ablation can be more clinically and cost effective when compared to drug therapy for the treatment of patients with AF



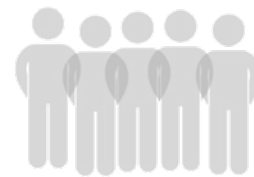
**94%**  
of patients are  
**FREE FROM ARRHYTHMIA RECURRENCE**  
**AT 1 YEAR**<sup>45-54</sup>



**PAROXYSMAL AF**

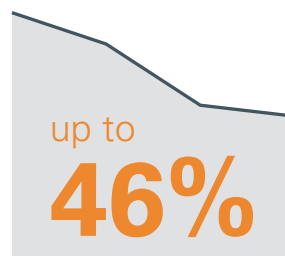


**PERSISTENT AF**



Patients with **paroxysmal AF** are almost  
**10 TIMES LESS LIKELY TO PROGRESS TO PERSISTENT AF**  
than **those on AADs**<sup>\*59</sup>

**CATHETER ABLATION**  
was also associated with



**significant reductions**  
in the probability of **AF-RELATED**  
**complications**



**Death**



**Stroke**



**Cardiac arrest**



**Cardiovascular  
hospitalization**

compared to drug therapy over 7-years follow-up.<sup>89</sup>

\*(HR 0.11; 95% CI 0.025-0.483; p=0.0034.)

**AF can be effectively and safely treated with rhythm control therapies; overall disease management focuses on controlling the irregular heart rhythm, improving symptoms, and reducing key complications based on shared decision-making between healthcare professionals and patients.**

**NEW**  
ESC 2020<sup>3</sup>

- Many patients are unaware that **AF is a life-threatening condition**, therefore, programs that increase knowledge and diagnosis of AF are important tools that can:
  - **Reduce the risk of stroke and death** in patients with undiagnosed AF.<sup>13, 14</sup>
  - **Lead to early treatment of AF** that may increase patient life expectancy and quality of life.<sup>16, 17</sup>
- **Patient values** need to be considered in treatment decision making and incorporated into the AF management pathways; the structured assessment of PRO measures is an important element to document and measure treatment success.<sup>3</sup>
- The **ABC pathway** streamlines integrated care of AF patients across healthcare levels and among different specialities.<sup>3</sup>
- The primary indication for rhythm control using cardioversion, AADs, and/or catheter ablation is **reduction in AF-related symptoms and improvement of QoL**.<sup>3</sup>
- Catheter ablation is a well-established treatment for prevention of AF recurrences. When performed by appropriately trained operators, **catheter ablation is a safe and superior alternative to AADs** for maintenance of sinus rhythm and symptom improvement.<sup>3</sup>
- **Identification and management of risk factors and concomitant diseases** is an integral part of the treatment of AF patients.<sup>3</sup>

## The 2020 ESC/EACTS guidelines for the management of AF highlights key areas of future research including the following:<sup>3</sup>

**NEW**  
ESC 2020<sup>3</sup>

### Major health modifiers causing AF

- What are the major the mechanisms causing AF in individual patients with pre-exisiting conditions (eg, cardiac structural remodelling, heart failure)?
- How do education interventions translate into actual behavioural change in patients and physician that leads to improvements in clinical management and outcomes, especially in the multi-morbid AF patient?

### Implementation of digital technologies for screening, diagnosis, and risk stratification in the AF patient

- How will new techniques for digital ECG analysis (eg, machine learning and artificial intelligence) and new technologies (eg, wearables and injectables) for detection and diagnosis of AF help to personalize therapy and stratify risk to the AF patient?
- Which patient groups would benefit most from these new techniques and new technologies for the detection and diagnosis of AF?

### Type of AF

- Recent data suggests that paroxysmal AF is not one entity and that according to the pattern, type of therapy and outcome may differ. Can paroxysmal AF be further classified?

### AF catheter ablation technique

- What is the best approach to safely and expeditiously achieve permanent pulmonary vein isolation in a single procedure?
- Does ablating additional targets improve outcomes of AF catheter ablation?

### Outcome of AF catheter ablation

- What is the value of early AF ablation in preventing AF progression?
- What is the optimal outcome measure (eg, AF 30 sec, AF burden, etc.) for AF-related outcome?
- How much reduction in AF burden is needed to achieve an effect on hard endpoints, including survival, stroke, and comorbidity?
- What is the main mechanism of PVI translating into freedom of AF?
- What is the potential effect of cardiac structure and function on the likelihood of success of AF ablation?
- What is the effect of AF catheter ablation on clinical outcomes, including death, stroke, serious bleeding, AF recurrence, QoL, and cardiac arrest?
- What is relationship between the degree of atrial dilation/fibrosis and successful AF ablation?
- What is the impact of specific components of structural heart disease, including left atrial structure/function, left ventricular function, etc. on:
  - > the success of AF catheter ablation?
  - > the likelihood of AF recurrence?

## ■ Who may benefit less from AF catheter ablation

- There are gaps in knowledge about subgroups of patients who may benefit less from AF catheter ablation, including:
  - Persistent and long-standing persistent AF
  - Patients with enlarged atrial size and/or atrial fibrosis
  - Patients with atypical atrial flutter
  - Patients with risk factors of AF recurrence, including obesity or sleep apnea

## ■ Personalized therapy

- Can improved assessment of the pathophysiological process involved in the individual patient through the use of clinical characteristics, blood biomarkers, and non-invasive substrate determination (ie, echo/MRI/CT) improve personalized therapy (eg, selection of rhythm control, treatment of risk factors and comorbidities, type of AAD, atrial ablation, and which type/techniques used for AF)?

1. Iazzo PA (2015). Handbook of Cardiac Anatomy, Physiology and Devices. Springer Science and Business Media, LLC: Switzerland.
2. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB et al. (2017) 2017 HRS/EHRA/ECAS/APHS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 14 (10): e275-e444.
3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ et al. (2020) 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *European Heart Journal*.
4. 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.
5. 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.
6. 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.
7. Boriani G, Proietti M (2017) Atrial fibrillation prevention: an appraisal of current evidence. *Heart* (0): 1-6
8. 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.
9. 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
10. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S (2014) Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 6 213-220.
11. 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.
12. Batul SA, Gopinathannair R (2017) Atrial Fibrillation in Heart Failure: a Therapeutic Challenge of Our Times. *Korean Circ J* 47 (5): 644-662.
13. 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):
14. 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.
15. 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):
16. Zulkifly H, Lip GYH, Lane DA (2018) Epidemiology of atrial fibrillation. *Int J Clin Pract* e13070
17. Paludan-Muller C, Svendsen JH, Olesen MS (2016) The role of common genetic variants in atrial fibrillation. *J Electrocardiol* 49 (6): 864-870.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. Nieuwlaet 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.
25. de Vos CB, Pisters R, Nieuwlaet 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.
26. Dilaveris PE, Kennedy HL (2017) Silent atrial fibrillation: epidemiology, diagnosis, and clinical impact. *Clin Cardiol* 40 (6): 413-418.
27. Schnabel R, Pecun L, Engler D, Lucerna M, Sellal JM et al. (2018) Atrial fibrillation patterns are associated with arrhythmia progression and clinical outcomes. *Heart*
28. 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.
29. 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.
30. 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.
31. 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.
32. Hoegh 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.
33. 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.
34. 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.
35. McBride D, Mattenklott AM, Willich SN, Bruggenjurgens B (2009) The costs of care in atrial fibrillation and the effect of treatment modalities in Germany. *Value Health* 12 (2): 293-301.
36. 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.
37. 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.
38. 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.
39. Ringborg A, Nieuwlaet 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.
40. Ben Freedman S, Lowres N (2015) Asymptomatic Atrial Fibrillation: The Case for Screening to Prevent Stroke. *JAMA* 314 (18): 1911-1912.
41. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M et al. (2017) Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. *Circulation* 135 (19): 1851-1867.
42. Peterson ED, Ho PM, Barton M, Beam C, Burgess LH et al. (2014) ACC/AHA/AACVPR/AAFP/ANA concepts for clinician-patient shared accountability in performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circulation* 130 (22): 1984-1994.
43. Valembais L, Audureau E, Takeda A, Jarzebowski W, Belmin J et al. (2019) Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 9 CD005049.
44. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P et al. (2008) Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 118 (24): 2498-2505.
45. Hussein A, Das M, Chaturvedi V, Asfour IK, Daryanani N et al. (2017) Prospective use of Ablation Index targets improves clinical outcomes following ablation for atrial fibrillation. *J Cardiovasc Electrophysiol* 28 (9): 1037-1047.
46. Taghji P, El Haddad M, Philips T, Wolf M, Knecht S et al. (2018) Evaluation of a Strategy Aiming to Enclose the Pulmonary Veins With Contiguous and Optimized



- Radiofrequency Lesions in Paroxysmal Atrial Fibrillation: A Pilot Study. *JACC Clin Electrophysiol* 4 (1): 99-108.
47. Philips T, Taghji P, El Haddad M, Wolf M, Knecht S et al. (2018) Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace* 20 (F1\_3): f419-f427.
  48. Solimene F, Schillaci V, Shopova G, Urraro F, Arestia A et al. (2019) Safety and efficacy of atrial fibrillation ablation guided by Ablation Index module. *J Interv Card Electrophysiol* 54 (1): 9-15.
  49. Di Giovanni G, Wauters K, Chierchia GB, Sieira J, Levinstein M et al. (2014) One-year follow-up after single procedure Cryoballoon ablation: a comparison between the first and second generation balloon. *J Cardiovasc Electrophysiol* 25 (8): 834-839.
  50. Jourda F, Providencia R, Marijon E, Bouzeman A, Hireche H et al. (2015) Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. *Europace* 17 (2): 225-231.
  51. Lemes C, Wissner E, Lin T, Mathew S, Deiss S et al. (2016) One-year clinical outcome after pulmonary vein isolation in persistent atrial fibrillation using the second-generation 28 mm cryoballoon: a retrospective analysis. *Europace* 18 (2): 201-205.
  52. Guhl EN, Siddoway D, Adelstein E, Voigt A, Saba S et al. (2016) Efficacy of Cryoballoon Pulmonary Vein Isolation in Patients With Persistent Atrial Fibrillation. *J Cardiovasc Electrophysiol* 27 (4): 423-427.
  53. Irfan G, de Asmundis C, Mugnai G, Poelaert J, Verborgh C et al. (2016) One-year follow-up after second-generation cryoballoon ablation for atrial fibrillation in a large cohort of patients: a single-centre experience. *Europace* 18 (7): 987-993.
  54. Boveda S, Metzner A, Nguyen DQ, Chun KRJ, Goehl K et al. (2018) Single-Procedure Outcomes and Quality-of-Life Improvement 12 Months Post-Cryoballoon Ablation in Persistent Atrial Fibrillation: Results From the Multicenter CRYO4PERSISTENT AF Trial. *JACC Clin Electrophysiol* 4 (11): 1440-1447.
  55. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD et al. (2019) Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*
  56. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN et al. (2019) Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*
  57. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L et al. (2018) Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 378 (5): 417-427.
  58. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L et al. (2019) Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA* 321 (11): 1059-1068.
  59. Kuck KH, Lebedev, D., Mikaylov, E., Romanov, A., Geller, L., Kalejs, O., Neumann, T., Davtyan, K., On, Y.K., Popov, S., Ouyang, F. (2019) Catheter ablation delays progression of atrial fibrillation from paroxysmal to persistent atrial fibrillation. ESC Late-breaking Science 2019. Paris, France. August 31, 2019.
  60. Kirchhof et al. (2014) Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention of thromboembolic events-European Registry in Atrial Fibrillation (PREFER in AF). *Europace* 16 (1): 6-14.
  61. Proietti M, Laroche C, Opolski G, Maggioni AP, Boriani G et al. (2017) 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. *Europace* 19 (5): 722-733.
  62. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y et al. (2009) Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2 (4): 349-361.
  63. Lakdawalla D, Turakhia MP, Jhaveri M, Mozaffari E, Davis P et al. (2013) Comparative effectiveness of antiarrhythmic drugs on cardiovascular hospitalization and mortality in atrial fibrillation. *J Comp Eff Res* 2 (3): 301-312.
  64. Camm J (2012) Antiarrhythmic drugs for the maintenance of sinus rhythm: risks and benefits. *Int J Cardiol* 155 (3): 362-371.
  65. Bruggenjürgen B, Kohler S, Ezzat N, Reinhold T, Willich SN (2013) Cost effectiveness of antiarrhythmic medications in patients suffering from atrial fibrillation. *Pharmacoeconomics* 31 (3): 195-213.
  66. Nilsson J, Akerborg O, Bego-Le Bagousse G, Rosenquist M, Lindgren P (2013) Cost-effectiveness analysis of dronedarone versus other anti-arrhythmic drugs for the treatment of atrial fibrillation—results for Canada, Italy, Sweden and Switzerland. *Eur J Health Econ* 14 (3): 481-493.
  67. Akerborg O, Nilsson J, Bascle S, Lindgren P, Reynolds M (2012) Cost-effectiveness of dronedarone in atrial fibrillation: results for Canada, Italy, Sweden, and Switzerland. *Clin Ther* 34 (8): 1788-1802.
  68. Weerasooriya R, Jais P, Le Heuzey JY, Scavee C, Choi KJ et al. (2003) Cost analysis of catheter ablation for paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 26 (1 Pt 2): 292-294.
  69. Hohnloser SH, Cappato R, Ezekowitz MD, Evers T, Sahin K et al. (2016) Patient-reported treatment satisfaction and budget impact with rivaroxaban vs. standard therapy in elective cardioversion of atrial fibrillation: a post hoc analysis of the X-VerT trial. *Europace* 18 (2): 184-190.
  70. Gonzalez-Juanatey JR, Alvarez-Sabin J, Lobos JM, Martinez-Rubio A, Reverter JC et al. (2012) Cost-effectiveness of dabigatran for stroke prevention in non-valvular atrial fibrillation in Spain. *Rev Esp Cardiol (Engl Ed)* 65 (10): 901-910.
  71. Saborido CM, Hockenhull J, Bagust A, Boland A, Dickson R et al. (2010) Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy. *Health Technol Assess* 14 (31): iii-iv, 1-75.
  72. National Institute for Health and Care Excellence (2014) Costing Report: atrial fibrillation. *Health Technology Assessment (HTA)*.
  73. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L et al. (2014) A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 7 (1): 31-38.
  74. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP et al. (2013) A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol* 61 (18): 1894-1903.
  75. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA et al. (2017) Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study. *J Am Coll Cardiol* 70 (16): 1949-1961.
  76. Santangeli P, Di Biase L, Mohanty P, Burkhardt JD, Horton R et al. (2012) Catheter ablation of atrial fibrillation in octogenarians: safety and outcomes. *J Cardiovasc Electrophysiol* 23 (7): 687-693.
  77. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL et al. (2011) Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *Journal of Cardiovascular Electrophysiology* 22 (8): 839-845.
  78. Rodgers MM, C. Palmer S, Chambers D, Van Hout, S. Golder, S., Pepper CT, D. Woolacott, N. (2008) Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. *Health Technol Assess* 12 (34):
  79. Reynolds MR, Zimetbaum P, Josephson ME, Ellis E, Danilov T et al. (2009) Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol* 2 (4): 362-369.
  80. Assasi NB, G. Xie, F. Gaebel, K. Robertson, D. Hopkins, R. Healey, J. Roy, D. Goeree, R. (2010) Ablation Procedures for Rhythm Control in Patients with Atrial Fibrillation: Clinical and Cost-Effectiveness Analyses. *Health Technology Assessment (HTA)*. 128
  81. McKenna C, Palmer S, Rodgers M, Chambers D, Hawkins N et al. (2009) Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom. *Heart* 95 (7): 542-549.
  82. Khaykin Y, Wang X, Natale A, Wazni OM, Skanes AC et al. (2009) Cost comparison of ablation versus antiarrhythmic drugs as first-line therapy for atrial fibrillation: an economic evaluation of the RAAFT pilot study. *J Cardiovasc Electrophysiol* 20 (1): 7-12.
  83. Aronsson M, Walfridsson H, Janzon M, Walfridsson U, Nielsen JC et al. (2015) The cost-effectiveness of radiofrequency catheter ablation as first-line treatment for paroxysmal atrial fibrillation: results from a MANTRA-PAF substudy. *Europace* 17 (1): 48-55.
  84. Samuel M, Avgil Tsadok M, Joza J, Behlouli H, Verma A et al. (2017) Catheter ablation for the treatment of atrial fibrillation is associated with a reduction in health care resource utilization. *J Cardiovasc Electrophysiol* 28 (7): 733-741.
  85. Chun KRJ, Brugada J, Elvan A, Geller L, Busch M et al. (2017) The Impact of Cryoballoon Versus Radiofrequency Ablation for Paroxysmal Atrial Fibrillation on Healthcare Utilization and Costs: An Economic Analysis From the FIRE AND ICE Trial. *J Am Heart Assoc* 6 (8):
  86. Zoni Berisso ML, M. Ermini, G. Parretti, D. Zingarini, GL. Degli Esposti, L. Cricelli, C. Boriani, G. (2017) The cost of atrial fibrillation in Italy: a five-year analysis of healthcare expenditure in the general population. From the Italian Survey of Atrial Fibrillation Management (ISAF) study. *European Review for Medical and Pharmacological Sciences* 21 (1): 175-183.
  89. Noseworthy PA, Gersh BJ, Kent DM, Piccini JP, Packer DL et al. (2019) Atrial fibrillation ablation in practice: assessing CABANA generalizability. *Eur Heart J* 40 (16):

1257-1264.

90. Jarman JWE, Hussain W, Wong T, Markides V, March J et al. (2018) Resource use and clinical outcomes in patients with atrial fibrillation with ablation versus antiarrhythmic drug treatment. *BMC Cardiovasc Disord* 18 (1): 211

91. Gwag HB, Chun KJ, Hwang JK, Park SJ, Kim JS et al. (2018) Which antiarrhythmic drug to choose after electrical cardioversion: A study on non-valvular atrial fibrillation patients. *PLoS One* 13 (5): e0197352.

92. Bunch TJ, May HT, Bair TL, Johnson DL, Weiss JP et al. (2013) Increasing time between first diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes. *Heart Rhythm* 10 (9): 1257-1262.

93. De Greef Y, Schwagten B, Chierchia GB, de Asmundis C, Stockman D et al. (2018) Diagnosis-to-ablation time as a predictor of success: early choice for pulmonary vein isolation and long-term outcome in atrial fibrillation: results from the Middelheim-PVI Registry. *Europace* 20 (4): 589-595.

Important information: Prior to use, refer to the instructions for use supplied with this device for indications, contraindications, side effects, warnings and precautions.  
This publication is not intended for distribution outside of the EMEA region.

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

126680-201219 EMEA  
© Johnson & Johnson Medical NV/SA 2021

