



ATRIAL FIBRILLATION MANAGEMENT

2019 FULL REPORT

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

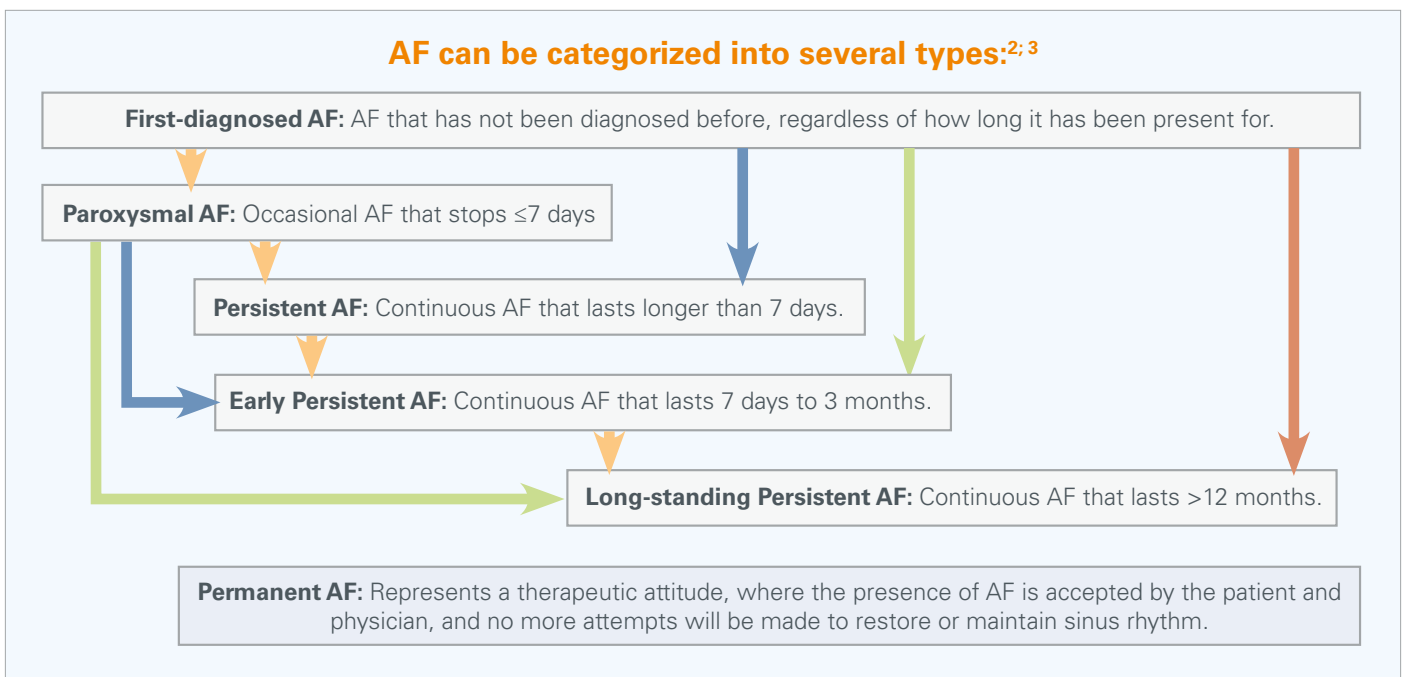


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The management of atrial fibrillation focuses on effectively and safely controlling the irregular heart rhythm, improving symptoms, and reducing key complications based on shared decision-making between healthcare professionals and patients.

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).¹



■ Risk factors for AF include:



LIFESTYLE FACTORS

Obesity⁴⁻⁷, smoking², alcohol consumption^{2, 7-8}



OTHER CONDITIONS

High blood pressure⁷, heart failure⁹⁻¹⁴, history of heart attack^{9,15}, coronary artery or other heart disease^{5,9}



NON-MODIFIABLE FACTORS

Older age^{2,16}, family history or other genetic factors^{9, 17-18}, male sex^{2, 9, 16}

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



15%-30%

OF PATIENTS EXPERIENCE
NO SYMPTOMS (i.e. silent AF)²³



1 in 5
PATIENTS PROGRESS
IN 1 YEAR²⁴⁻²⁷



PAROXYSMAL
AF

PERSISTENT
AF

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

5x Increase heart failure



2.4x Increase stroke



2x Increase cardiovascular mortality



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

The 2016 (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.

AF patient care pathway management includes:²

MANAGEMENT of underlying cardiovascular risk factors and **REDUCING STROKE RISK** → to improve life expectancy and quality of life

ELECTRICAL OR PHARMACEUTICAL CARIOVERSION → when a patient is experiencing an AF episode

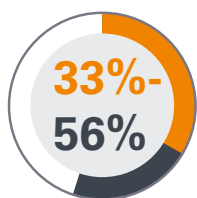
RATE CONTROL THERAPIES → to control heart rate

RHYTHM CONTROL THERAPIES → including antiarrhythmic drugs and catheter ablation, to maintain normal sinus rhythm

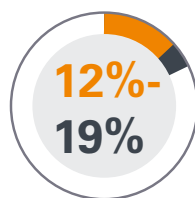
- Education and screening programs aimed at **increasing awareness and diagnosis of AF are critical to reducing the risk of stroke and death** in patients with undiagnosed AF.⁴⁰⁻⁴¹
 - Ideally, patients will recognize AF symptoms and contact their clinicians when symptoms arise.⁴²
- **Early treatment of AF is important**, as it may improve patient life expectancy and quality of life.²

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 YEAR⁴³**



of patients **WITHDRAW FROM TREATMENT DUE TO ADVERSE EVENTS⁴³**



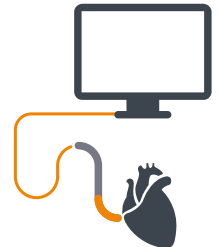
of patients **IMPROVEMENT IN QUALITY OF LIFE⁴⁴**

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.

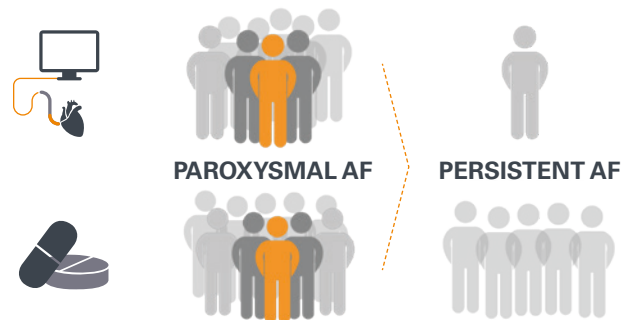
With catheter ablation treatment:



1.8% of patients experience **AN ABLATION-RELATED ADVERSE EVENT**⁵⁵



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:



Patients with **paroxysmal AF** are almost **10 TIMES LESS LIKELY TO PROGRESS TO PERSISTENT AF** than **those on AADs**^{*59}

Similarly **LOW RATES OF AF-RELATED COMPLICATIONS**^{55, 57-58}



Death



Stroke



Cardiac arrest



Cardiovascular hospitalization

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

Guidance on the delivery of good care to patients with AF are available from the 2016 ESC/EACTS guidelines and 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement.

WHAT ARE THE RECOMMENDATIONS FOR MANAGING A PATIENT WITH AF?

The ESC/EACTS guidelines and the HRS/EHRA/ECAS/APHRS/SOLAECE consensus statement recommend an integrated approach to AF management that involves patients and multidisciplinary teams of healthcare professionals to improve access to care and patient compliance. The use of anticoagulants, cardioversion, rate control therapies, and rhythm control therapies are recommended to manage AF.²⁻³

1 Integrated Management of AF & Collaborative Decision Making

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 in a central role in decision-making.²

■ Key aims are to:



REDUCE MORTALITY



TAILOR MANAGEMENT TO PATIENT PREFERENCES



REDUCE HOSPITALIZATIONS



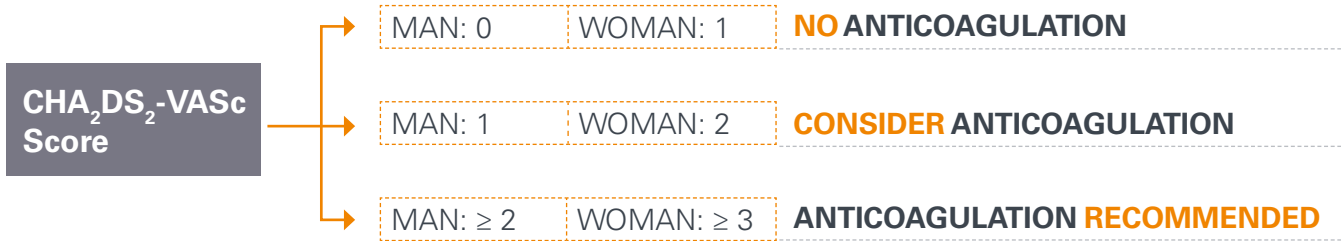
IMPROVE ADHERENCE TO LONG-TERM THERAPY



IMPROVE ADHERENCE TO GUIDELINES

MANAGEMENT OF AF PATIENTS

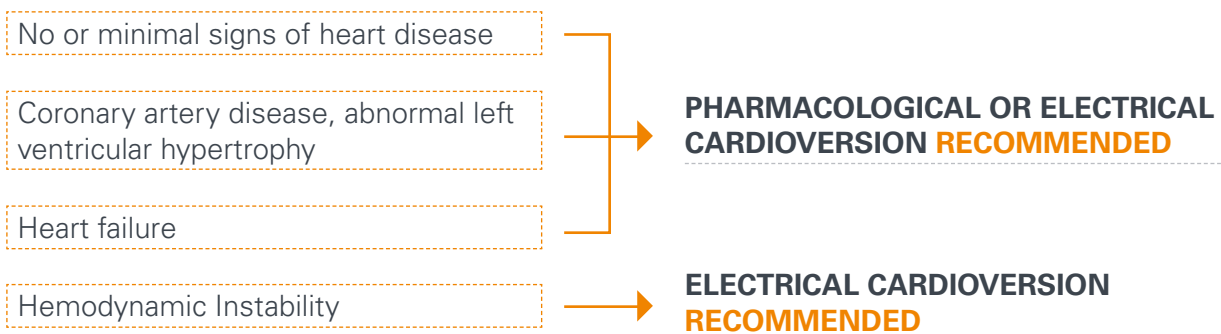
2 Oral Anticoagulation Therapy for Stroke Prevention in Patients with AF²



3 Rate Control Therapy to Lower and Control Heart Rate and Improve Symptoms of AF²



4 Acute Rhythm Control Therapy to Restore Normal Sinus Rhythm²

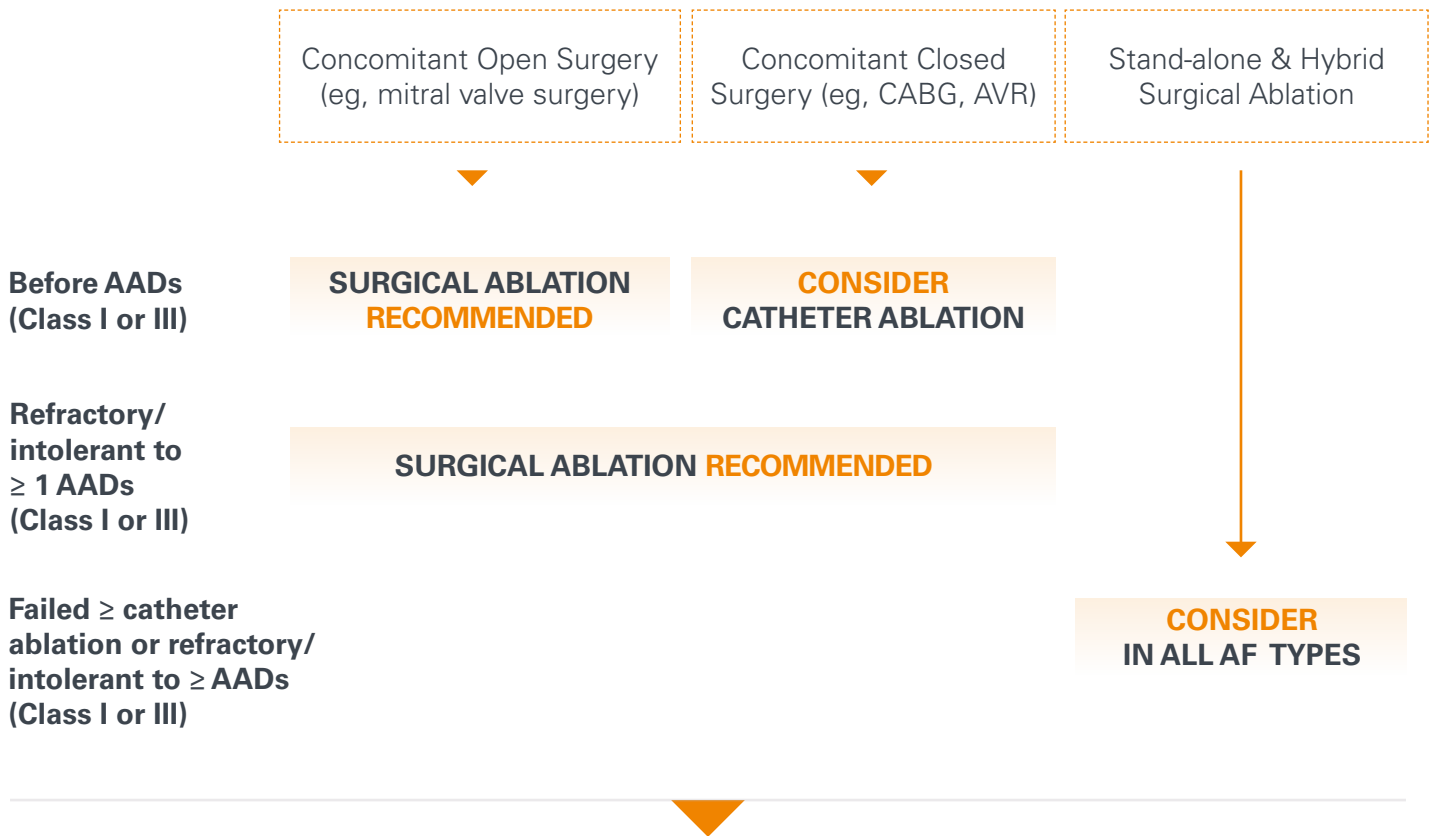


5 Rhythm Control Therapy to Maintain Normal Sinus Rhythm and Improve Symptoms of AF^{2,3}

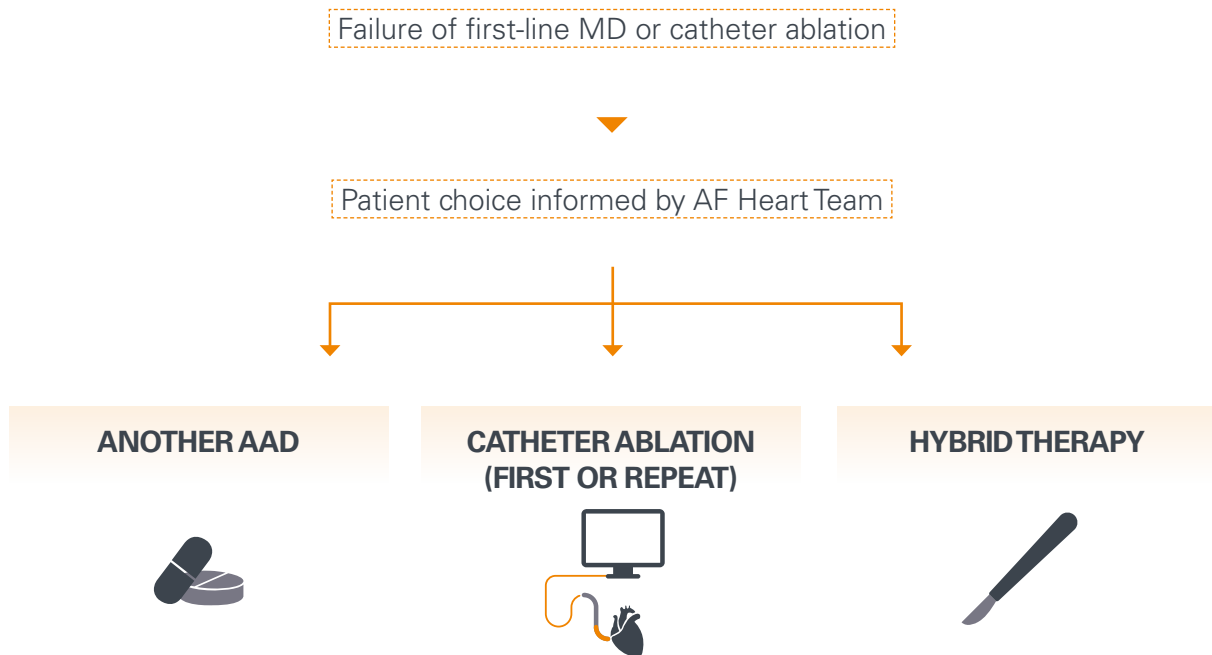
- Guidelines recommend that treatment with AADs, catheter ablation, and/or surgical ablation be dependent on patient choice.^{2,3}
- The choice of AADs needs to consider the presence of comorbidities, cardiovascular risk, potential for proarrhythmia, toxic effects, symptom burden, and patient preference.²



MANAGEMENT OF AF PATIENTS



6 Selection of 2nd rhythm control therapy after failure of 1st rhythm control therapy²



Abbreviations: AAD = antiarrhythmic drug; AF = atrial fibrillation; AVR = aortic valve replacement; CABG = coronary artery bypass graft; CHA2DS2-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: 2016 ESC Guidelines², and 2017 HRS/EHRA Consensus Statement³

The goal of AF patient care pathway management includes detection and management of key complications and cardiovascular risk factors.

WHAT IS THE GOAL OF AF MANAGEMENT?

The therapeutic goal of the initial management strategy for AF is to **treat any underlying cardiovascular conditions and reduce the risk of stroke.**²



THE PRESENCE OF **CARDIOVASCULAR RISK FACTORS**

often exacerbates AF²



AF IS ASSOCIATED WITH AN **INCREASED RISK OF STROKE**

compared to patients in sinus rhythm²⁸

■ Cardiovascular risk factors and key disease-related complications assessed include:²



■ Stroke



■ Heart failure



■ Hyper tension



■ Valvular heart disease



■ Diabetes mellitus



■ Obesity



■ Obstructive sleep apnea



■ Chronic kidney disease

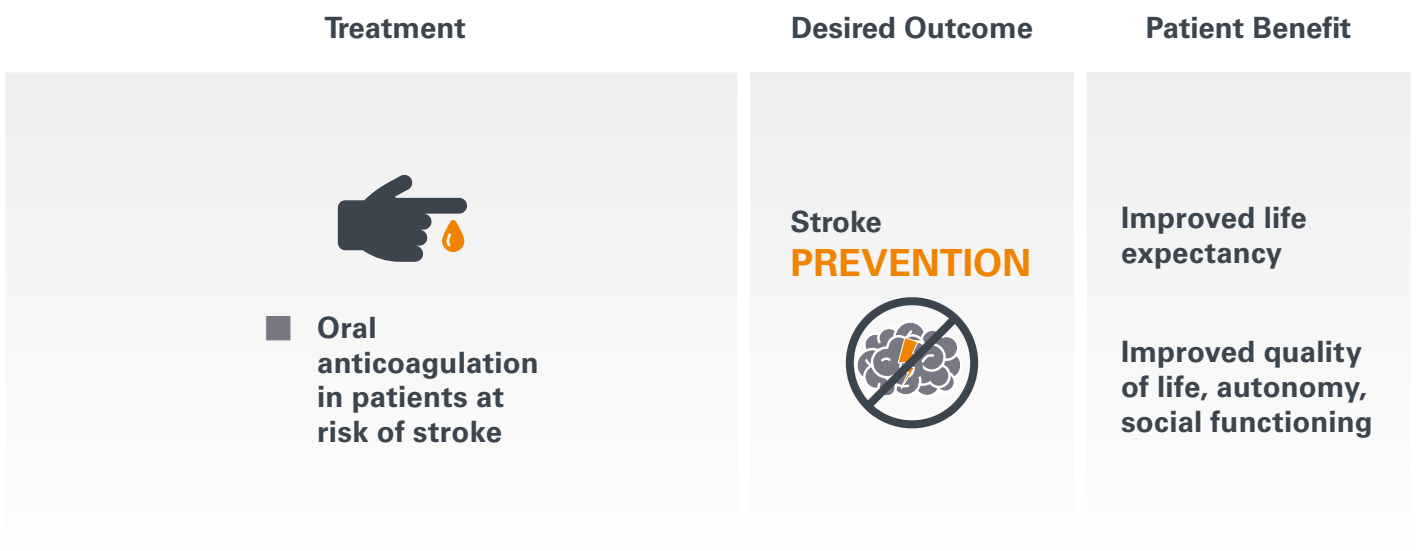
MANAGEMENT OF AF PATIENTS

The management of cardiovascular risk factors and stroke risk across the AF care pathway, includes:²

MANAGE PRECIPITATING FACTORS



ASSES STROKE RISK



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 available 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



INTERVENTIONAL



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:²



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



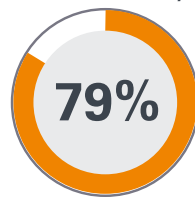
PACEMAKERS are only recommended for use in patients with **SICK SINUS SYNDROME** and/or **BRADYCARDIA**

- 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, and patient choice.**²

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.**⁶⁰

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**^{2, 45-50}

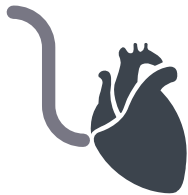
■ MANAGEMENT OF AF PATIENTS

The choice of an alternative rhythm control therapy requires **patient involvement, consideration of patient preferences, and informed decision-making with a multidisciplinary team** of healthcare professionals, should the first rhythm control strategy fail.²

Patients who experience recurrence of symptomatic AF while on AADs or after catheter ablation may choose to:²



RECEIVE
TREATMENT WITH A DIFFERENT AAD



REPEAT
CATHETER ABLATION



RECEIVE
HYBRID THERAPY
(ie, combining AADs with ablation)



START
RATE CONTROL THERAPIES
TO CONTROL AF

Antiarrhythmic drug therapy is an integral part of maintaining sinus rhythm after cardioversion²

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
<p>Class I: Sodium Channel Blockers</p> <p>IA AC</p>	<p>Disopyramide, Quinidine Flecainide, Propafenone</p>
<p>Class III: Potassium Channel Blockers</p>	<p>Amiodarone, Dronedarone, Dofetilide, Sotalol</p>

- Choice of AAD is primarily guided by safety considerations, including:²

ABSOLUTE or **RELATIVE** CONTRAINDICATIONS

RISK FACTORS for adverse events

such as onset of **new arrhythmia** or **exacerbation of existing arrhythmia** and **effects outside the heart**

FACTORS that influence **DRUG DISPOSITION**

such as patient age and **renal or hepatic function**

PATIENT PREFERENCE

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.²

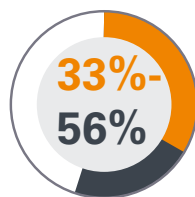
NB: Bolded antiarrhythmic drugs represent those with Class IA recommendations for preventing recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy per the 2016 ESC Guidelines².

Abbreviations: AAD = antiarrhythmic drugs, AE = adverse event
Source: Lafuente-Lafuente et al. (2015)

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.⁴³

48% of patients with AF are not well managed on AADs.⁶²

- Recurrence of AF can be asymptomatic and symptomatic.⁶¹
- Reported event rates for stroke, heart failure, and mortality are **low** and the potential **benefits** of AADs in reducing these events **have yet to be established**.^{2,43,63}

0%-3%



STROKE

1%-3%



HEART FAILURE

0%-11%*



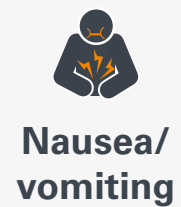
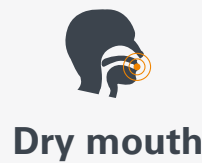
MORTALITY

*Based on pooled event rates.
Abbreviations: AAD = antiarrhythmic drug
Source: Lafuente-Lafuente et al. (2015); Gwag et al. (2018)

- The toxicity profile of AADs is varied, frequently including **drug-induced arrhythmia in 2%-4% of patients**, and adverse events leading to **treatment discontinuation in 12%-19% of patients**: ^{2,43,64}

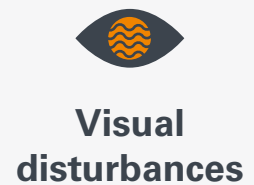
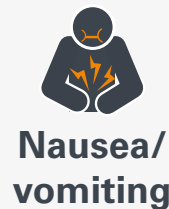
COMMON ADVERSE EVENTS

CLASS IA



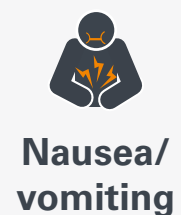
19% TREATMENT WITHDRAWALS DUE TO AES (%)

CLASS IC



12% TREATMENT WITHDRAWALS DUE TO AES (%)

CLASS III



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:

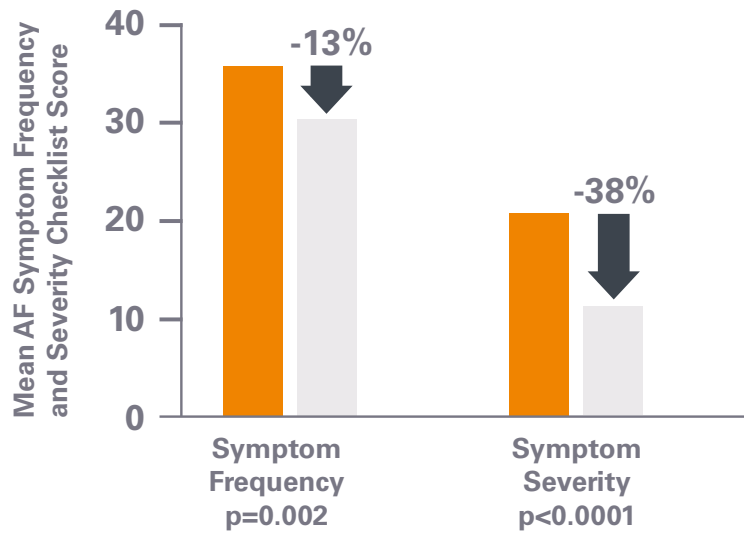
	AF SYMPTOM FREQUENCY AND SEVERITY CHECKLIST	SF-36
OUTCOMES MEASURED	AF-related symptom frequency and severity	QoL
ITEMS/ SUBSCALES	16 items	8 subscales, including physical, mental, and general health
SCORE RANGE	Symptom frequency: 0-64 Symptom severity: 0-48	0-100
SCORE INTERPRETATION	Lower scores indicate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



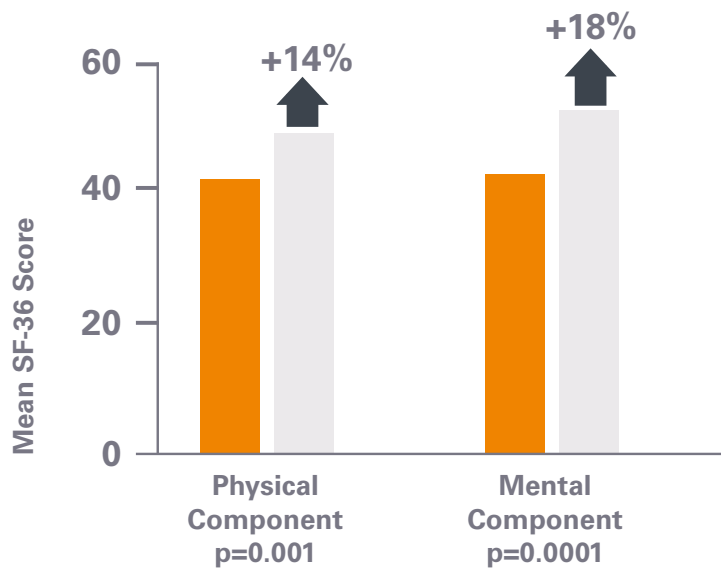
**IMPROVEMENT
IN QUALITY OF LIFE
WITH AAD THERAPY ⁴⁴**



REDUCED SYMPTOMS WITH AAD THERAPY⁴⁴



IMPROVED QUALITY OF LIFE WITH AAD THERAPY⁴⁴



■ 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.**⁶⁵⁻⁶⁷

Initial cost of AAD treatment is **LOW**

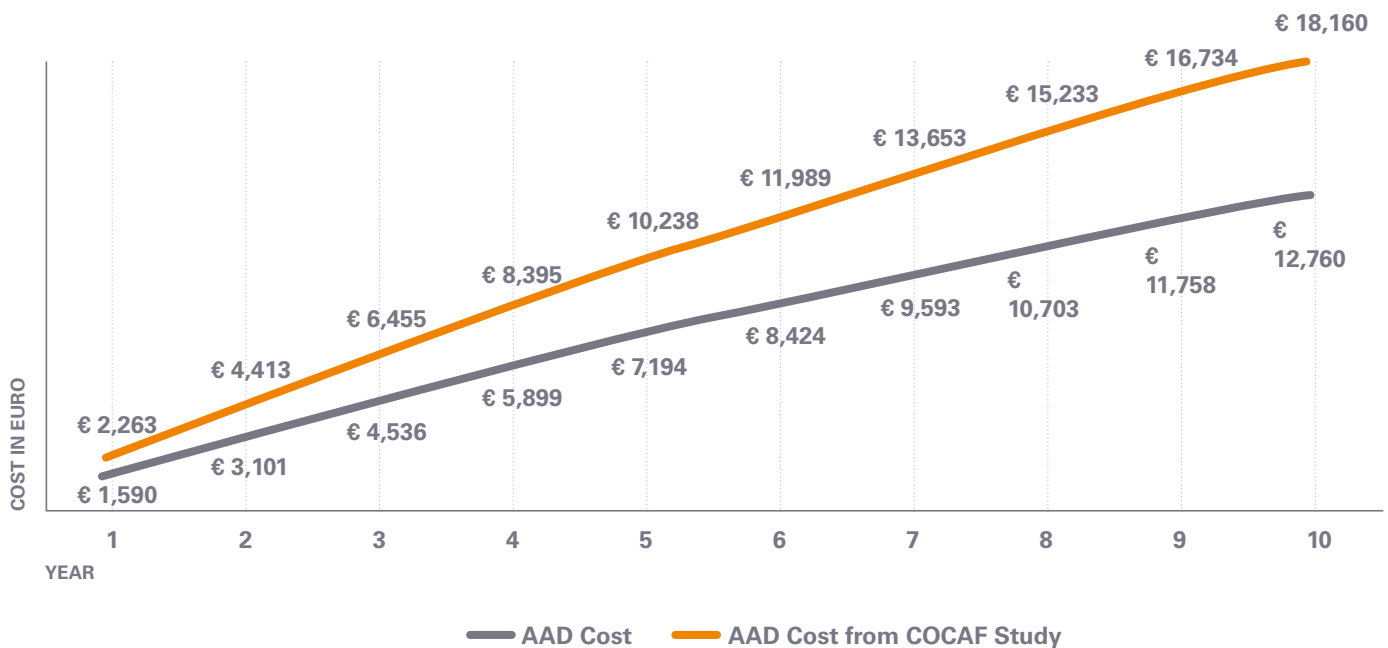


however

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

INCREASES 28% ANNUALLY over 9 years*⁶⁸

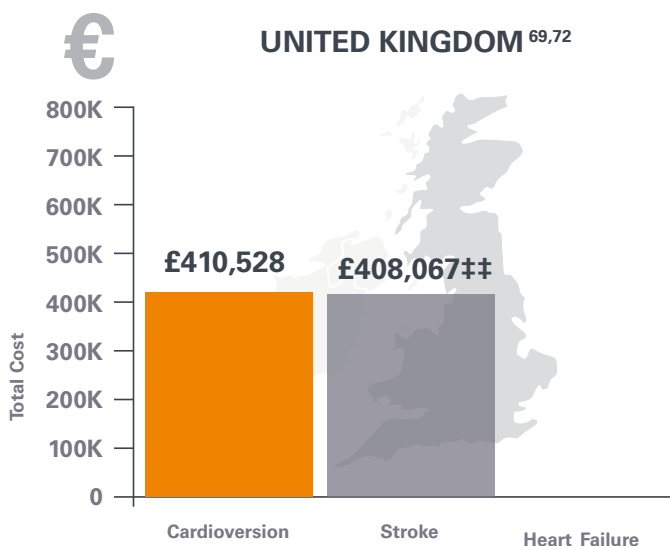
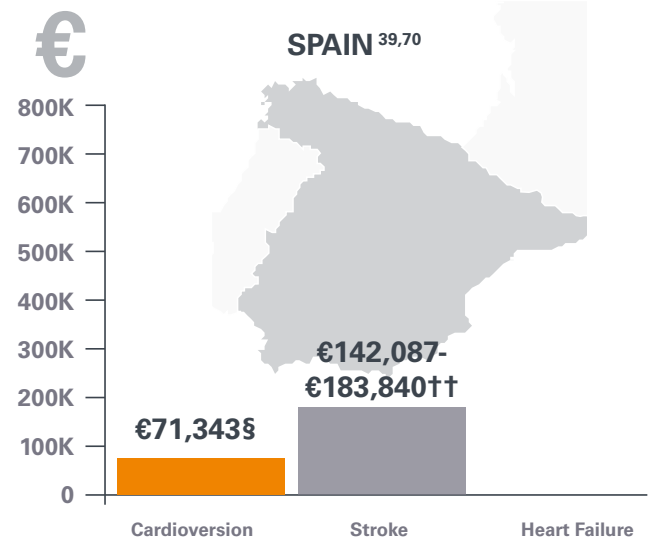
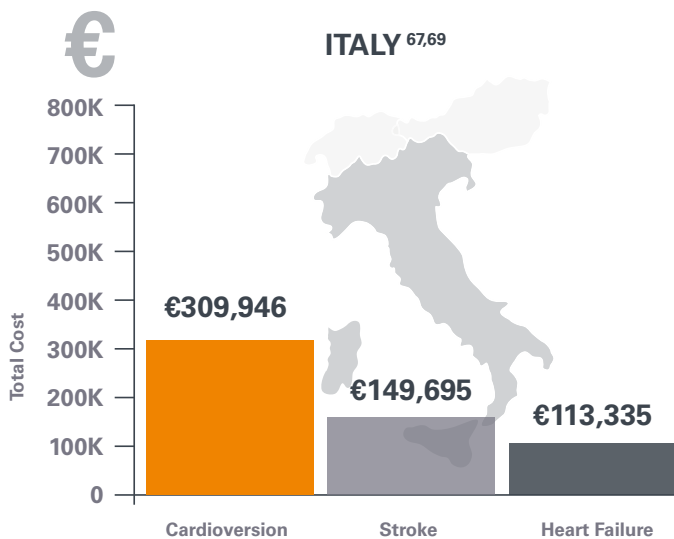
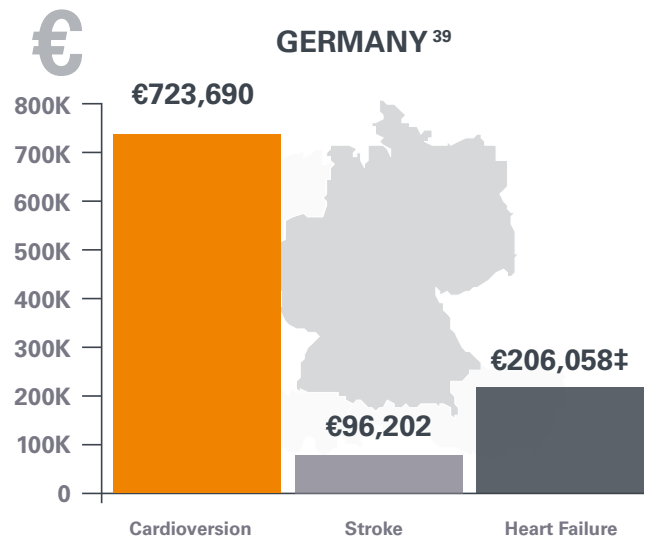
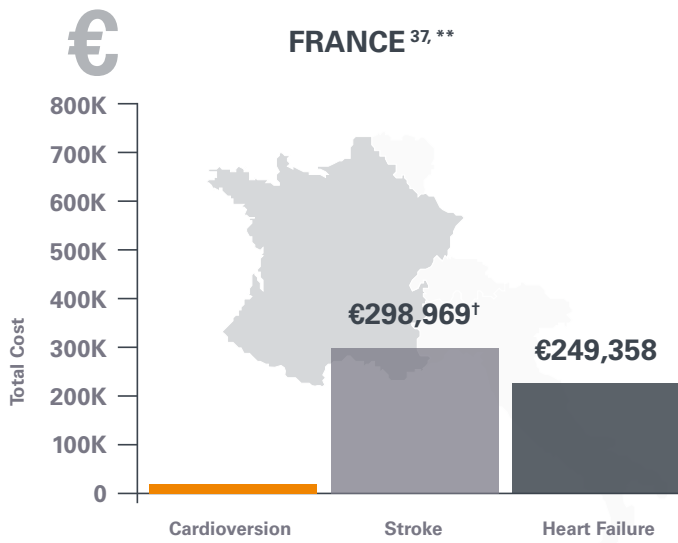
CUMULATIVE COST OF AADS OVER 10 YEARS IN PAROXYSMAL AF UNSUCCESSFULLY TREATED WITH 2 AADS



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

*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 Euros⁶¹;
 ** 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 used to create small scars on targeted parts of heart tissue that block the abnormal electrical signals causing the arrhythmia.^{2, 3}

HOW IS CATHETER ABLATION USED IN THE MANAGEMENT OF AF?

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

Key considerations for treating patients with catheter ablation include:³

- Type of AF
- Degree of symptoms
- Presence of structural heart disease and other comorbidities
- Candidacy for alternative therapies (eg, rate control, AADs)
- Risk of complications
- Patient age and frailty
- Patient preference

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



UPTO 94% PAROXYSMAL AF⁴⁵⁻⁵⁰



UPTO 83% PERSISTENT AF^{45, 48, 51-54}

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**⁷³⁻⁷⁵



37%-75%

PATIENT with **AF ≥75 YEARS** of age⁷⁶

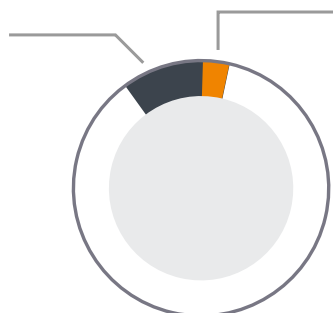


78%

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






UP to 10%

of patients **MAY EXPERIENCE A COMPLICATION**²



2%-3%





of patients **MAY EXPERIENCE POTENTIALLY LIFE-THREATENING**, but manageable, complications^{2, 3}

	COMMON ADVERSE EVENTS	INCIDENCE (%)
LIFE-THREATENING COMPLICATION	<ul style="list-style-type: none"> ■ Periprocedural death  ■ Esophageal perforation or fistula ■ Periprocedural stroke*  ■ Cardiac tamponade 	2%-3%
SEVERE COMPLICATIONS	<ul style="list-style-type: none"> ■ Pulmonary vein stenosis  ■ Persistent phrenic nerve palsy ■ Vascular complications  	5%-7%
	OTHER MODERATE OR MINOR COMPLICATIONS	1%-2%
UNKNOWN SIGNIFICANCE	<ul style="list-style-type: none"> ■ Asymptomatic cerebral embolism (silent stroke)  ■ Radiation exposure 	5%-20%

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.⁵⁵

*Includes transient ischemic attack or air embolism.
Abbreviations: AE = adverse event
Source: 2016 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)
 MORTALITY	6%	9%
 STROKE	2%	2%
 ALZHEIMER'S DEMENTIA	0.2%	0.5%
 NON-ALZHEIMER'S DEMENTIA	0.4%	0.7%

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.⁷⁷

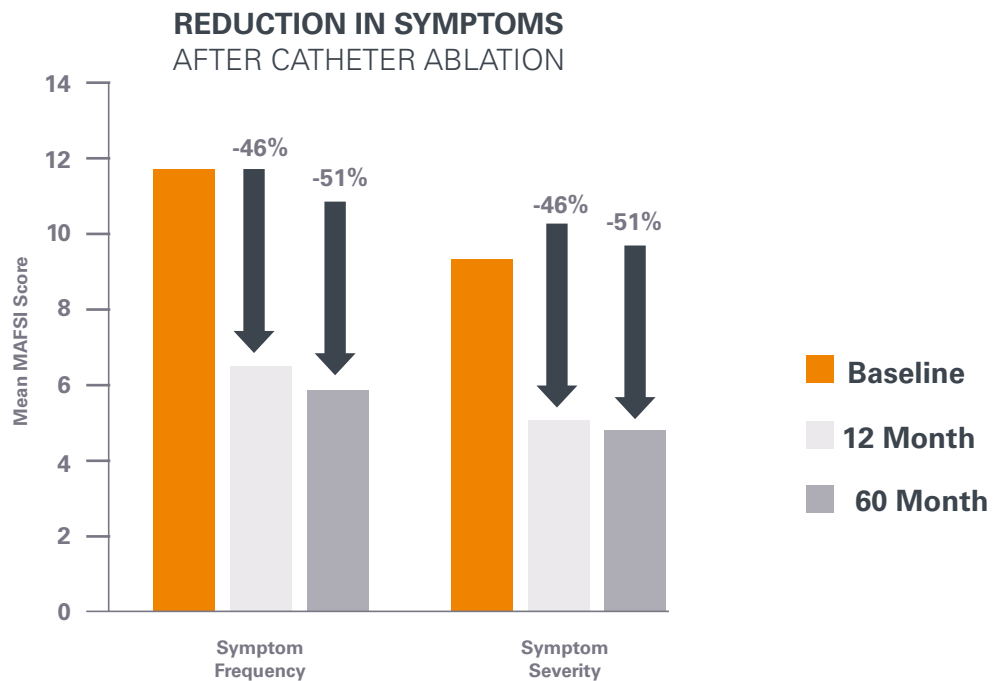
WHAT IS THE PATIENT IMPACT OF CATHETER ABLATION?

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**.⁵⁶



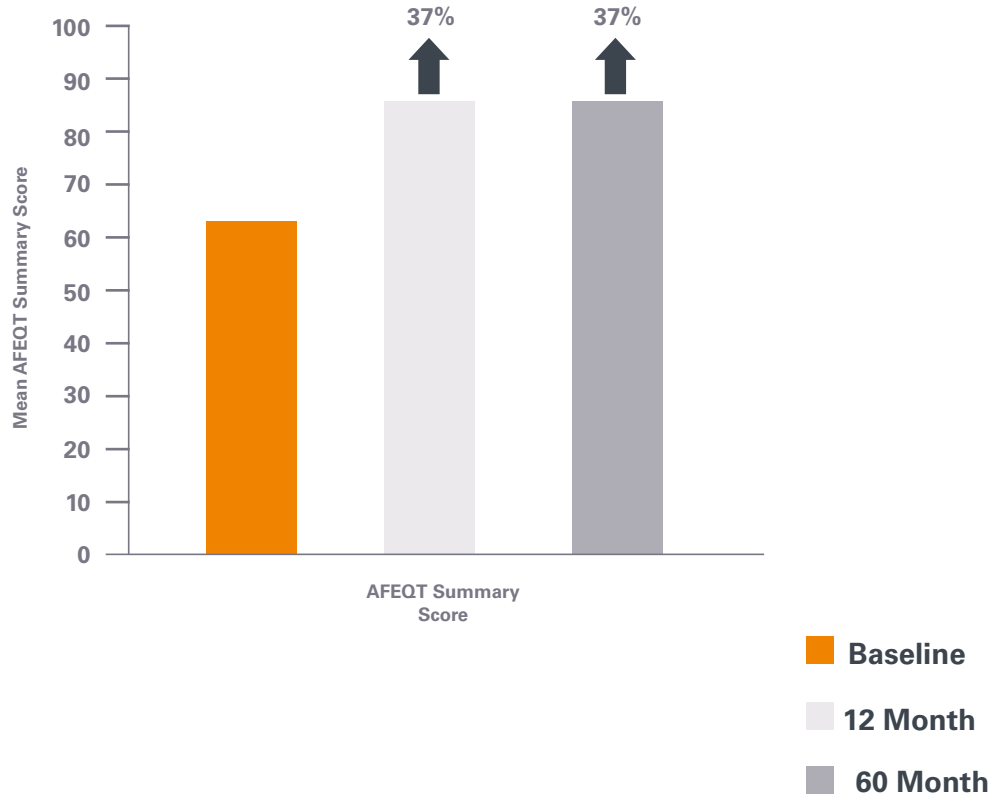
**IMPROVEMENT
IN QUALITY OF LIFE⁵⁶**



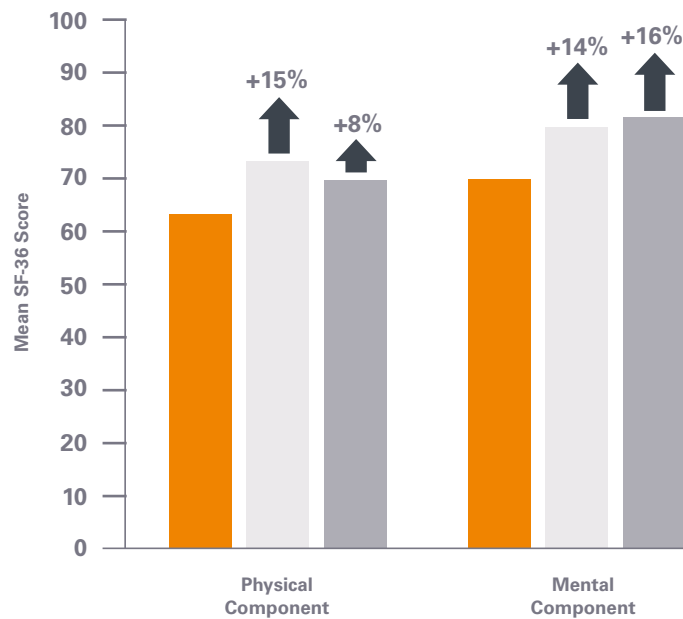
Source: Mark et al. (2019)

Abbreviations: AFECT = Atrial Fibrillation Effect on Quality of Life; MAFSI = Mayo Atrial Fibrillation-Specific Symptom Inventory; SF-36 = Short Form 36 questionnaire Source: Mark et al. (2019)

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, thus, 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^{68,78-83}

Key drivers include:



IMPROVED QUALITY OF LIFE

REDUCED COST OF FOLLOW-UP TREATMENT*

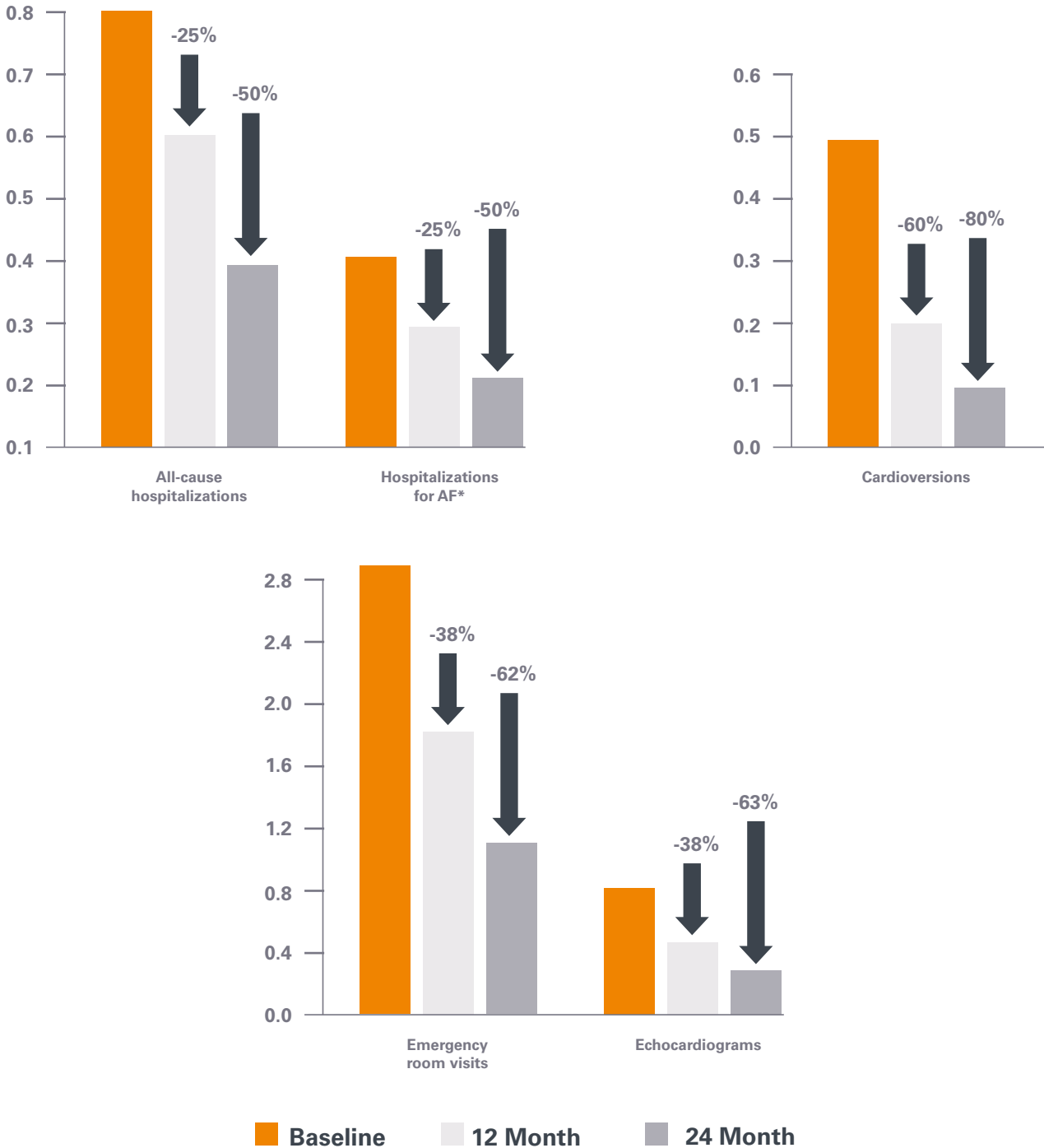
CATHETER ABLATION reduces the need for **unplanned medical visits**

by up to
80%

as compared to before ablation**⁸⁴

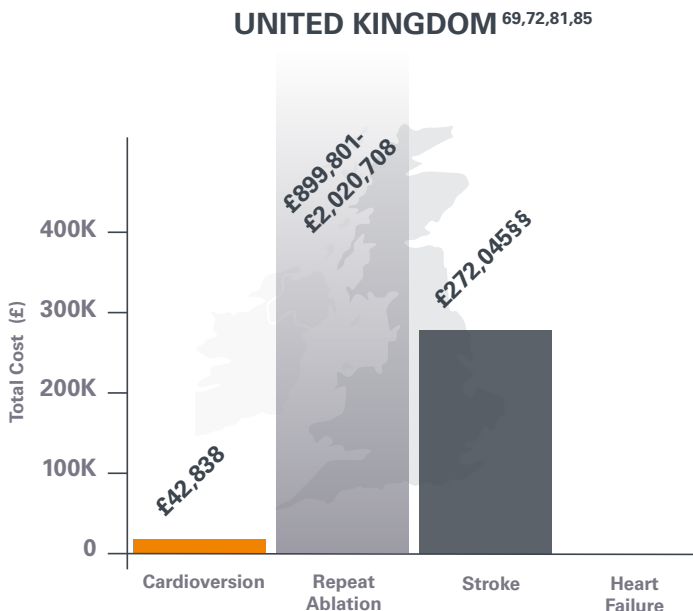
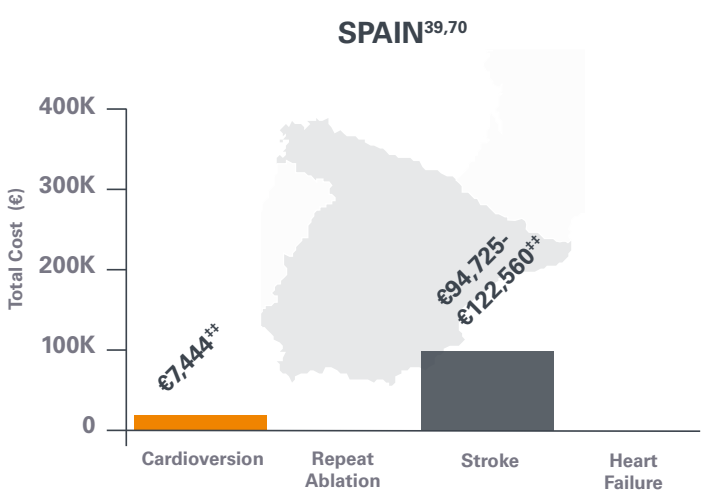
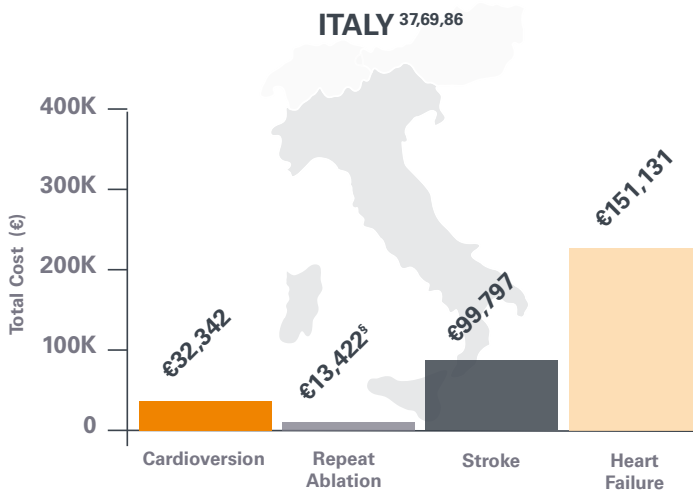
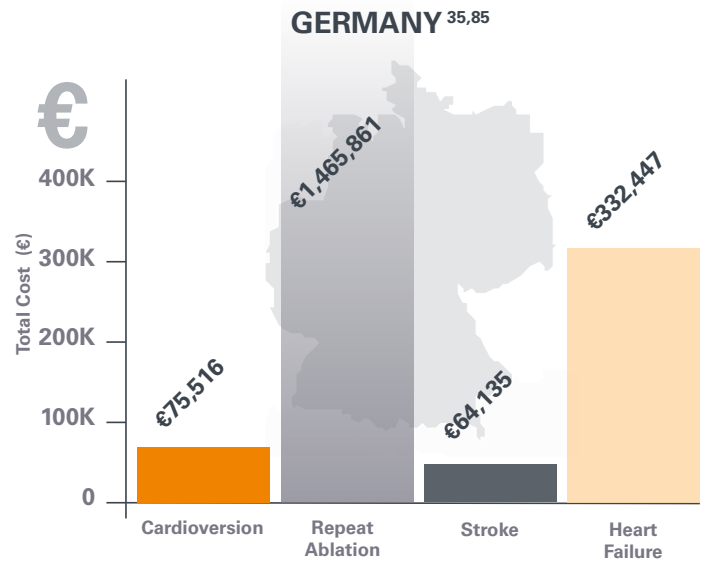
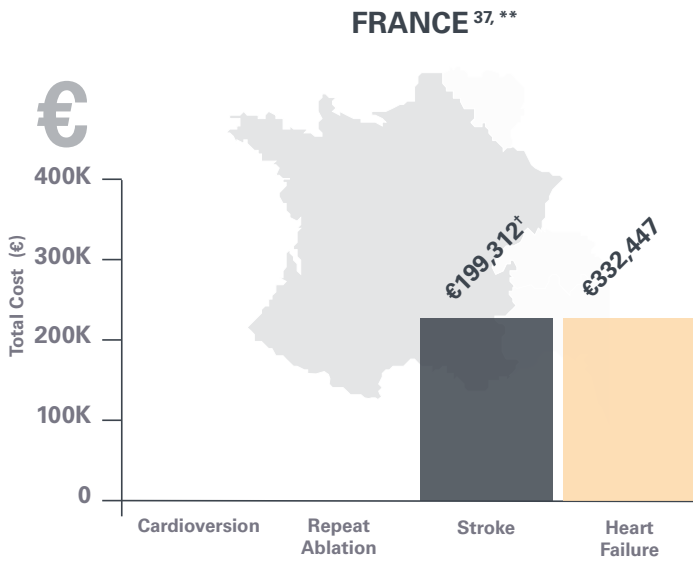
Significant reductions in event rates 1 and 2 years after catheter ablation compared to 1 year before ablation (per patient per year)⁸⁴

(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.^{67,84}

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 Euros⁶¹;
 ** 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.

- Key recent trials that compare the clinical efficacy of catheter ablation to drug therapy, including rate and rhythm control, are as follow:

TRIAL	CABANA ⁵⁵	NOSEWORTHY ET AL. ⁸⁹	CASTLE-AF ⁵⁷	ATTEST ⁵⁹
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

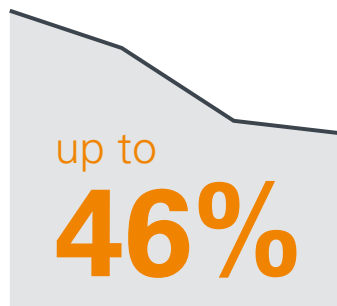
The **CABANA** trial found that **CATHETER ABLATION** was more **EFFECTIVE** at preventing recurrence of AF with



more patients

FREE FROM ATRIAL ARRHYTHMIA
over **4 years** compared to drug therapy⁵⁵

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.^{55,89}

* (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

In the CASTLE-AF trial:



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

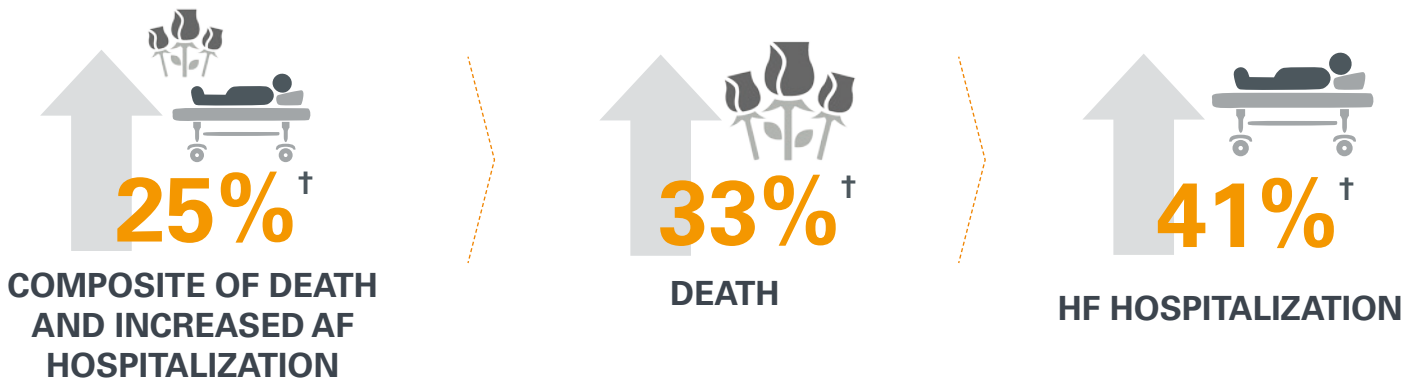
compared to ~25% of patients on drug therapy at 1 year follow-up ($p > 0.001$).⁵⁷



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

as compared to drug therapy over a 5 year follow-up.⁵⁷

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.

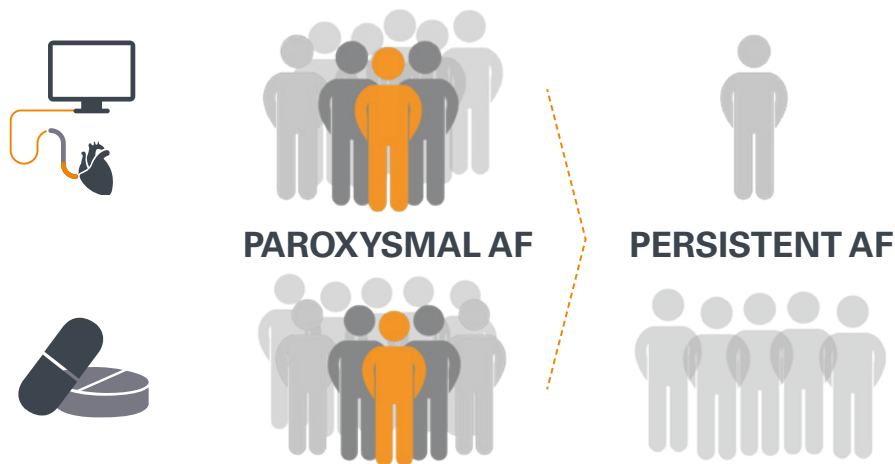


*Modified intention-to-treat analysis which excluded the following: patients who had died or withdrew during the trial run-in period; end-point events occurring during the run-in period; events other than death during the 3-month blanking period after ablation; ** $p=0.007$; † $p=0.01$; ‡ $p=0.004$.

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***⁵⁹



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**.^{55,57,58}

* (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 ⁵⁵	CAPTAF ⁵⁸
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

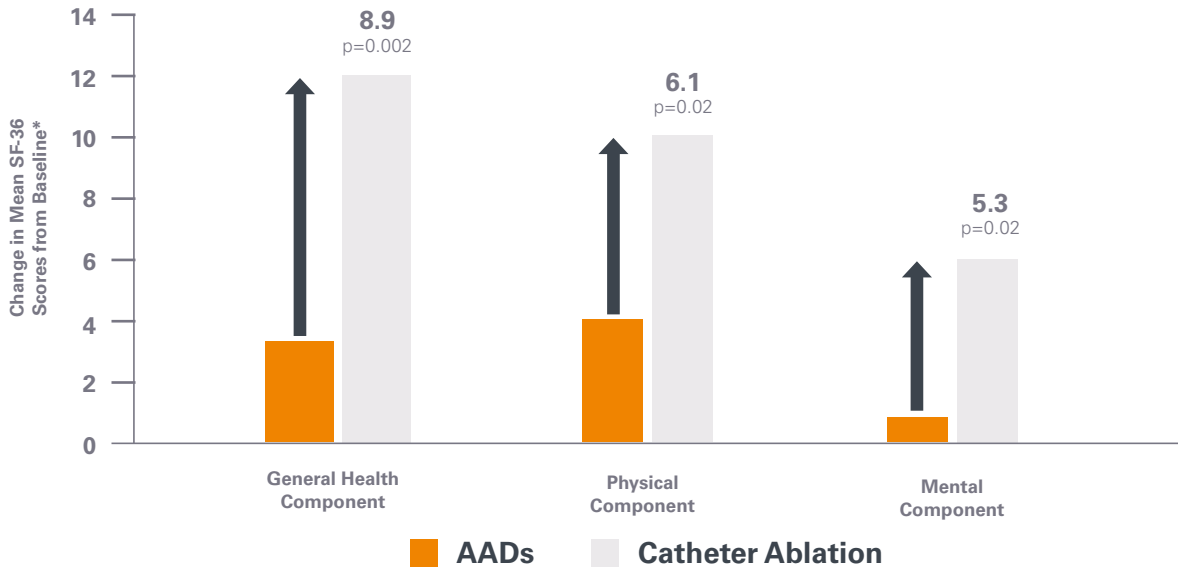
The **CABANA trial** reported significantly **GREATER IMPROVEMENT** from baseline in quality of life **WITH CATHETER ABLATION** than with drug therapy at 1 year.



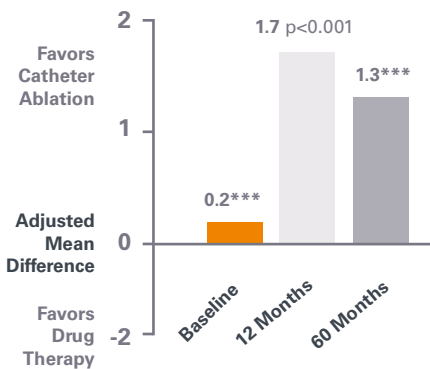
Greater improvement in quality of life from baseline was **MAINTAINED OVER 5 YEARS**.⁵⁶

■ COMPARISON OF TREATMENTS

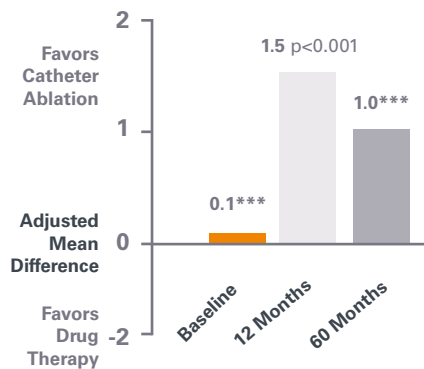
- The CAPTAF trial reported a **significantly** and **clinically** relevant **improvement** from baseline in patient-reported quality of life with catheter ablation than AADs at 1 year.⁵⁸



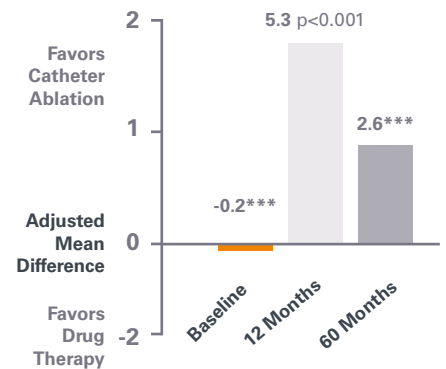
MAFSI SYMPTOM FREQUENCY SCORES**



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 use⁹⁰

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.**⁹⁰



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

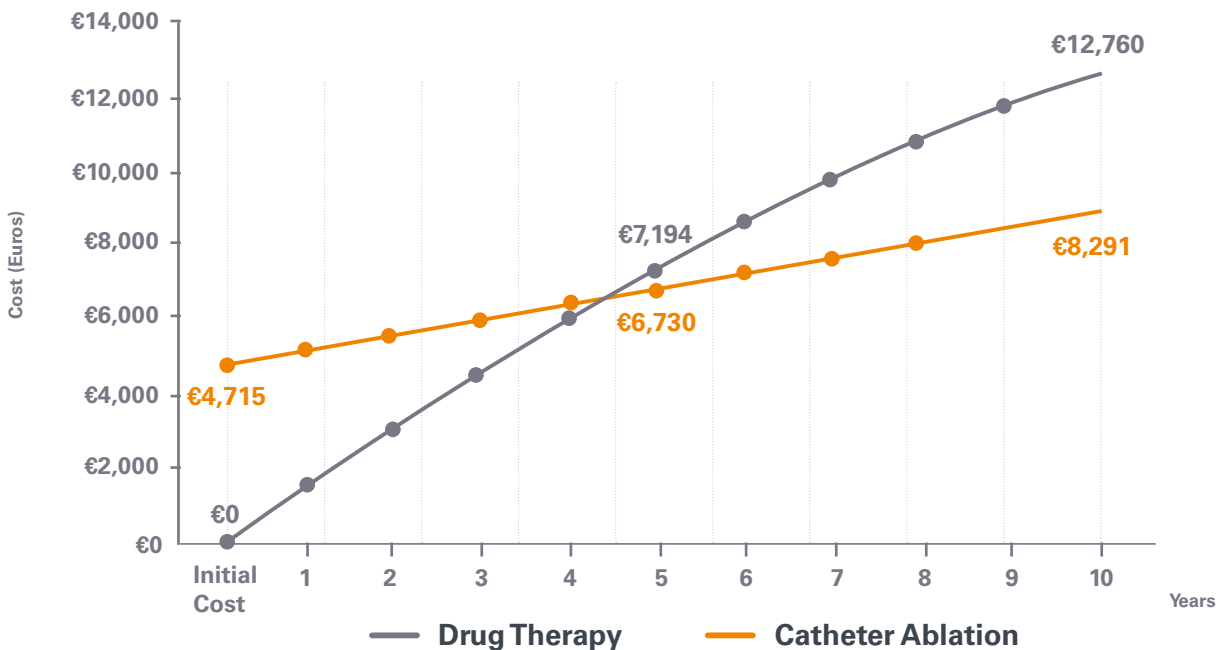
**1 year time frame excludes resource use during the 3 month post-ablation blanking period

■ 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.^{68,78-83}

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

French study highlights the cumulative costs of PAROXYSMAL AF treatment over 10 Year ⁶⁶



PROJECTING COSTS TO 10 YEARS AFTER ABLATION*

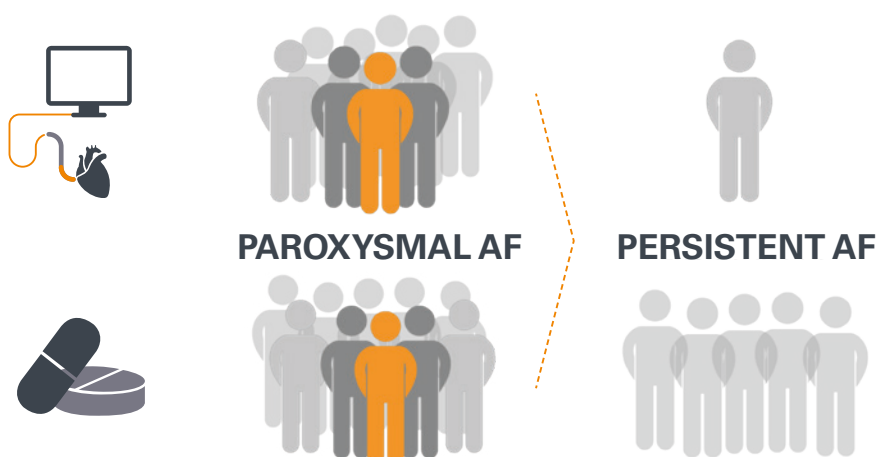


catheter ablation was associated with a
35% SAVINGS
IN COSTS COMPARED TO DRUG THERAPY ⁶⁸

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 YEAR⁴⁵⁻⁵⁴



Patients with **paroxysmal AF** are almost
10 TIMES LESS LIKELY TO PROGRESS TO PERSISTENT AF
than **those on AADs**^{*59}

CATHETER ABLATION
was also associated with

up to
46%

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



Death



Stroke



Cardiac arrest



**Cardiovascular
hospitalization**

compared to drug therapy over 7-years follow-up.⁸⁹

The 2016 ESC/EACTS guidelines for the management of AF and the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF highlight key areas of future research including the following:^{2, 3}

INTEGRATED HEALTHCARE MANAGEMENT TEAM



- Does a **team approach lead to better outcomes** for patients with AF than isolated pillars of care?
- What are the **roles of each member** of the heart team?

RHYTHM CONTROL OUTCOMES



- Does rhythm control therapy have a **prognostic benefit** in patients with AF?
- What are the outcomes of catheter ablation in **high risk patients**?
- What is the **clinical relevance of catheter ablation outcomes** and how do these outcomes relate to quality of life and stroke risk?
- What are the **characteristics of patients** who are most likely to benefit from catheter ablation?

ORAL ANTICOAGULATION THERAPY



- It is unclear if a patient who has subclinical or no AF after successful catheter ablation needs oral anticoagulation. Are there patients who can **safely discontinue oral anticoagulation therapy**?

PROGRESS IN RHYTHM CONTROL THERAPY



- What is the **value of new technologies** for catheter ablation and new AADs in the treatment of patients with AF?

RECURRENCE OF AF AFTER CATHETER ABLATION



- There is limited data on the **optimal treatment strategy** for patients who experience recurrence of AF after catheter ablation. Should patients receive a repeat catheter ablation, surgical ablation, AADs or hybrid therapy (ie, combining AADs with ablation)?

1. Iuzzo PA (2015). Handbook of Cardiac Anatomy, Physiology and Devices. Springer Science and Business Media, LLC: Switzerland.
2. 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.
3. 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.
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. 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.
25. 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.
26. Dilaveris PE, Kennedy HL (2017) Silent atrial fibrillation: epidemiology, diagnosis, and clinical impact. *Clin Cardiol* 40 (6): 413-418.
27. 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*
28. Odutayo 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 Tuluca 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, Ranchar 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, 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.
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. Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J (2015) Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* (3): 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 (FI_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, Giszarson 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. Bruggenjurgan 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, Rosenqvist M, Lindgren P (2013) Cost-effectiveness analysis of dronedarone versus other antiarrhythmic 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, Hockenull 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, Behloul 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. Parreth, 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.

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