



ATRIAL FIBRILLATION MANAGEMENT

2019 Executive Summary

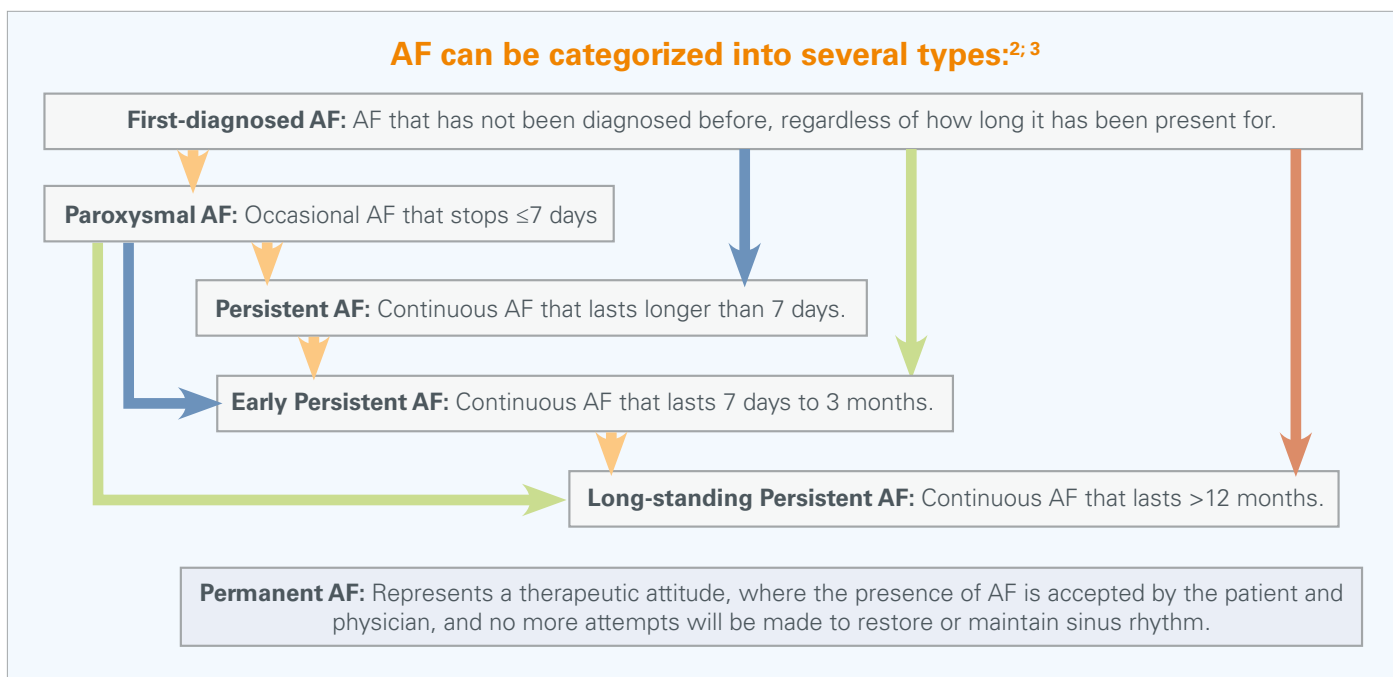
**Overview of Atrial Fibrillation Management
and Treatment Outcomes**



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




PAROXYSMAL
AF

1 in 5
PATIENTS PROGRESS
IN 1 YEAR²⁴⁻²⁷



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.

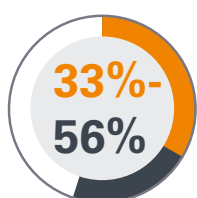
AF patient care pathway management includes:²

- 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

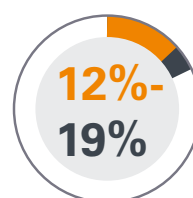
- Education and screening programs aimed at **increasing awareness and diagnosis of AF are critical to reducing the risk of stroke and death** in patients with undiagnosed AF.⁴⁰⁻⁴¹
 - Ideally, patients will recognize AF symptoms and contact their clinicians when symptoms arise.⁴²
- **Early treatment 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.

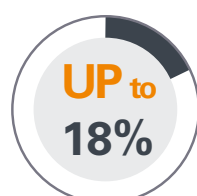
With drug therapy treatment:



of patients are in **NORMAL SINUS RHYTHM AT 1 YEAR⁴³**



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



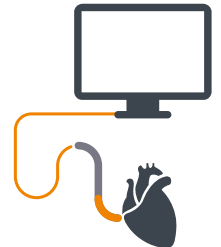
of patients **UP to IMPROVEMENT IN QUALITY OF LIFE⁴⁴**

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:

 **94%** of patients are **FREE FROM ARRHYTHMIA RECURRENCE AT 1 YEAR**⁴⁵⁻⁵⁴

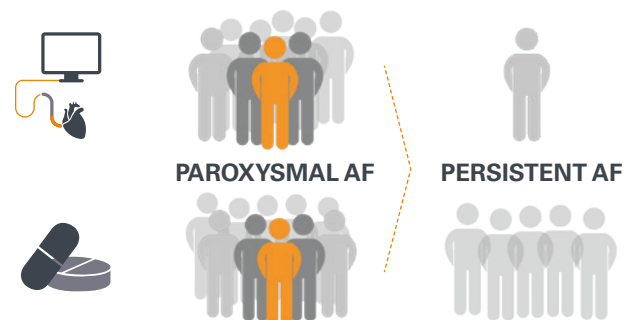
1.8% of patients experience **AN ABLATION-RELATED ADVERSE EVENT**⁵⁵



 **UP to 37% IMPROVEMENT IN QUALITY OF LIFE**⁵⁶ 

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:

 improvement in survival **UP to 48%** **FREE FROM ATRIAL ARRHYTHMIA** over **4 years** after ablation⁵⁵



Patients with **paroxysmal AF** who undergo catheter ablation 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}



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

Guidance on the delivery of good care to patients with AF and on the use of catheter and surgical ablation to treat AF are available from the 2016 ESC/EACTS guidelines² & 2017 HRS/EHRA/ECAS/APHRs/SOLAECE expert consensus statement on catheter and surgical ablation³

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



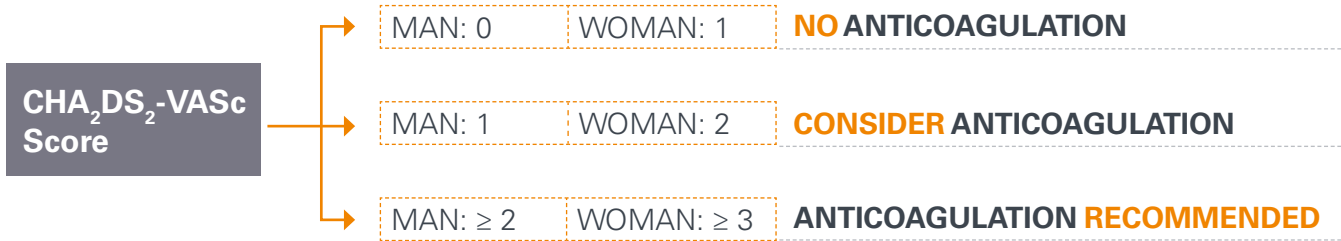
IMPROVE ADHERENCE TO LONG-TERM THERAPY



IMPROVE ADHERENCE TO GUIDELINES

MANAGEMENT OF AF PATIENTS

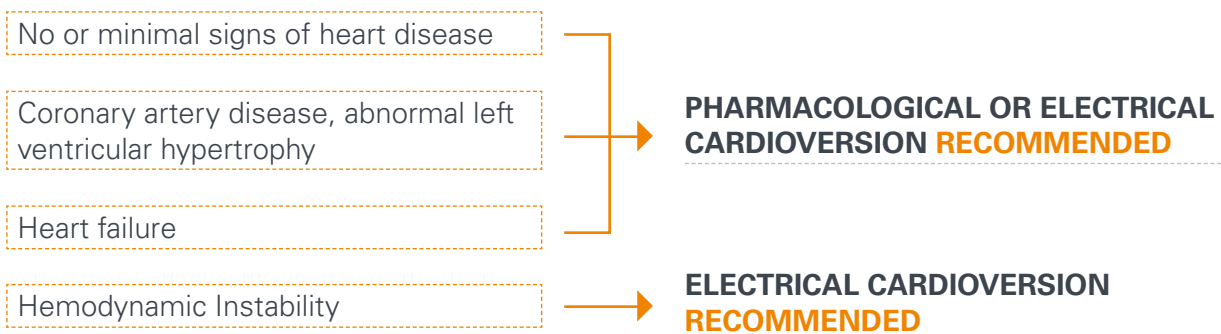
2 Oral Anticoagulation Therapy for Stroke Prevention in Patients with AF²



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

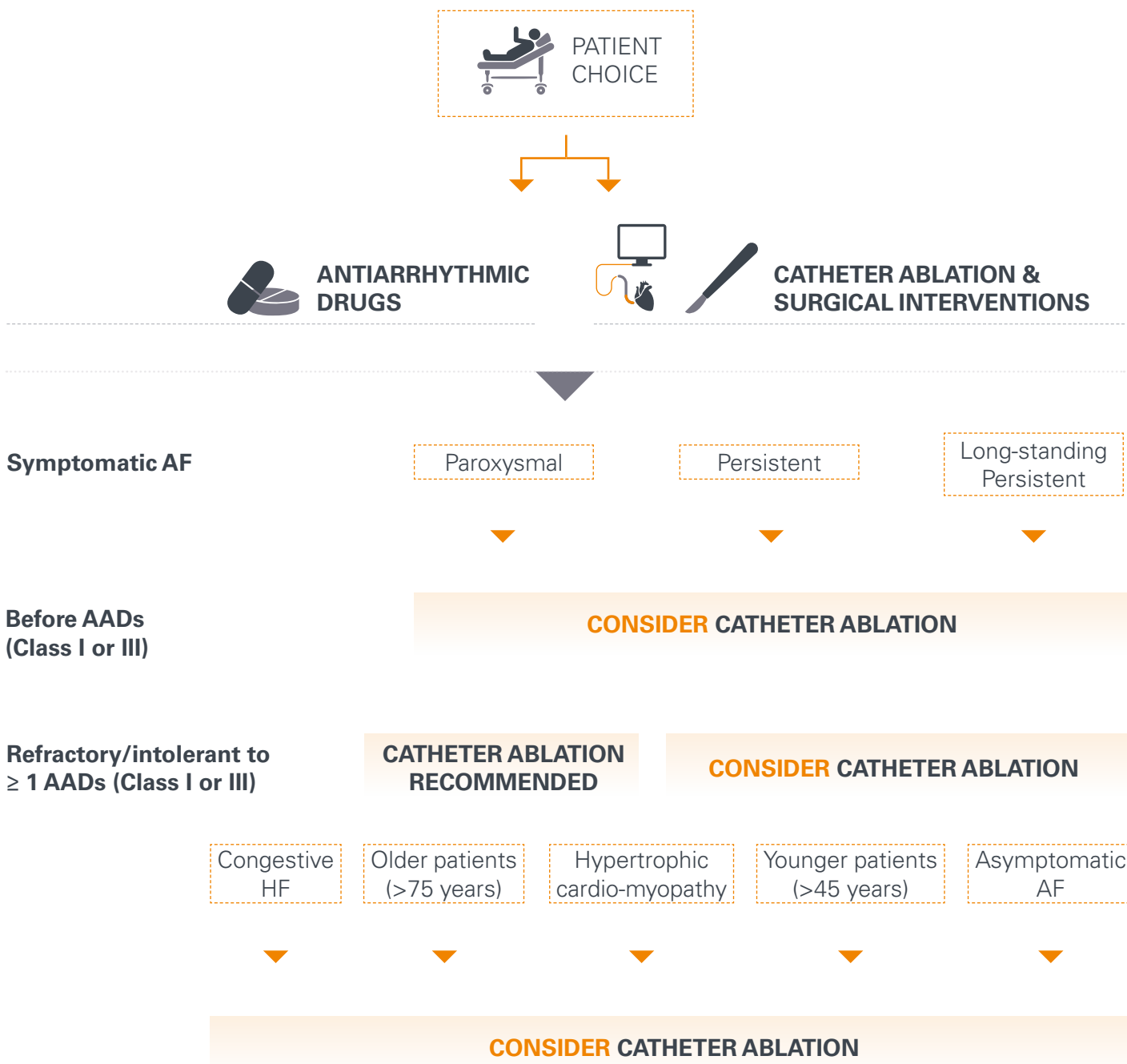


4 Acute Rhythm Control Therapy to Restore Normal Sinus Rhythm²

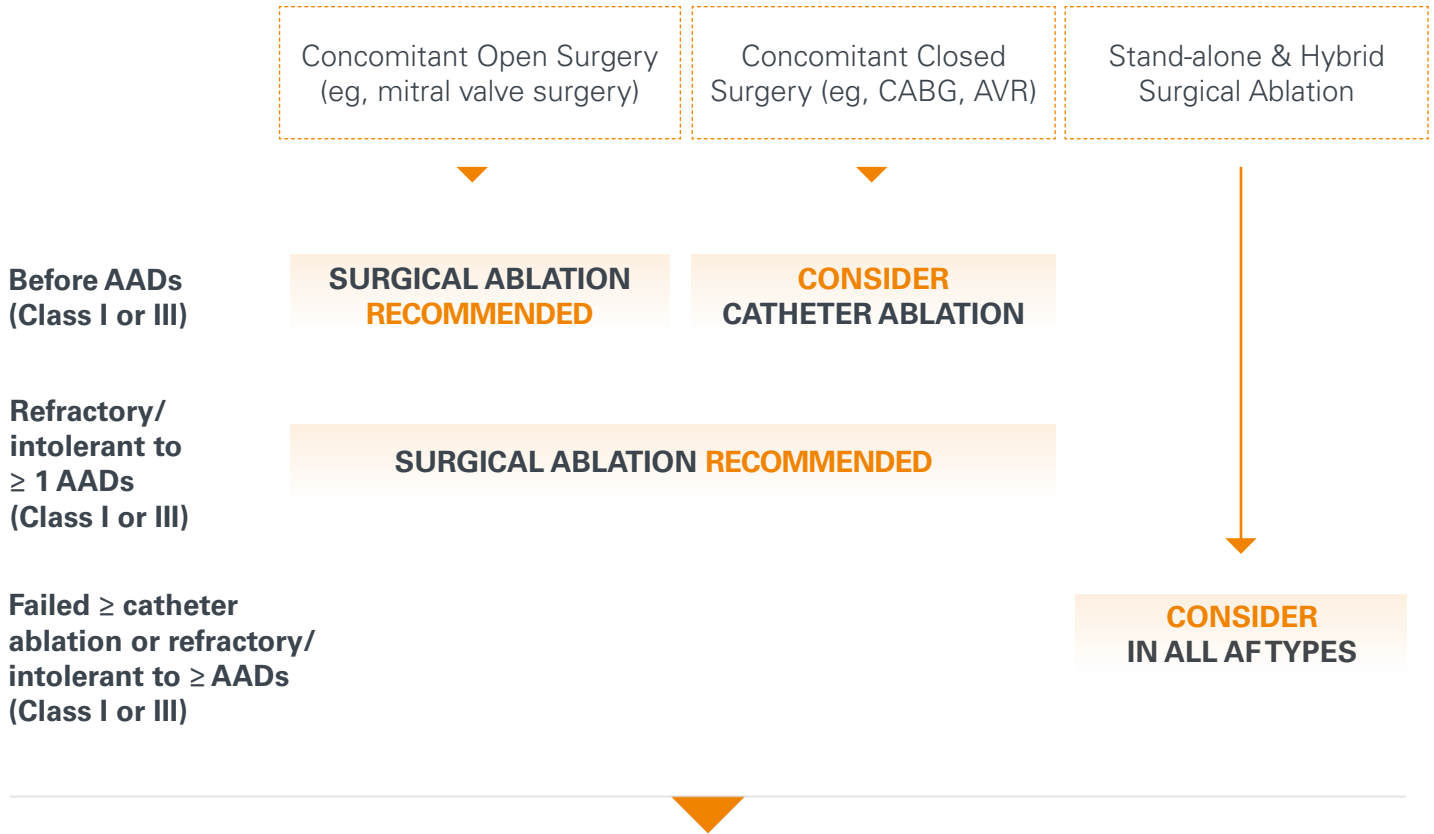


5 Rhythm Control Therapy to Maintain Normal Sinus Rhythm and Improve Symptoms of AF^{2,3}

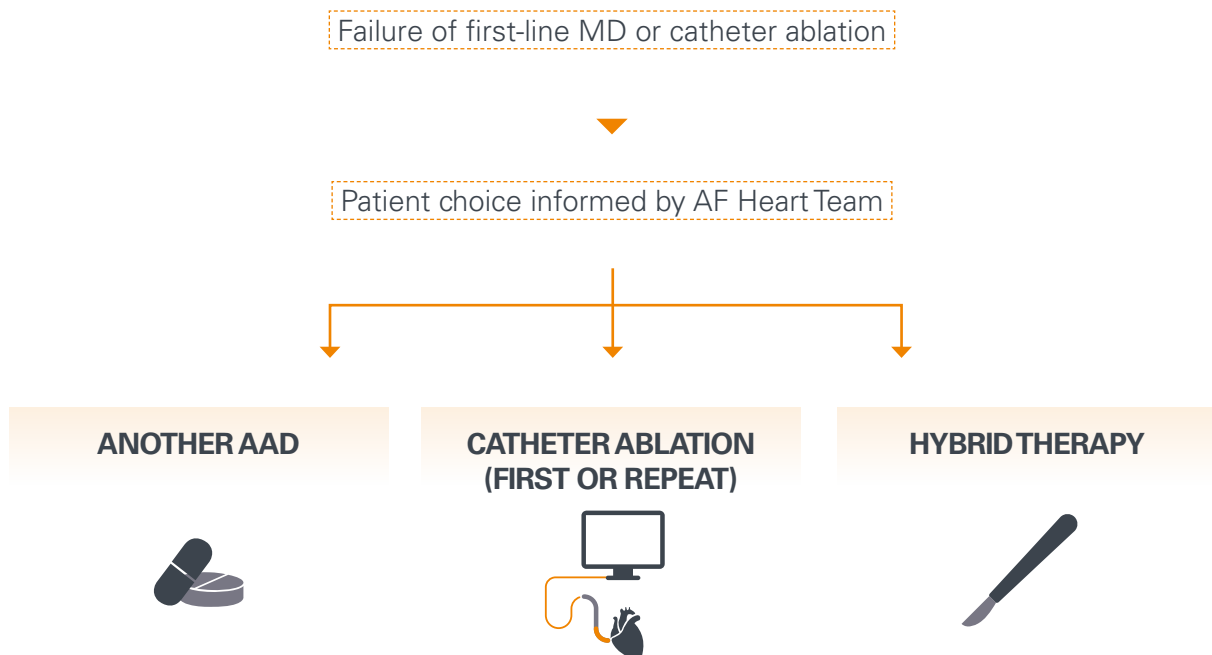
- Guidelines recommend that treatment with AADs, catheter ablation, and/or surgical ablation be dependent on patient choice.^{2,3}
- The choice of AADs needs to consider the presence of comorbidities, cardiovascular risk, potential for proarrhythmia, toxic effects, symptom burden, and patient preference.²



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, including stroke and heart failure.

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 over the long-term.²⁻³

- 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 rhythm⁶⁰

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

ACUTE RHYTHM CONTROL THERAPIES

RHYTHM CONTROL THERAPIES FOR AN EPISODE OF AF

Electrical and pharmacological cardioversion

NON- EPISODIC RHYTHM CONTROL THERAPIES



PHARMACOLOGICAL



INTERVENTIONAL



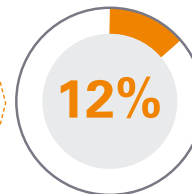
SURGICAL

Over the long-term:

RATE CONTROL THERAPIES

are indicated to lower and control the heart rate in patients with AF

may also be sufficient **TO CONTROL SYMPTOMS OF AF**



of patients being in **SINUS RHYTHM AT 1-YEAR FOLLOWUP**⁶¹

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}

Antiarrhythmic drug therapy is an integral part of maintaining sinus rhythm after cardioversion; antiarrhythmic drugs act to suppress the firing of or depress the transmission of abnormal electrical signals.²

WHAT IS THE IMPACT OF ANTIARRHYTHMIC DRUG THERAPY IN MANAGING AF?

Antiarrhythmic drug therapy is fairly safe, cost effective and affordable in the short term but can be costly over the long term. Although moderately effective at maintaining normal sinus rhythm, it is effective at controlling symptoms of AF and improving patient quality of life.

- 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**

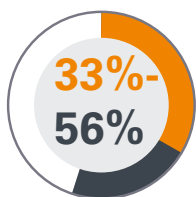
such as patient age and **renal or hepatic function**

PATIENT PREFERENCE

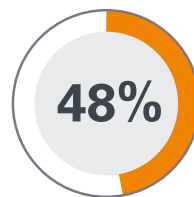
CLINICAL IMPACT

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.

AADs are moderately effective:



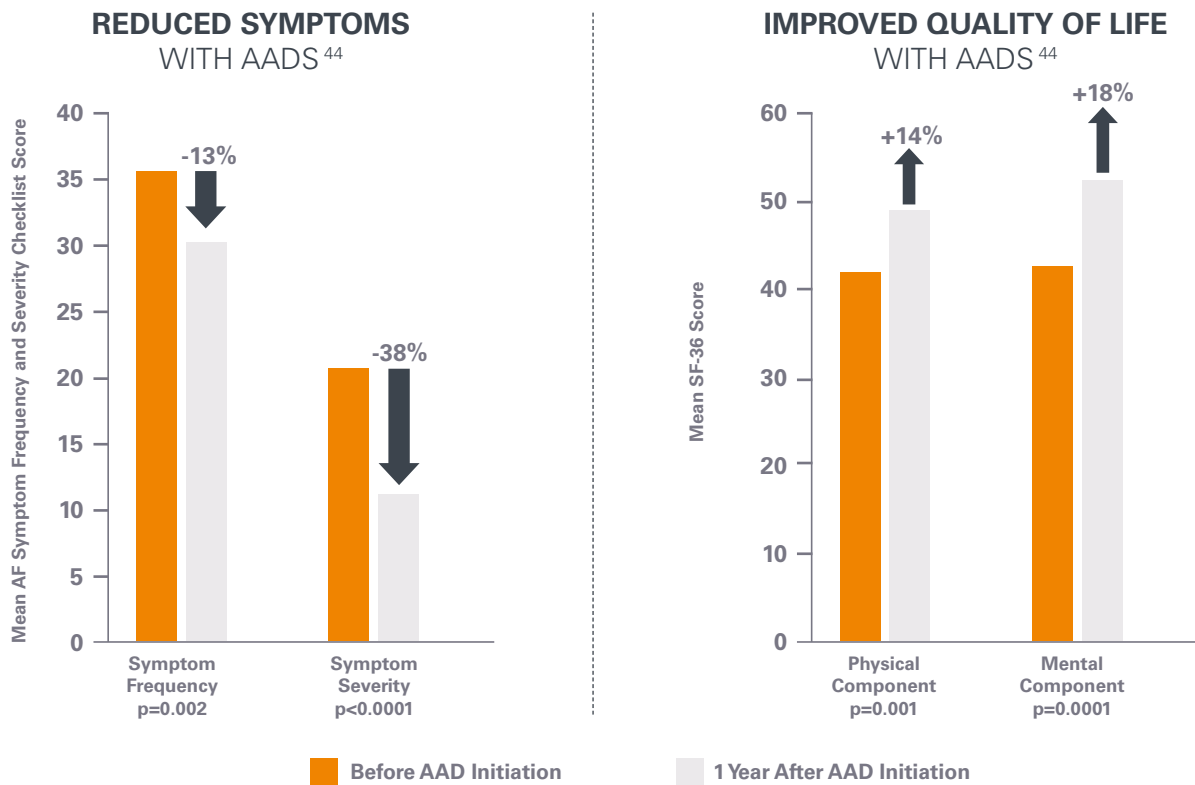
rate for **maintaining normal sinus rhythm** at 1 year.⁴³



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

PATIENT IMPACT

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



Abbreviations: AAD = antiarrhythmic drug; AF = atrial fibrillation; SF-36 = Short Form 36 questionnaire. Source: Jais et al. (2008)

ECONOMIC IMPACT

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, heart failure and mortality.⁶³⁻⁶⁵

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*⁶⁶

- Cost of AAD therapy is influenced by its **toxicity level** and **effectiveness** in restoring sinus rhythm and **reducing the risk of AF-related consequences**.^{65, 67-72}

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

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}

WHAT IS THE IMPACT OF CATHETER ABLATION IN MANAGING AF?

Catheter ablation is highly effective at maintaining sinus rhythm, has a low rate of complications, reduces patient risk of AF-related complications, controls symptoms and significantly improves patient quality of life. It has been proven to be cost effective by reducing the need for unplanned medical visits and overall healthcare cost.

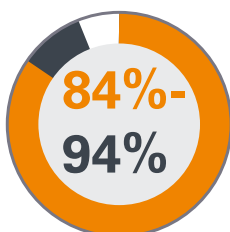
Key considerations for treating patients with catheter ablation include:³

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

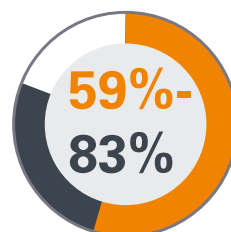
CLINICAL IMPACT

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 highly 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:



PAROXYSMAL
AF⁴⁵⁻⁵⁰

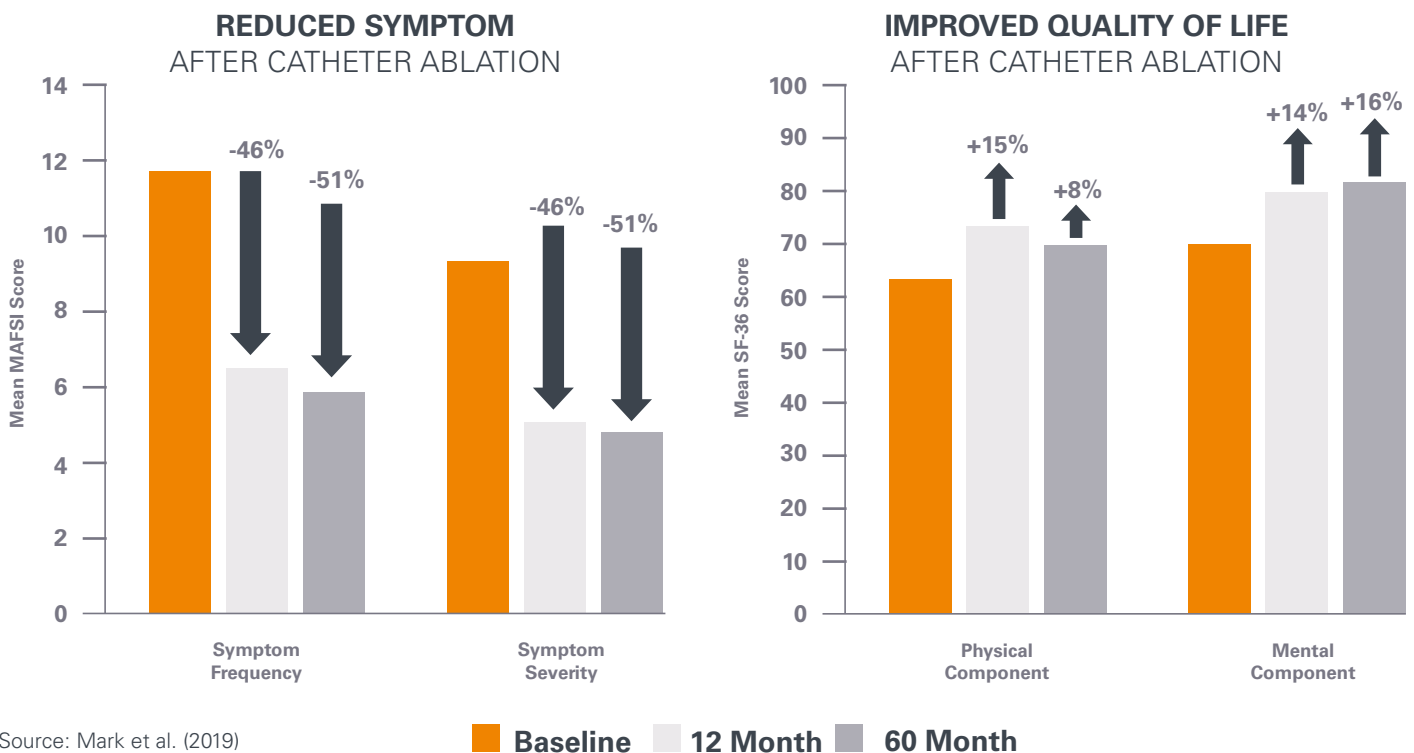


PERSISTENT
AF^{45, 48, 51-54}

PATIENT IMPACT

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



Source: Mark et al. (2019)

ECONOMIC IMPACT

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, in turn, reducing overall healthcare cost.

CATHETER ABLATION

reduces the need for unplanned ER visits and hospitalizations

by up to
80%

as compared to before ablation*⁷³

*at 2 years based on evidence outside of Europe

Recent studies have examined the comparative clinical and cost effectiveness of catheter ablation and drug therapy, including rate and rhythm control drugs, 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.

CLINICAL IMPACT

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

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



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

CATHETER ABLATION was also associated with

up to **46%**

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



Death



Stroke



Cardiac arrest



Cardiovascular hospitalization

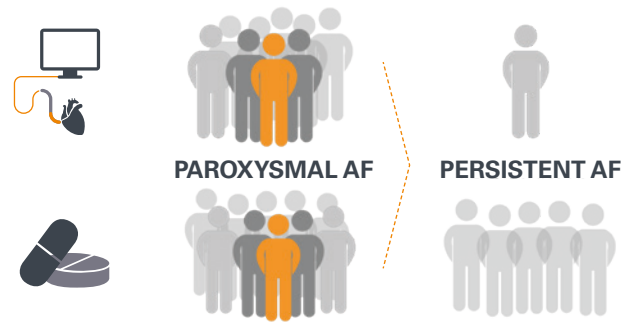
compared to drug therapy over 7-years follow-up.⁷⁴

* (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

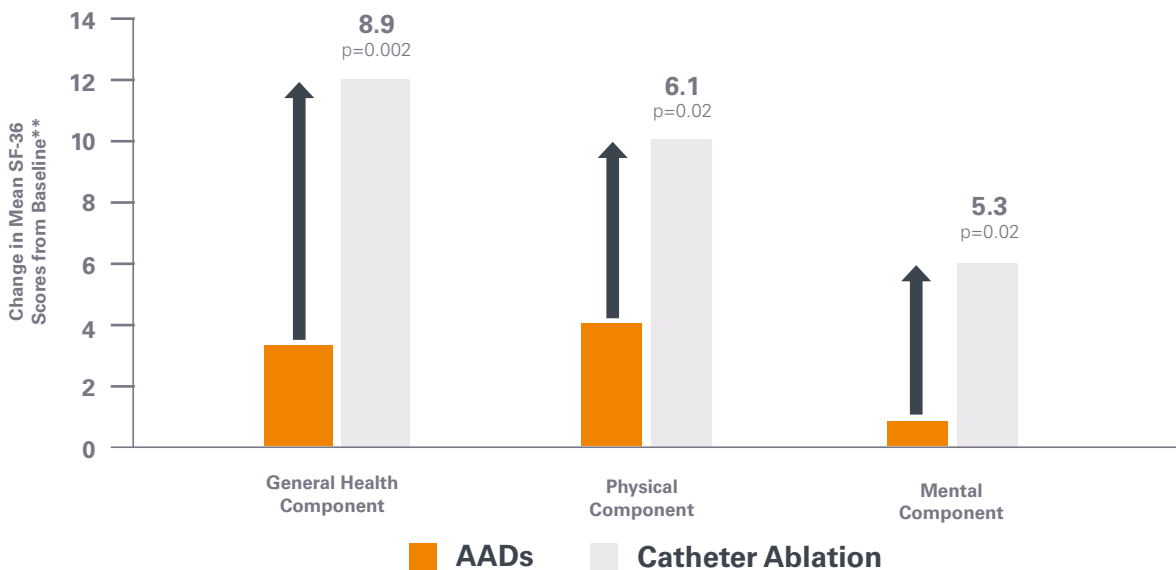
The **ATTEST randomized controlled** trial found that patients receiving ablation, with **paroxysmal AF** are almost **10 TIMES LESS LIKELY TO PROGRESS TO PERSISTENT AF** than **those on AADs***⁵⁹



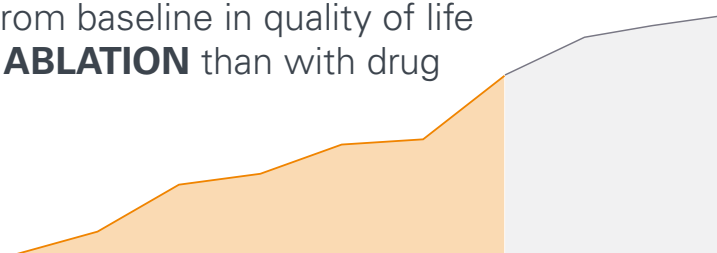
PATIENT IMPACT

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

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



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

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

**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)

COMPARISON OF TREATMENTS

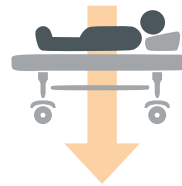
ECONOMIC IMPACT

Catheter ablation is cost effective compared to antiarrhythmic drugs for the long term treatment of patient with AF.

- A UK database analysis found that catheter ablation treatment was associated with reduced resource utilization compared to drugs over 1 year (excluding the 3 month blanking period).⁷⁶



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



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

- Despite the initial investment, costs become favorable for catheter ablation at 5 years after the initial ablation procedure when compared to antiarrhythmic drugs.⁶⁶

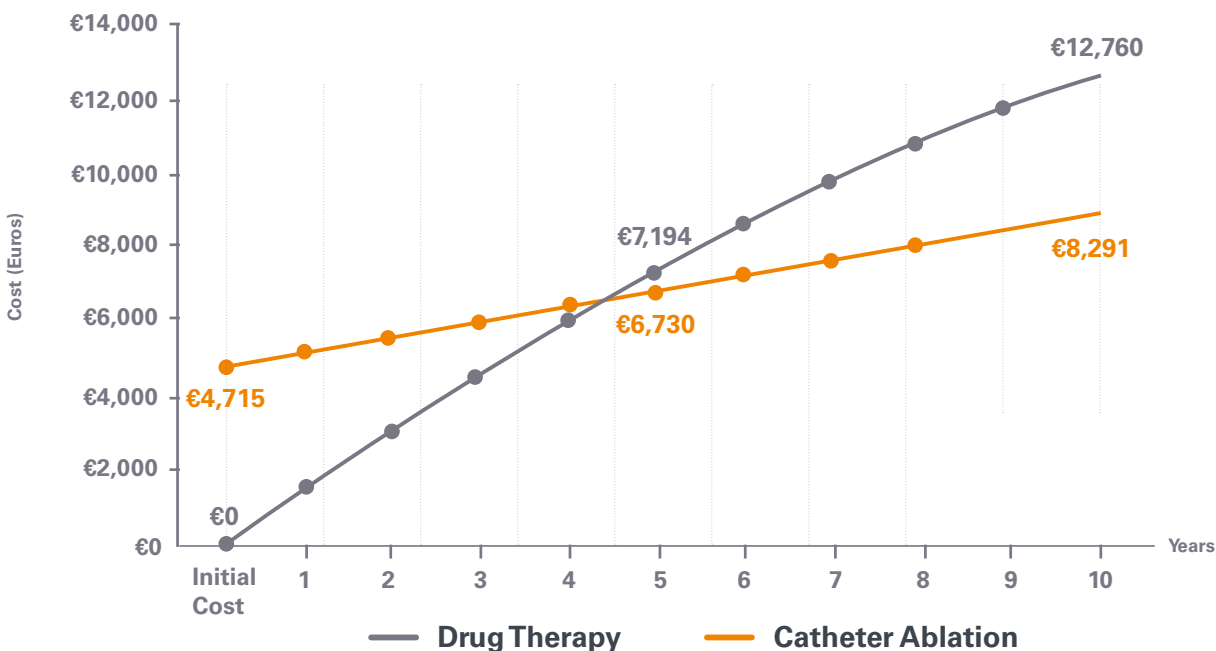


PROJECTING COSTS TO 10 YEARS AFTER ABLATION*



catheter ablation was associated with a **35% SAVINGS** IN COSTS COMPARED TO DRUG THERAPY⁶⁶

CUMULATIVE COSTS OF PAROXYSMAL AF TREATMENT OVER 10 YEARS

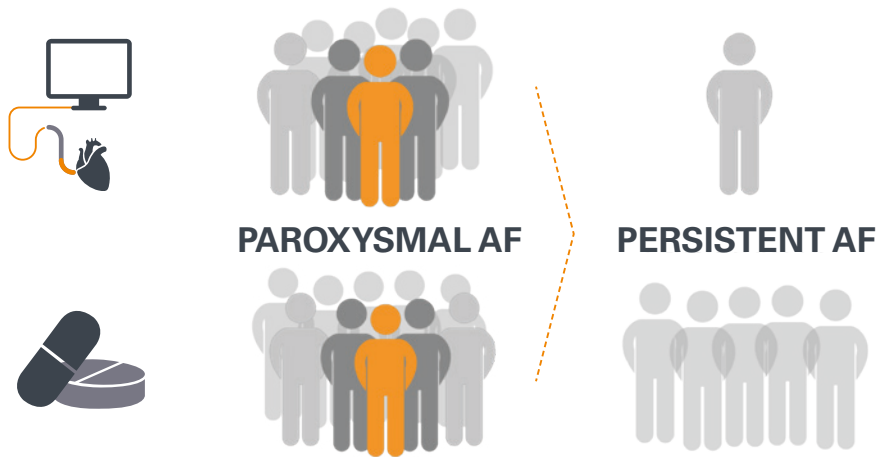


*Study performed in France; data were limited for other European countries.

Catheter ablation is more clinically effective and cost effective compared to drug therapy for the treatment of patients with AF.^{55, 57-59,66, 74}



94%
of patients are
FREE FROM ARRHYTHMIA RECURRENCE
AT 1 YEAR⁴⁵⁻⁵⁴



Patients with **paroxysmal AF** who undergo catheter ablation 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.⁷⁴

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?

RECURRENCE OF AF AFTER CATHETER ABLATION



- There is limited data on the **optimal treatment strategy** in 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)?

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?

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, Gopinathnair 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, 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, Soular 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, Bruggenjurgan 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 (Fl_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. 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.
61. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S et al. (2003) Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol* 41 (10): 1690-1696.
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. 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.
64. Nilsson J, Akerborg O, Bego-Le Bagousse G, Rosenquist 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.
65. 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.
66. 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.
67. 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.
68. McBride D, Mattenklott AM, Willich SN, Bruggenjürgen B (2009) The costs of care in atrial fibrillation and the effect of treatment modalities in Germany. *Value Health* 12 (2): 293-301.
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. 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.
72. 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.
73. Samuel M, AvgilTsadok 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.
74. 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.
75. 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.
76. 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.

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.

123104-200130 EMEA
© Johnson & Johnson Medical NV/SA 2020

