Overview of Atrial Fibrillation Management and Treatment Outcomes
## TABLE OF CONTENTS

### OVERVIEW

Atrial Fibrillation ........................................................................................................ 4

### MANAGEMENT OF AF PATIENTS

What are the recommendations for managing a patient with AF? ......................... 8
What is the goal of AF management? ........................................................................ 12
How is the patient with AF treated? ......................................................................... 14

### DRUG THERAPY

How to choose an AAD for managing AF? ............................................................... 17
What is the clinical impact of AAD therapy? .......................................................... 18
What is the patient impact of AAD therapy? ............................................................ 20
What is the economic impact of AAD therapy? ....................................................... 22

### CATHETER ABLATION

How is catheter ablation used in the management of AF? ..................................... 24
What is the clinical impact of catheter ablation? ..................................................... 24
What is the patient impact of catheter ablation? ..................................................... 28
What is the economic impact of catheter ablation? ................................................ 30

### COMPARISON OF TREATMENTS

What is the impact of catheter ablation compared to drug therapy in managing AF? 33
What is the clinical impact of catheter ablation as compared to AADs? .............. 34
What is the impact of catheter ablation on patients as compared to AAD treatment? 38
What is the economic impact of catheter ablation compared to AAD therapy? ... 40

### CONCLUSION

................................................................................................................................. 42

### REFERENCES

................................................................................................................................. 44
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).\(^1\)

**AF can be categorized into several types:**\(^2,3\)

- **First-diagnosed AF:** AF that has not been diagnosed before, regardless of how long it has been present for.
- **Paroxysmal AF:** Occasional AF that stops ≤7 days
- **Persistent AF:** Continuous AF that lasts longer than 7 days.
- **Early Persistent AF:** Continuous AF that lasts 7 days to 3 months.
- **Long-standing Persistent AF:** Continuous AF that lasts >12 months.
- **Permanent AF:** Represents a therapeutic attitude, where the presence of AF is accepted by the patient and physician, and no more attempts will be made to restore or maintain sinus rhythm.

**Risk factors for AF include:**

- **LIFESTYLE FACTORS**
  - Obesity\(^4-7\), smoking\(^2\), alcohol consumption\(^2,7-8\)
- **OTHER CONDITIONS**
  - High blood pressure\(^7\), heart failure\(^9,14\), history of heart attack\(^4,15\), 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

Increase heart failure 5x
Increase stroke 2.4x
Increase cardiovascular mortality 2x

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
AF patient care pathway management includes:

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

**ELECTRICAL OR PHARMACEUTICAL CARDIOVERSION**
- 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. Ideally, patients will recognize AF symptoms and contact their clinicians when symptoms arise.

Early treatment of AF is important, as it may improve patient life expectancy and quality of life.

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:**

- **33%-56%** of patients are in **NORMAL SINUS RHYTHM AT 1 YEAR**
- **12%-19%** of patients **WITHDRAW FROM TREATMENT DUE TO ADVERSE EVENTS**
- **UP to 18%** of patients **IMPROVE IN QUALITY OF LIFE**
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**

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

**UP TO 37% IMPROVEMENT IN QUALITY OF LIFE**

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

More patients **FREE FROM ATRIAL ARRHYTHMIA OVER 4 YEARS** after ablation

**RATES OF AF-RELATED COMPLICATIONS**

Deaths, Strokes, Cardiac arrest, and Cardiovascular hospitalizations are **LOW**

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

* (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.²³

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**
- **TAILORED MANAGEMENT TO PATIENT PREFERENCES**
- **REDUCE HOSPITALIZATIONS**
- **IMPROVE ADHERENCE TO LONG-TERM THERAPY**
- **IMPROVE ADHERENCE TO GUIDELINES**
2 Oral Anticoagulation Therapy for Stroke Prevention in Patients with AF

- **CHA\_DS\_2-VASc Score**
  - MAN: 0 | WOMAN: 1 | **NO ANTICOAGULATION**
  - MAN: 1 | WOMAN: 2 | **CONSIDER ANTICOAGULATION**
  - MAN: ≥ 2 | WOMAN: ≥ 3 | **ANTICOAGULATION RECOMMENDED**

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

- **LVEF <40% or Signs of Congestive HF**
  - **LOW DOSE β-BLOCKERS RECOMMENDED**
- **LVEF ≥40%**
  - **β-BLOCKERS OR NONDIHYDROPYRIDINE CALCIUM CHANNEL ANTAGONIST RECOMMENDED**

4 Acute Rhythm Control Therapy to Restore Normal Sinus Rhythm

- No or minimal signs of heart disease
- Coronary artery disease, abnormal left ventricular hypertrophy
- Heart failure
- Hemodynamic Instability
  - **PHARMACOLOGICAL OR ELECTRICAL CARDIOVERSION RECOMMENDED**
  - **ELECTRICAL CARDIOVERSION RECOMMENDED**

 Recommended Target Heart Rate: <110 bpm
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

**Symptomatic AF**
- Paroxysmal
- Persistent
- Long-standing Persistent

**Before AADs (Class I or III)**

**Refractory/intolerant to ≥1 AADs (Class I or III)**

**CATHETER ABLATION RECOMMENDED**
- Congestive HF
- Older patients (>75 years)
- Hypertrophic cardio-myopathy
- Younger patients (>45 years)

**CATHETER ABLATION**
- Asymptomatic AF

**CONSIDER CATHETER ABLATION**

**PATIENT CHOICE**

**ANTIARRHYTHMATIC DRUGS**

**CATHETER ABLATION & SURGICAL INTERVENTIONS**
Selection of 2nd rhythm control therapy after failure of 1st rhythm control therapy

Before AADs (Class I or III)

- Concomitant Open Surgery (eg, mitral valve surgery)
- Concomitant Closed Surgery (eg, CABG, AVR)
- Stand-alone & Hybrid Surgical Ablation

Refractory/ intolerant to ≥1 AADs (Class I or III)

- Surgically Ablation RECOMMENDED
- Consider Catheter Ablation

Failed ≥catheter ablation or refractory/ intolerant to ≥AADs (Class I or III)

- Consider in all AF Types

6 Failure of first-line MD or catheter ablation

Patient choice informed by AF Heart Team

- Another AAD
- Catheter Ablation (First or Repeat)
- Hybrid Therapy
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
The management of cardiovascular risk factors and stroke risk across the AF care pathway, includes:

### MANAGE PRECIPITATING FACTORS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Desired Outcome</th>
<th>Patient Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes (e.g., increased activity, smoking cessation, reduced alcohol intake)</td>
<td><strong>Cardiovascular RISK REDUCTION</strong></td>
<td>Improved life expectancy</td>
</tr>
<tr>
<td>Treatment of underlying cardiovascular conditions</td>
<td></td>
<td>Improved quality of life, autonomy, social functioning</td>
</tr>
</tbody>
</table>

### ASSES STROKE RISK

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Desired Outcome</th>
<th>Patient Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulation in patients at risk of stroke</td>
<td><strong>Stroke PREVENTION</strong></td>
<td>Improved life expectancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved quality of life, autonomy, social functioning</td>
</tr>
</tbody>
</table>
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**
Several therapies previously used to treat AF are no longer recommended or are only recommended for use in select patient populations:

**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.

**RATE CONTROL THERAPIES** are effective at lowering and controlling heart rate in patients with AF, with as many as 79% of patients in the target heart rate range of 60-100 BEATS PER MINUTES.

**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.
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.  

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

- RECEIVE treatment with a different AAD  
- REPEAT catheter ablation  
- RECEIVE hybrid therapy (ie, combining AADs with ablation)  
- START rate control therapies to control AF
Antirhythmic drug therapy is an integral part of maintaining sinus rhythm after cardioversion.\(^2\)

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

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

**AADs Available for Rhythm Control**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I: Sodium Channel Blockers</strong></td>
<td>Disopyramide, Quinidine, Flecaïnide, Propafenone</td>
</tr>
<tr>
<td>IA</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td></td>
</tr>
<tr>
<td><strong>Class III: Potassium Channel Blockers</strong></td>
<td>Amiodarone, Dronedarone, Dofetilide, Sotalol</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 antirhythmic 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 Guidelines.\(^2\)

Abbreviations: AAD = antirhythmic 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:**

- **33%-56%** rate for maintaining normal sinus rhythm at 1 year.  
  
- **48%** of patients with AF are not well managed on AADs.  
  
- Recurrence of AF can be asymptomatic and symptomatic.  
  
- 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.

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0%-3%</td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1%-3%</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0%-11%*</td>
<td>Based on pooled event rates.</td>
</tr>
</tbody>
</table>

*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.\textsuperscript{2,43,64}

**COMMON ADVERSE EVENTS**

**CLASS IA**
- Urinary retention
- Diarrhea
- Dry mouth
- Nausea/vomiting

19% TREATMENT WITHDRAWALS DUE TO AES (%)

**CLASS IC**
- Congestive heart failure
- Dizziness
- Nausea/vomiting
- Visual disturbances

12% TREATMENT WITHDRAWALS DUE TO AES (%)

**CLASS III**
- Dyspnea
- Diarrhea
- Headache
- Nausea/vomiting

13% TREATMENT WITHDRAWALS DUE TO AES (%)
### WHAT IS THE PATIENT IMPACT OF AAD THERAPY?

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

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

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

**Abbreviations:** AAD = antiarrhythmic drug; AF = atrial fibrillation; SF-36 = Short Form 36 questionnaire; QoL = quality of life. Source: Jais et al. (2008), Mark et al. (2019), Aliot et al. (2014), and Walfridsson (2012)
REDUCED SYMPTOMS
WITH AAD THERAPY

Mean AF Symptom Frequency
and Severity Checklist Score

Before AAD Initiation 1 Year After AAD Initiation

IMPROVED QUALITY OF LIFE
WITH AAD THERAPY

Mean SF-36 Score

Before AAD Initiation 1 Year After AAD Initiation

Abbreviations: AAD = antiarrhythmic drug; AF = atrial fibrillation; SF-36 = Short Form 36 questionnaire. Source: Jais et al. (2008)
WHAT IS THE ECONOMIC IMPACT OF AAD THERAPY?

Antiarhythmic 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\(^*\).

**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

FRANCE**

GERMANY

ITALY

SPAIN

UNITED KINGDOM

* Costs are estimates for 1000 patients, based on efficacy and event rates for AADs reported earlier and unit costs reported in the literature. Unit costs were inflated to 2019 Euros.

** 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 pacemaker implantation represents heart failure hospitalization.

§ Electrical cardioversion only.

†† Includes fatal ischemic stroke, and mild, moderate, and severe ischemic stroke events.

‡‡ Includes intracranial hemorrhage, hemorrhagic stroke, and ischemic 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.\textsuperscript{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.\textsuperscript{3}

Key considerations for treating patients with catheter ablation include:\textsuperscript{3}

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

**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%** for Paroxysmal AF 45-50
- **UPTO 83%** for 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**

37%-75%

**PATIENT with AF ≥75 YEARS of age**

78%

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

**UP to 10%**

of patients **MAY EXPERIENCE A COMPLICATION**

2%-3%

of patients **MAY EXPERIENCE POTENTIALLY LIFE-THREATENING**, but manageable, complications²,³
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.\(^5\)

*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

<table>
<thead>
<tr>
<th>AF-RELATED EVENTS</th>
<th>CATHETER ABLATION (N = 4,212)</th>
<th>NO AF (N = 16,848)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORTALITY</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>STROKE</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>ALZHEIMER’S DEMENTIA</td>
<td>0.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>NON-ALZHEIMER’S DEMENTIA</td>
<td>0.4%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

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.\textsuperscript{77}

Abbreviations: AF = atrial fibrillation; N = number
Source: Bunch et al. (2011)
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.\(^6\)

---

**UP to 37% IMPROVEMENT IN QUALITY OF LIFE\(^5\)**

---

**REDUCTION IN SYMPTOMS AFTER CATHETER ABLATION**

![Bar chart showing reduction in symptom severity and symptom frequency after catheter ablation.]

- **Mean MAFSI Score**
  - Baseline
  - 12 Month
  - 60 Month

---

Source: Mark et al. (2019)

Abbreviations: AFEQT = Atrial Fibrillation Effect on Quality of Life; MAFSI = Mayo Atrial Fibrillation-Specific Symptom Inventory; SF-36 = Short Form 36 questionnaire \(\text{Source: Mark et al. (2019)}\)
IMPROVED QUALITY OF LIFE AFTER CATHETER ABLATION

**Physical Component**

- Baseline: 37%
- 12 Month: +15%
- 60 Month: +8%

**Mental Component**

- Baseline: 37%
- 12 Month: +14%
- 60 Month: +16%
Catheter ablation is cost effective; it reduces the need for unplanned medical visits, additional treatments to control AF, and subsequent treatment for long-term consequences of AF, turn, reducing overall healthcare cost.

Several studies show that CATHETER ABLATION OF AF is COST EFFECTIVE when BENEFITS ARE MAINTAINED OVER THE MEDIUM TO LONG-TERM.

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.**

*Cost of follow-up treatment included AADs, subsequent ablation for patients initially on AADs, or cardiac events.
**At 2 years based on evidence outside of Europe.
Significant reductions in event rates 1 and 2 years after catheter ablation compared to 1 year before ablation (per patient per year)\textsuperscript{84}

**REduced Event Rates After Catheter Ablation**

- All-cause hospitalizations
- Hospitalizations for AF\textsuperscript{*}
- Cardioversions
- Emergency room visits
- Echocardiograms

**Improved efficacy and reductions in unplanned medical visits** after catheter ablation can lead to reduced costs for managing AF.\textsuperscript{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 Euros.

*** 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;

|| Includes fatal ischemic stroke, and mild, moderate, and severe ischemic stroke events;

††† Includes intracranial hemorrhage, hemorrhagic stroke, and ischaemic stroke. Abbreviations: AF = atrial fibrillation
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.

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:

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>CABANA(^55)</th>
<th>NOSEWORTHY ET AL.(^89)</th>
<th>CASTLE-AF(^57)</th>
<th>ATTEST(^59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGION</td>
<td>Global</td>
<td>US</td>
<td>Global</td>
<td>Global</td>
</tr>
<tr>
<td>STUDY DESIGN</td>
<td>Multi-Centre RCT</td>
<td>Database* analysis</td>
<td>Multi-Centre RCT</td>
<td>Multi-Centre RCT</td>
</tr>
<tr>
<td>NUMBER OF PATIENTS</td>
<td>2,204</td>
<td>183,760</td>
<td>363</td>
<td>255</td>
</tr>
<tr>
<td>DISEASE STATE OF PATIENTS</td>
<td>Symptomatic AF</td>
<td>AF</td>
<td>AF &amp; Heart Failure</td>
<td>Symptomatic paroxysmal AF</td>
</tr>
<tr>
<td>REQUIREMENT THAT PATIENT FAILED DRUG THERAPY</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FOLLOW-UP DURATION</td>
<td>5 years</td>
<td>Up to 7 years</td>
<td>5 years</td>
<td>3 years</td>
</tr>
</tbody>
</table>

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

more patients **FREE FROM ATRIAL ARRHYTHMIA** over **4 years** compared to drug therapy.\(^5\text{5}\)\(^5\)

**CATHETER ABLATION** was also associated with

**up to 46%** reduction in the probability of **AF-RELATED complications**\(^\ast\)^\(^\ast\)

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

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

compared to drug therapy over 7-years follow-up.\(^5\text{5,89}\)\(^5\)

*Death*  
*Stroke*  
*Cardiac arrest*  
*Cardiovascular hospitalization*
In the CASTLE-AF trial:

- **Over 60%**
  - 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).

- **Up to 47%**
  - Greater improvement in survival or reduction in heart failure hospitalization in patients as compared to drug therapy over a 5 year follow-up.

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.

- **25%**
  - Composite of death and increased AF hospitalization

- **33%**
  - Death

- **41%**
  - HF hospitalization

*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)*
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:

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

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

Abbreviations: AF = atrial fibrillation; CABANA = Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation; CAPTAF = Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation; N = number; RCT = randomized controlled trial
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.\textsuperscript{58}

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

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

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

***Statistical significance not reported.

**Abbreviations:** AFEQT = Atrial Fibrillation Effect on Quality of Life; MAFSI = Mayo Atrial Fibrillation-Specific Symptom Inventory

Source: Mark et al. (2019)
**WHAT IS THE ECONOMIC IMPACT OF CATHETER ABLATION COMPARED TO AAD THERAPY?**

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

An important recent study compared one-year resource utilization after catheter ablation to antiarrhythmic drug use.

### TRIAL

<table>
<thead>
<tr>
<th>REGION</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY DESIGN</td>
<td>Retrospective database analysis*</td>
</tr>
<tr>
<td>NUMBER OF PATIENTS</td>
<td>2,428</td>
</tr>
<tr>
<td>PATIENT DISEASE STATE</td>
<td>AF</td>
</tr>
<tr>
<td>REQUIREMENT THAT PATIENTS FAILED DRUG THERAPY</td>
<td>No</td>
</tr>
<tr>
<td>FOLLOW-UP DURATION</td>
<td>1 year</td>
</tr>
</tbody>
</table>

A UK database analysis found that catheter ablation treatment was associated with reduced resource utilization compared to drugs over 1 year.

**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*
Several economic analyses show that RF ablation is cost effective compared to antiarrhythmic drugs due to improved clinical effectiveness over long term follow.\textsuperscript{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.\textsuperscript{68}

French study highlights the cumulative costs of PAROXYSMAL AF treatment over 10 years\textsuperscript{66}

![Graph showing cost comparison between Drug Therapy and Catheter Ablation](image)

**PROJECTING COSTS TO 10 YEARS AFTER ABLATION***

Catheter ablation was associated with a **35% SAVINGS IN COSTS COMPARED TO DRUG THERAPY**\textsuperscript{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 YEAR.\(^{45-54}\)

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 compared to drug therapy over 7-years follow-up.\(^{89}\)

\(^{*}(HR \ 0.11; \ 95\% \ CI \ 0.025-0.483; \ p=0.0034.)\)
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:\textsuperscript{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)?