Cabins, castles, and constant hearts
rhythm control therapy in patients with atrial fibrillation

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Recent innovations have the potential to improve rhythm control therapy in patients with atrial fibrillation (AF). Controlled trials provide new evidence on the effectiveness and safety of rhythm control therapy, particularly in patients with AF and heart failure. This review summarizes evidence supporting the use of rhythm control therapy in patients with AF for different outcomes, discusses implications for indications, and highlights remaining clinical gaps in evidence. Rhythm control therapy improves symptoms and quality of life in patients with symptomatic AF and can be safely delivered in elderly patients with comorbidities (mean age 70 years, 3–7% complications at 1 year). Atrial fibrillation ablation maintains sinus rhythm more effectively than antiarrhythmic drug therapy, but recurrent AF remains common, highlighting the need for better patient selection (precision medicine). Antiarrhythmic drugs remain effective after AF ablation, underpinning the synergistic mechanisms of action of AF ablation and antiarrhythmic drugs. Atrial fibrillation ablation appears to improve left ventricular function in a subset of patients with AF and heart failure. Data on the prognostic effect of rhythm control therapy are heterogeneous without a clear signal for either benefit or harm. Rhythm control therapy has acceptable safety and improves quality of life in patients with symptomatic AF, including in elderly populations with stroke risk factors. There is a clinical need to better stratify patients for rhythm control therapy. Further studies are needed to determine whether rhythm control therapy, and particularly AF ablation, improves left ventricular function and reduces AF-related complications.

**Keywords**

Atrial fibrillation • Rhythm control therapy • AF ablation • Antiarrhythmic drugs • Heart failure • Stroke • Mortality
Introduction

The prevalence of atrial fibrillation (AF) and its associated mortality and morbidity are expected to double or triple within the next two to three decades, driven by population ageing and increased incidence of AF. Even on optimal anticoagulation and rate control therapy, patients with AF are at high risk of cardiovascular death, particularly sudden death and death due to heart failure. Rhythm control therapy using antiarrhythmic drugs, cardioversion, and AF ablation, is clinically used to improve AF-related symptoms. Currently, there is no established indication for rhythm control therapy apart from improvement of AF-related symptoms. The CABANA (Catheter Ablation vs. Anti-arrhythmic Drug Therapy for Atrial Fibrillation) trial recently provided new confirmation on the safety of AF ablation in contemporary AF patients at risk of stroke. The smaller CASTLE-AF (Catheter Ablation vs. Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) suggests that AF ablation could improve outcomes in patients with AF and severe heart failure compared to drug therapy, combining rate control therapy and antiarrhythmic drug therapy. Here, we review the available evidence supporting the use of rhythm control therapy in patients with AF, discuss potential implications for indications, and highlight clinical evidence gaps.

Rhythm control therapy improves atrial fibrillation-related symptoms

Restoring and maintaining sinus rhythm indicated to minimize symptoms is a main goal in patients who remain symptomatic despite adequate rate control. Interestingly, the effects of rhythm control on quality of life are less uniform than their clear effects on maintaining sinus rhythm (Table 1). Both natural variation in patient-reported quality of life, imprecise instruments to assess quality of life, and variable effects of rhythm control therapy on quality of life in individual patients can explain this heterogeneity. The European Heart Rhythm Association (EHRA) symptom score was introduced in 2007 as a simple clinical tool to quantify AF-related symptoms, with subsequent refinement and validation. Several disease-specific instruments are available, all with specific strengths and limitations. In addition, perceived AF-related symptoms may not always be due to AF, and concomitant cardiovascular diseases and risk factors may affect patient’s health perception in addition to the arrhythmia itself. Furthermore, patients with paroxysmal AF can be expected to report variable quality of life depending on their rhythm at the time of assessment, on their ability to memorize past symptoms during clusters of AF episodes, and by anxiety related to future episodes of AF.

Effectiveness and safety of rhythm control therapy

The success of rhythm control therapy depends on multiple factors including the number, type, and severity of underlying conditions, age, gender, adherence to antiarrhythmic drug therapy, and factors related to the quality of the AF ablation procedure. Furthermore, AF recurrence rates depend on the intensity of electrocardiogram (ECG) monitoring and duration of follow-up. Thus, comparing absolute recurrence rates between studies and comparisons to historical controls can be misleading (Table 1).

Effectiveness and safety of antiarrhythmic drug therapy

On average, antiarrhythmic drugs double the proportion of patients who maintain sinus rhythm. Amiodarone is more effective than other antiarrhythmic drugs in maintaining sinus rhythm, and catheter ablation is more effective than antiarrhythmic drugs. The long-term complication rates of antiarrhythmic drug therapy are comparable to complications in patients treated with AF ablation. Although amiodarone has been associated with adverse outcomes in non-randomized analyses of patients at very high risk, the safety of antiarrhythmic drug therapy found in recent randomized trials in patients with AF attenuates historical safety concerns, particularly in patients with heart failure. Unlike earlier trials of antiarrhythmic drugs compared to placebo or rate control therapy (Table 1), antithrombotic drug therapy with dronedarone was associated with reduced cardiovascular hospitalizations and cardiovascular deaths compared to placebo. The same substance, dronedarone, used as a rate-controlling agent, was associated with higher rates of heart failure, stroke, and cardiovascular death in patients with permanent AF in the PALLAS trial. Patients included in PALLAS were not considered suitable for rhythm control therapy, did not receive interventions to restore sinus rhythm (e.g. cardioversion, AF ablation) and had severe heart failure. Hence, they were deprived of any potential benefit of sinus rhythm. Patients treated with dronedarone in ATHENA, in contrast, received that therapy to restore sinus rhythm. Taken together, these data may suggest that the beneficial effects found in ATHENA could be associated with its rhythm controlling effect, but more data are needed.

Antiarrhythmic drugs are also effective after AF ablation. Two recent randomized studies (AMIO-CAT and POWDER-AF) showed that adding antiarrhythmic drug therapy to AF ablation improves sinus rhythm maintenance for the duration of therapy. This synergistic effect of antiarrhythmic drugs with AF ablation reflects the common (approximately 50% of patients) use of antiarrhythmic drugs 1 year after AF ablation. A substudy within AMIO-CAT measuring brain natriuretic peptide suggested that biomarkers may improve identification of patients at risk for recurrent AF, pointing potentially towards personalized or stratified selection of patients for specific rhythm control therapies.
Table 1  Effects of rhythm control therapy using antiarrhythmic drugs in controlled clinical trials

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Mean age</th>
<th>Sex</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>AF pattern</th>
<th>Comparator therapy</th>
<th>Primary endpoint</th>
<th>Method for detecting recurrent AF</th>
<th>Sinus rhythm maintenance</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIAF</td>
<td>CTAF</td>
<td>RACE</td>
<td>AFFIRM</td>
<td>STAF</td>
<td>SAFE-T</td>
<td>AF-CHF</td>
<td>ATHENA</td>
<td>Flec-SL</td>
<td>24-h Holter every 3 months</td>
<td>56% at 52 weeks on amiodarone, 10% on diltiazem</td>
<td>Improved 6MWT in rhythm control patients</td>
</tr>
<tr>
<td>2000</td>
<td>252</td>
<td>60</td>
<td>73% male</td>
<td>Symptomatic persistent AF &lt; 1 year duration</td>
<td>NYHA IV, unstable angina</td>
<td>Persistent AF</td>
<td>Rate control (diltiazem)</td>
<td>Recurrent AF</td>
<td>90% at 2 years on sotalol, &gt; 80% on amiodarone</td>
<td>56% at 3 months on sotalol, &gt; 80% on amiodarone</td>
<td>No difference in QoL between groups</td>
</tr>
<tr>
<td>2000</td>
<td>403</td>
<td>65</td>
<td>56% male</td>
<td>Symptomatic AF eligible for antiarrhythmic drug therapy</td>
<td>NYHA III–IV, severe CKD, QTc &gt; 0.48</td>
<td>Persistent AF</td>
<td>Rate control</td>
<td>Recurrent AF</td>
<td>&gt; 70% at 2 years on sotalol, &lt; 80% on amiodarone</td>
<td>&gt; 70% at 3 months on sotalol, &lt; 80% on amiodarone</td>
<td>No difference in mortality or QoL between groups</td>
</tr>
<tr>
<td>2002</td>
<td>522</td>
<td>68</td>
<td>64% male</td>
<td>Recurrent persistent AF &lt; 1 year duration</td>
<td>NYHA IV, previous amiodarone, pacemaker</td>
<td>Persistent AF</td>
<td>Sotalol or propafenone</td>
<td>Cardiovascular death, HF, stroke, bleeding, pacemaker, or SAE</td>
<td>40% at 2 years on sotalol, 10% on amiodarone</td>
<td>No difference in mortality or QoL between groups</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>4060</td>
<td>70</td>
<td>61% male</td>
<td>&gt; 65 years or &lt; 65 years with additional risk factor for stroke with AF likely to be recurrent and likely to cause illness or death</td>
<td>NYHA III–IV, CKD, QTc &gt; 0.48</td>
<td>Persistent AF</td>
<td>Rate control</td>
<td>Death</td>
<td>Not specified</td>
<td>70% at 3 months on sotalol, 10% on amiodarone</td>
<td>No difference in mortality or QoL between groups</td>
</tr>
<tr>
<td>2003</td>
<td>520</td>
<td>66</td>
<td>64% male</td>
<td>Persistent AF &gt; 2 years</td>
<td>NYHA III–IV, CKD, QTc &gt; 0.48</td>
<td>Persistent AF</td>
<td>Placebo</td>
<td>MACCE</td>
<td>Monthly ECG</td>
<td>60% at 2 years on amiodarone, 10% on diltiazem</td>
<td>No difference in mortality or QoL between groups</td>
</tr>
<tr>
<td>2005</td>
<td>665</td>
<td>67</td>
<td>99% male</td>
<td>Persistent AF on anticoagulation</td>
<td>NYHA III–IV, CKD, QTc &gt; 0.48</td>
<td>Persistent AF</td>
<td>Placebo</td>
<td>Recurrent AF</td>
<td>Yearly ECG</td>
<td>60% at 2 years on amiodarone, 10% on diltiazem</td>
<td>No difference in mortality or QoL between groups</td>
</tr>
<tr>
<td>2008</td>
<td>1376</td>
<td>67</td>
<td>81% male</td>
<td>Symptomatic HF (NYHA II–IV), LVEF &gt; 36%</td>
<td>NYHA III–IV, CKD, QTc &gt; 0.48</td>
<td>Persistent AF</td>
<td>Placebo</td>
<td>Cardiovascular death</td>
<td>Daily Holter</td>
<td>60% at 2 years on amiodarone, 10% on diltiazem</td>
<td>Lower mortality and less hospitalizations in patients randomized to dronedarone</td>
</tr>
<tr>
<td>2009</td>
<td>4628</td>
<td>72</td>
<td>53% male</td>
<td>Patients with AF, and &gt; 70 years with one comorbidity or &gt; 75 years</td>
<td>NYHA III–IV, CKD, QTc &gt; 0.48</td>
<td>Persistent AF</td>
<td>Placebo</td>
<td>Cardiovascular hospitalization or death</td>
<td>Daily Holter</td>
<td>Improved quality of life in all groups</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>635</td>
<td>64</td>
<td>66% male</td>
<td>Patients undergoing planned cardioversion</td>
<td>NYHA III–IV, CKD, QTc &gt; 0.48</td>
<td>Persistent AF</td>
<td>Placebo</td>
<td>Cardiovascular death</td>
<td>Daily Holter</td>
<td>Improved quality of life in all groups</td>
<td></td>
</tr>
</tbody>
</table>

All studies found reduced AF recurrences in patients randomized to rhythm control therapy. Several studies reported improved quality of life in patients with successful sinus rhythm maintenance, e.g. in SAFE-T and AF-CHF. AAD antiarrhythmic drug. 6MWT, six minute walking test; QoL, quality of life.
Atrial fibrillation ablation compared to antiarrhythmic drug therapy after CABANA

CABANA was designed to test whether AF ablation can reduce mortality compared to antiarrhythmic drugs in patients with AF in need for rhythm control therapy and with stroke risk factors. In early 2013, a planned, blind data review identified slow enrolment and lower event rates than anticipated. This resulted in a change in primary endpoint from all-cause mortality to a composite of death, disabling stroke, serious bleeding, or cardiac arrest. In addition, the sample size was reduced. The results have just been reported. Of the 2204 patients randomized (median age, 68 years; 37% female; 57% persistent AF), 89.3% completed the trial. In patients randomized to AF ablation, 91% underwent the procedure, while AF ablation was performed in 27.5% of the patients randomized to drug therapy, in line with expectations at the start of the trial. Safety of rhythm control therapy was good in this elderly patient population (mean age 68 years), with low complication rates in both arms: Patients randomized to AF ablation experienced tamponade (0.8%), haematoma (2.3%), and pseudoaneurysms (1.1%). Patients randomized to antiarrhythmic drug therapy experienced thyroid disorders (1.6%) and proarrhythmia (0.8%). The primary outcome was not different between groups. Over a median follow-up of 48.5 months, the primary endpoint occurred in 8.0% of patients randomized to AF ablation, and in 9.2% of patients randomized to antiarrhythmic drug therapy [hazard ratio (HR) 0.86, 95% CI 0.65–1.15; P = 0.30]. Key secondary outcomes were not different between random groups, including all-cause mortality was 5.2% and 6.1% (HR 0.85, 95% CI 0.60–1.21; P = 0.38), death or cardiovascular hospitalization rates were 51.7% and 58.1% for (HR 0.83, 95% CI 0.74–0.93; P = 0.001). Recurrent AF was less common in patients randomized to AF ablation in the subgroup of 1240 patients undergoing systematic ECG monitoring (HR 0.52, 95% CI 0.45–0.60; P < 0.001). Both treatment groups showed improved quality of life, as assessed by the Atrial Fibrillation Effect on Quality of Life (AFEQT) summary score and the Mayo AF-Specific Symptom Inventory (MAFSI). Patients randomized to catheter ablation showed a greater improvement in quality of life (mean difference of 5.3 points). This greater effect of AF ablation on quality of life is consistent with the main finding of the Swedish CAPTAF trial.

Similar to other observational data sets, on-treatment analysis suggested improved outcomes in patients undergoing AF ablation. These findings are additionally supported by a recent study using a large US administrative database of routine patient data, analysing patients who meet the CABANA inclusion criteria. Unknown and known confounders, censoring of events—either intentionally by study design or unintentionally because of loss to follow-up—, self-selection of low risk patients to cross over to ablation, and immortal time bias are some of the sources of bias that can explain these findings.

Rhythm control therapy in patients with atrial fibrillation and heart failure

Atrial fibrillation and heart failure (AF+HF) frequently coexist and this is associated with high morbidity and mortality. To improve outcomes, restoring and maintaining sinus rhythm has been proposed in patients with AF+HF. Amiodarone is the only antiarrhythmic drug with sufficient safety data in patients with reduced left ventricular ejection fraction. Online randomized trials of antiarrhythmic drugs compared to rate control in patients with AF+HF did not find differences in all-cause mortality, cardiovascular mortality, or heart failure hospitalizations. Likewise, patients who maintain sinus rhythm (‘successful rhythm control therapy’) did not have better survival than those with recurrent AF. Several small case series and controlled trials found that patients undergoing AF ablation have improved left ventricular function, often using echocardiography to assess left ventricular (LV) function (Table 2): four out of five relatively small studies found improved left ventricular function in patients with AF+HF randomized to AF ablation (Table 2), largely seen in trials that assessed left ventricular function by echocardiography, which is less reliable in AF than in sinus rhythm. There were associated improvements in exercise capacity and brain natriuretic peptide (BNP) levels (Take home figure, bottom panel). Improved exercise capacity and to some extent improved left ventricular function, but not lower BNP, could be partially explained by bias in unblinded trials. These effects have been extrapolated with a certain enthusiasm. The largest trial comparing AF ablation with ‘medical therapy’ (mostly rate control, but including antiarrhythmic drugs) in patients with AF+HF is CASTLE-AF (Table 2). The quality of rate control therapy may have affected changes in LV function in the control group of the published trials that used rate control as comparator. Thirty-four of the 363 randomized patients were lost to follow-up despite an implanted device allowing home monitoring. In the remaining patients, catheter ablation reduced mortality and HF hospitalizations (28.5% compared with 45%), but had no effect on all-cause hospitalizations and stroke. Details of the drug therapy given to patients randomized to ‘medical therapy’ have not been published. One-third of the patients assigned to medical therapy were on antiarrhythmic drugs at their final follow-up, 22% were in sinus rhythm at 60 months (compared to 63% in the AF ablation arm, Table 2). In line with these findings, the recent update of the AHA/ACC/HRS guidelines for AF...
Table 2  Randomized studies comparing pharmacological rate or rhythm control, or, in PABA-CHF, AV nodal ablation and biventricular pacing, with catheter ablation in patients with AF and systolic dysfunction with reduced ejection fraction

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Age</th>
<th>Sex</th>
<th>Type of patients</th>
<th>Exclusion criteria</th>
<th>Proportion with ischaemic HF etiology</th>
<th>AF pattern</th>
<th>Duration of AF at baseline</th>
<th>Comparator therapy</th>
<th>Primary endpoint</th>
<th>Method for AF recurrence assessment</th>
<th>Sinus rhythm maintenance at end of follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PABA-CHF</td>
<td>2008</td>
<td>61</td>
<td>&gt;80% male</td>
<td>NYHA II–III, LVEF &lt;40%</td>
<td>Post-operative AF, reversible causes of AF or HF, prior AF ablation</td>
<td>70%</td>
<td>52% paroxysmal</td>
<td>48 months</td>
<td>Rate control (AV nodal ablation + biventricular ICD)</td>
<td>Change in LVEF from randomization to last study visit</td>
<td>Improvement of LVEF, 6MWT distance, and MLHFQ score</td>
<td>External loop recorder (AF ablation patients only)</td>
<td>No difference in LVEF or RV function (measured by cardiac MRI), 6MWT, or BNP between groups</td>
</tr>
<tr>
<td>MacDonald</td>
<td>2011</td>
<td>63</td>
<td>&gt;80% male</td>
<td>NYHA II–III, LVEF &lt;35%</td>
<td>Paroxysmal AF, QRS duration &gt;150 ms, myocarditis</td>
<td>49%</td>
<td>100% chronic</td>
<td>48 months</td>
<td>Pharmacological rate control</td>
<td>Change in LVEF from last study visit</td>
<td>Peak VO₂</td>
<td>Change in LVEF from last study visit</td>
<td>88%</td>
</tr>
<tr>
<td>ARC-AF</td>
<td>2013</td>
<td>63</td>
<td>&gt;80% male</td>
<td>NYHA II–I, LVEF &lt;35%</td>
<td>Reversible causes of AF and HF</td>
<td>33%</td>
<td>100% chronic</td>
<td>51 months</td>
<td>Pharmacological rate control</td>
<td>LVEF at 6 months</td>
<td>48-hour Holter at 1.3, and 6 months (and 12 months in AF ablation patients)</td>
<td>No difference in LVEF or RV function (measured by cardiac MRI), 6MWT, or BNP between groups</td>
<td></td>
</tr>
<tr>
<td>CAMTAF</td>
<td>2014</td>
<td>58</td>
<td>&gt;80% male</td>
<td>NYHA II–IV, LVEF &lt;35%</td>
<td>Previous AF ablation, reversible HF cause</td>
<td>26%</td>
<td>100% chronic</td>
<td>24 months</td>
<td>Pharmacological rate control</td>
<td>Freedom from AF, AFL, or AT of &gt;30 s duration off AAD at follow-up</td>
<td>Device interrogation at 3.6, 12, and 24 months</td>
<td>Improvement of LVEF, 6MWT distance, and QOL (MLHFQ) in AF ablation patients</td>
<td></td>
</tr>
<tr>
<td>AATAC</td>
<td>2016</td>
<td>58</td>
<td>&gt;80% male</td>
<td>NYHA II–IV, LVEF &lt;35%</td>
<td>Amiodarone therapy, AF &lt;3 months duration, reversible AF</td>
<td>64%</td>
<td>100% chronic</td>
<td>9 months</td>
<td>Rhythm control with amiodarone</td>
<td>Change in LVEF from baseline at 6 months on cardiac MRI</td>
<td>Implanted loop recorder in AF ablation patients</td>
<td>No difference in LVEF or RV function (measured by cardiac MRI), 6MWT, or BNP between groups</td>
<td></td>
</tr>
<tr>
<td>CAMERA-MRI</td>
<td>2017</td>
<td>66</td>
<td>&gt;80% male</td>
<td>NYHA II–III, LVEF &lt;40%, dual-chamber ICD or CRT</td>
<td>Paroxysmal AF, contraindications to ablation or MRI, ischaemic cardiomyopathy</td>
<td>0%</td>
<td>100% chronic</td>
<td>22 months</td>
<td>Pharmacological rate control</td>
<td>Composite of all-cause mortality or worsening of HF requiring unplanned hospitalization</td>
<td>Device interrogation at 3, 6, 12, 24, 36, 48, and 60 months</td>
<td>No difference in LVEF or RV function (measured by cardiac MRI), 6MWT, or BNP between groups</td>
<td></td>
</tr>
<tr>
<td>CASTLE-AF</td>
<td>2018</td>
<td>64</td>
<td>&gt;80% male</td>
<td>NYHA II–I, LVEF &lt;45%</td>
<td>Prior AF ablation, LA diameter &gt;60 mm</td>
<td>46%</td>
<td>33% paroxymal</td>
<td>Not known</td>
<td>Mixture of rate control and rhythm control</td>
<td>Less mortality and HF hospitalizations in AF ablation patients</td>
<td>75% (56% without antarrhythmic drugs)</td>
<td>Greater improvement of LVEF at 6 months in AF ablation patients</td>
<td></td>
</tr>
</tbody>
</table>

*aNumber of randomized patients.
*b6-Min walk distance and serum brain natriuretic peptide did not support the presence of heart failure in all patients. 6MWT, six minute walking test; AF, atrial fibrillation; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy device; ICD, implantable defibrillator; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRI, magnetic resonance imaging; NYHA class, New York Heart Association functional class; QOL, quality of life; RV, right ventricle.
included a Class IIb recommendation for AF ablation in patients with heart failure. So far, there is no information about outcomes following catheter ablation for AF in patients with heart failure and a preserved ejection fraction. Despite these limitations, CASTLE-AF and the AATAC trial contribute evidence that selected patients with AF \(\text{+} \) HF benefit from AF ablation (Table 2), but open questions remain regarding selection of adequate patients and validity of the findings in ‘all-comer’ patients. More research is needed to determine the effect of AF ablation on cardiovascular outcomes in patients with AF \(\text{+} \) HF.

**Rhythm control therapy and stroke**

The clear association of AF and ischaemic stroke may suggest that maintaining sinus rhythm can help to prevent strokes. There is no signal for reduced strokes in the earlier ‘rate vs. rhythm’ studies (Table 1), including the reasonably large AF-CHF trial. There were only three and seven disabling strokes in each arm in CABANA, without differences between groups. Interestingly, in a post hoc analysis of the ATHENA trial (Table 1), patients randomized to dronedarone had a lower risk of stroke or transient ischaemic attack (1.2% vs. 1.8%). A retrospective, propensity-score matched analysis of a subset of AF patients taken from the Swedish patient registry also suggested that AF ablation may be associated with a lower incidence of ischaemic stroke. This is similar to propensity-matched patient comparisons in the largest health maintenance organization in Israel, comparing 969 AF patients undergoing AF ablation to 3772 AF controls. These analyses are prone to several biases, including known, unmeasured and unknown confounders, and others.

**Rhythm control therapy and cognitive decline**

Atrial fibrillation is associated with cognitive dysfunction and dementia. Anticoagulation appears to reduce dementia in patients with AF in a nationwide cohort analysis. While it is unlikely that antiarrhythmic drug therapy causes cerebral complications (stroke, transient ischaemic attack, or cognitive decline), there is a peri-procedural risk of ischaemic stroke (0.3–1%) as well as a risk of magnetic resonance imaging (MRI)-detected clinically silent ischaemic brain lesions in patients undergoing AF ablation. This can increase brain damage and subsequently lead to cognitive decline. Interestingly, the AXAFA–AFNET 5 study found small MRI-detected brain lesions in
ca. 30% of patients undergoing a first AF ablation on continuous anticoagulation, but also detected an improved cognitive function as assessed by Montreal Cognitive Assessment (MoCA) 3 months after AF ablation.38

Rhythm control therapy may reduce AF-related stroke risk by reducing AF burden and subsequent improvement in atrial cardiomyopathy,68 potentially reducing silent embolic lesions, and possibly improving perfusion and metabolism of the brain. A large retrospective observational study found a lower rate of new-onset dementia in 4212 patients undergoing AF ablation compared to 16848 non-ablated AF patients, while a substudy in the randomized AFFIRM trial did not find a difference in cognitive function between patients randomized to rate or rhythm control therapy, while the AXAFA study found improved cognitive function in 674 patients 3 months after AF ablation compared to baseline.38 The possible cognitive benefits of restoring sinus rhythm in AF patients can be attenuated by atrial cardiomyopathy and by concomitant cardiovascular conditions and other unknown confounders that can cause brain damage, stroke, and cognitive dysfunction in the absence of AF.56,67 Unfortunately, neither CABANA nor CASTLE-AF reported cognitive function outcomes. Ongoing research such as the case–control DIAL-F cohort (NCT01816308) and the randomized EAST-AFNET 4 trial68 will provide further information on the impact of rhythm control therapy including AF ablation on cognitive function.

Rhythm control therapy and atrial cardiomyopathy

The term ‘atrial cardiomyopathy’ summarizes the structural, architectural, contractile, or electrophysiological changes in diseased atria. Cardiovascular diseases (e.g. hypertension, heart failure, valvular heart disease, ischaemic heart disease, or diabetes) but also ageing can contribute to an atrial cardiomyopathy. Atrial fibrillation itself accelerates the underlying disease processes, thus contributing to atrial cardiomyopathy.69 Left atrial enlargement, a summative clinical proxy for atrial cardiomyopathy, is partially reversed after AF ablation.70,71 Early rhythm control therapy, including AF ablation, has been suggested to slow these processes, thereby simplifying rhythm control therapy and potentially improving long-term outcomes.68 Hence, early rhythm control therapy could slow atrial cardiomyopathy. However, this hypothesis requires confirmation in further studies and trials.

Summary and conclusions

Recent randomized trials and observational data sets including CASTLE-AF and CABANA provide important reassurance on the safety of rhythm control therapy in contemporary patients with AF, including in elderly patients with concomitant cardiovascular diseases. The data confirm the superior effectiveness of AF ablation compared to antiarrhythmic drugs to restore and maintain sinus rhythm, and demonstrate that antiarrhythmic drugs remain effective after AF ablation. Several smaller studies suggest that AF ablation can improve left ventricular function assessed by echocardiography in selected patients with AF and heart failure. Further studies to investigate the impact of rhythm control therapy on LV function in different, clearly defined subsets of patients with AF are warranted. The effects of rhythm control therapy on cardiovascular death, stroke, heart failure, acute coronary syndromes, as well as secondary outcomes such as left atrial, ventricular, and cognitive function require further research, such as the on-going EAST–AFNET 4 trial.68

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