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Atrial fibrillation rhythm management: a matter of timing

Philipp Krisai and Michael Kühne *

Department of Cardiology and Cardiovascular Research Institute Basel, University Hospital Basel, University of Basel, Petersgraben 4, 4031 Basel, Switzerland

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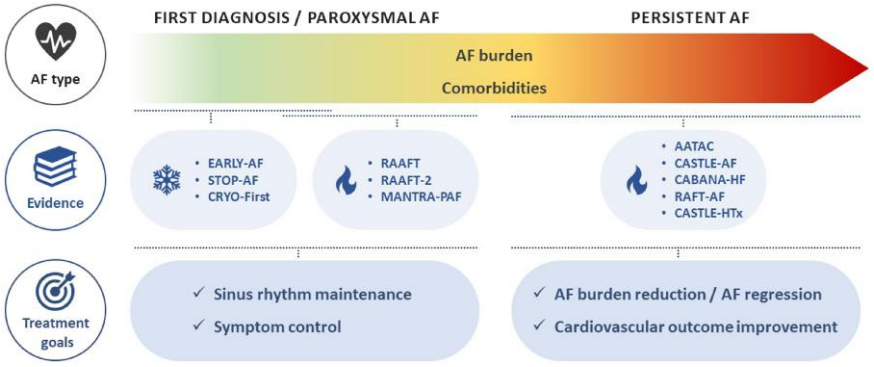
Rhythm control in patients with atrial fibrillation (AF) has evolved dramatically in the last decades. Several studies have informed us of the benefits of an early rhythm control strategy and primary rhythm control by catheter ablation (CA). Similarly, several studies have investigated the effects of CA in patients with longer AF duration and more comorbidities, especially heart failure. In the current review, we summarize the current evidence on rhythm control at different time points during the disease course of AF [*Table 1* and Central illustration].

Central illustration Treatment goals according to atrial fibrillation (AF) type, AF burden and comorbidities, and supporting evidence.



*Corresponding author. Tel: +41 61 265 25 25, Fax: +41 265 45 98, Email: michael.kuehne@usb.ch

What is early?

As time is relative, *early* rhythm control (ERC) needs to be defined in its respective context. For example, the EAST-AFNET 4 trial defined early AF—and consecutively ERC—within 1 year after AF diagnosis.[1] In the trial, the effective time from AF diagnosis to study inclusion was a median of only 36 days. However, the first AF diagnosis might be late in relation to the first AF manifestation, which may have been months or sometimes years before. Thus, rhythm control might be early, when we start the clock at first diagnosis, but late in relation to the first manifestation.

Early might also be defined by its comparator. Traditionally, interventional rhythm control by CA was considered as a second-line therapy after failed antiarrhythmic drug (AAD) therapy. Consequently, failed AAD was an inclusion criterion in older CA ablation trials[2,3] or was frequently present in the majority of patients in more recent trials.[4] In this context, CA ablation may be considered as ERC in trials investigating CA vs. AAD in patients naïve to AAD.[5–8]

A special case of super early, or rather preventive, rhythm control by CA was investigated in trials for common right atrial flutter in patients without known AF. For example, the CRAFT (Cryoballoon pulmonary vein isolation (PVI) as first-line treatment for typical atrial flutter) trial compared cryoballoon PVI with cavotricuspid isthmus ablation as an initial therapy in patients with common flutter but without known AF.[9] With this approach, the risk for clinical AF >2 min was reduced by 54%.[9]

Based on this background the term ‘early’ rhythm control has to be viewed in its respective context and might not always be an interchangeable term.

Early rhythm control

In the current era, the EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) study is the largest trial that investigated an ERC strategy compared with usual care in 2789 patients with an AF diagnosis <1 year before enrolment.[1] The investigators could choose

Table 1 Selected randomized-controlled trials comparing catheter ablation with medical therapy

Study acronym	Enrolment period	*n* randomized	AF duration	Main primary endpoint	Findings
Trials comparing CA with AAD as a first-line therapy					
EARLY-AF[7]	2017–18	303	~1 year	AA >30 s	Less AA recurrence and AF progression by CA after 1 year
STOP-AF[8]	n/a	203	~1.3 years	AA >30 s or procedure failure	Less AA recurrence by CA after 1 year
Cryo-FIRST[6]	2014–18	218	~0.8 years	AA >30 s	Less AA recurrence by CA after 1 year
RAAFT[29]	2001–02	70	~0.4 years	AF >15 s	Less symptomatic AF recurrence by CA within 1 year
RAAFT-2[30]	2006–10	127	n/a	AA >30 s	Less AA recurrence by CA after 2 years
MANTRA-PAF[5]	2005–09	294	n/a	AF burden per Holter recording and cumulative	No difference in cumulative AF burden over 2 years
Trials comparing CA with AAD for alternative endpoints					
ATTEST[31]	2012–18	255	~4.2 years	Progression to persistent AF	Less AF progression by CA after 3 years
CAPTAF[3]	2008–13	155	~3.5–5.6 years	Quality of life	Greater quality of life improvement by CA at 1 year
REMEDIAL[36]	2018–21	100	n/a	Psychological distress	Psychological distress reduction by CA at 1 year
Trials comparing CA with AAD in patients with HF					
AATAC[37]	n/a	203	~0.7 years	AA >30 s	Less AA, hospitalizations, and reduced mortality after 2 years by CA
CASTLE-AF[38]	2008–16	363	n/a	Composite of all-cause death or hospitalization for worsening HF	Reduced primary outcome by CA after ~3 years
CABANA-HF[4a]	2009–16	778	~1.1 years	Composite of all-cause death, disabling stroke, serious bleeding, or cardiac arrest	Reduced primary outcome by CA after 4 years
RAFT-AF[39]	2011–18	411	~1.3 years	Composite of all-cause death and HF events	No difference in the primary outcome. Terminated early
CASTLE-HTx[40]	2020–22	194	~3–4 years	Composite of all-cause death, implantation of a left ventricular assist device, or urgent heart transplantation	Reduced primary outcome by CA after 1.5 years

AA, atrial arrhythmia; AAD, antiarrhythmic drug; AF, atrial fibrillation; CA, catheter ablation; HF, heart failure.
[a]CABANA-HF is a substudy of the CABANA trial.[44]

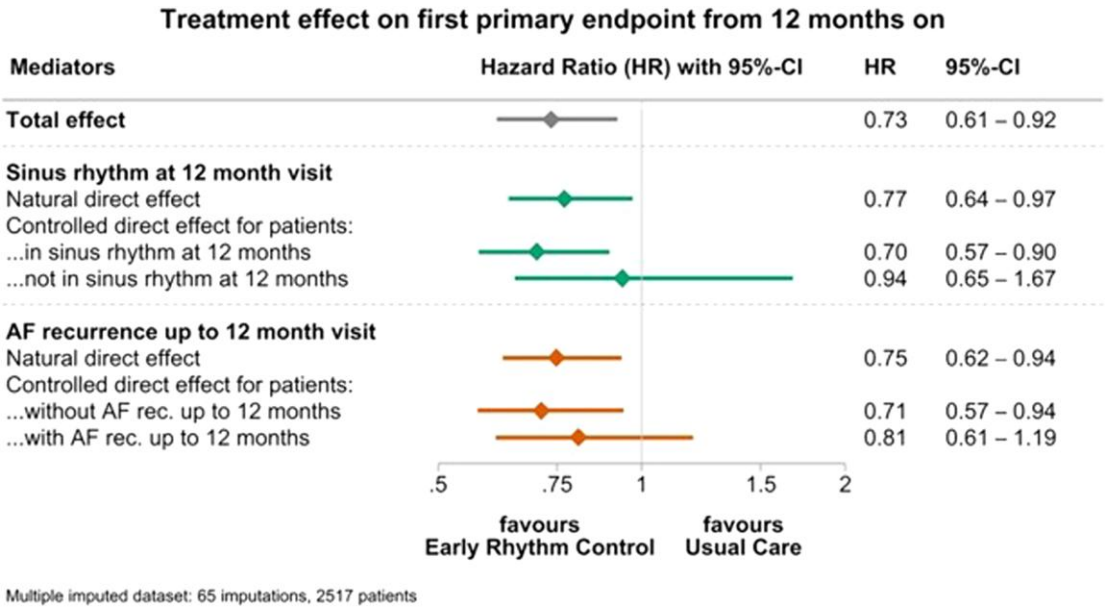


Figure 1 Causal mediation analysis in EAST-AFNET 4 indicating a strong effect of sinus rhythm after 1 year and a weaker effect of atrial fibrillation recurrence on the first primary outcome. Figure reused with permission.[11]

from different options for rhythm control, thereby allowing conclusions on a wide range of rhythm control strategies, but limiting conclusions on individual therapies. In the rhythm control arm, CA was used in only 8% at baseline and increased to ~19% after 2 years, while AAD was used in 87% at baseline and in 46% after 2 years. The trial enrolled a typical, early AF population with a mean age of 70 years, the majority having their first AF episode or paroxysmal AF and more than half being in sinus rhythm at enrolment. The trial showed a significant reduction of the primary, composite outcome (death from cardiovascular causes, stroke, hospitalization due to worsening HF, hospitalization due to acute coronary syndrome) in the ERC group [3.9 events/100 patient-years (py)] compared with the usual care arm (5.0 events/100 py) [HR (95% CI) 0.79 (0.66–0.94), $P = 0.005$] with very low rates of safety events in the ERC group. It is worth noting, that the individual endpoint of stroke was also lower in the early rhythm arm (0.6 events/100 py) compared with the usual care arm (0.9 events/100 py) [HR (95% CI) 0.65 (0.44–0.99)]. These results were received very positively in the cardiac rhythm care community since the negative results of the AFFIRM trial from 20 years ago, albeit in a different patient population with AF, questioned the positive effects of rhythm control.[10]

While the main results of the EAST-AFNET 4 trial answered some questions, it raised even more: what were the mechanisms that caused the reduced outcome events—purely the ERC or a generally more comprehensive care in the active arm? What were subgroups that benefited more from the rhythm control strategy, or were there patient groups that even experienced harm? Is the presence of AF-related symptoms important for treatment decisions? Does an ERC strategy make sense from an economical point of view? Are the results applicable outside of the study population? Since the publication of the main study, the investigators have published several, hypothesis-generating sub-studies to answer these questions.

In order to understand mediating mechanisms, the investigators have performed several informative analyses. In a causal mediation analysis, they investigated potential mediators of ERC and found that sinus rhythm after 1 year explained 81%, AF recurrence 31%, and systolic blood pressure 10% of the treatment effect, while CA for AF did not affect the primary outcome (*Figure 1*).[11] The strong mediation effect of sinus rhythm was surprising as the in-between group difference for the presence of sinus rhythm was only 20%[1] but supported the hypothesis of sinus rhythm maintenance as an important mechanism. While sinus rhythm itself seems important, so is the patient population. AF patients with concomitant HF in the ERC group had a reduction in the primary outcome consistent with the overall study population and a lower incidence of the primary safety outcome (18% vs. 22%) and similar improvements in left ventricular ejection fractions (5% vs. 5%) compared with the usual care group.[12] Similarly, patients with or without a prior stroke, patients across all AF patterns, patients of both sexes, and patients with or without symptoms experienced benefits from ERC consistent with the main study findings.[13-16] Looking at overall comorbidity burden, the investigators found a differential effect according to CHA_2DS_2-VASc score categories <4 and ≥4 points: patients in the higher score category benefitted from ERC [HR (95% CI) 0.64 (0.51–0.81)], while those in the lower score category experienced no consistent benefit [HR (95% CI) 0.93 (0.73–1.19)] (P for interaction = 0.04). Moreover, patients in the lower score category had a higher rate of safety outcomes compared with the usual care group [HR (95% CI) 1.39 (1.05–1.82)] (P for interaction compared with the higher score category = 0.008).[17] These analyses suggest that patients with more comorbidities

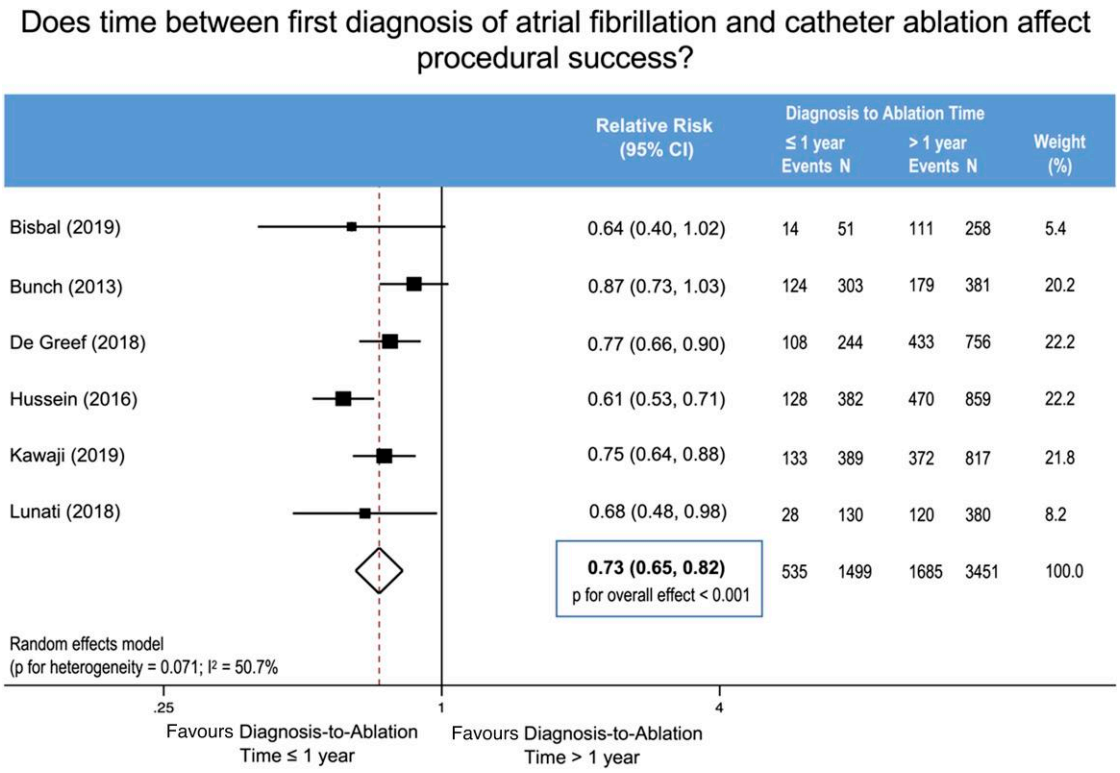


Figure 2 Forest plot showing recurrence of atrial fibrillation after catheter ablation stratified by diagnosis-to-ablation time ≤1 year vs. >1 year. Figure reused with permission.[27]

and a subsequently higher risk of adverse cardiovascular outcomes, including stroke, have more to gain from a comprehensive rhythm control strategy from a prognostic perspective. This hypothesis was further strengthened by observational data from the OptumLabs and the UK Biobank databases pointing in the same direction of a larger benefit of ERC in patients with a higher comorbidity burden.[18] Finally, on an economical level, ERC seems to be cost-effective, at least in the investigated German healthcare system.[19] Regarding the generalizability of the study findings, the investigators applied the eligibility criteria to the UK Biobank AF population and found 80% to be eligible for ERC.[20]

In summary, AF patients undergoing an ERC strategy experienced less cardiovascular events with consistent effects across subgroups including sex, HF, prior stroke, asymptomatic AF, and different AF patterns in the EAST-AFNET 4 trial.[1,12–16] Patients with a higher comorbidity burden seemed to benefit the most, while patients with a lower comorbidity burden experienced more safety events in the absence of a clear prognostic benefit.[17] The main mechanism of these effects seems to be sinus rhythm maintenance.[11] Finally, the data indicate that a large proportion of the general AF population is eligible for ERC.[20]

Early catheter ablation for atrial fibrillation

The optimal timing of CA for AF is still a moving target. Several observational studies have found an increased risk of AF recurrence in patients with a longer time period from AF diagnosis to CA.[21–26] A meta-analysis of these trials, including nearly 5000 patients, showed a decreased risk of AF recurrence after CA for patients with <1 year from diagnosis to ablation [36% vs. 49%, RR (95% CI) 0.73 (0.62–0.82), $P < 0.001$] (*Figure 2*).[27] The first and to date only randomized trial to investigate the effect of an early vs. delayed CA for AF on atrial arrhythmia (AA) recurrence was published recently in 2023.[28] In this trial, Kalman *et al.* enrolled 100 AF patients and finally randomized 89 patients to either CA within 1 month or to an optimized medical rhythm control therapy with CA after 1 year. They did not find a difference between the two arms for the primary endpoint of freedom from AA recurrence [56% vs. 59%, HR (95% CI) 1.12 (0.59–2.13), $P = 0.7$]. Putting these results into context, it is important to note that both treatment arms received ERC, the trial might have been underpowered to detect smaller treatment effects due to limited patient numbers, and the delayed arm received CA after 1 year, just at the cut-off found in observational data.[27]

Three randomized-controlled trials, published in 2021, compared Cryoballoon-CA to AAD as initial treatment in patients with mainly paroxysmal AF: the EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) study, the STOP-AF (Cryoballoon Catheter Ablation in Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation) study, and the Cryo-FIRST (Catheter Cryoablation vs. Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation) study.[6–8] All three trials had comparable designs, primary endpoints of AA recurrence, follow-up durations, and enrolled patient

populations, but they differed in the intensity of rhythm monitoring during follow-up. Across the three trials, nearly 750 patients were enrolled with a mean age ranging from ~52–60 years, 60–70% being male, and a time from AF diagnosis of 0.7–1.3 years. In this patient population with early AF, all three trials reported consistent treatment effects for their primary efficacy endpoint in favour of Cryoballoon-CA compared with AAD after 1 year: 43% vs. 68% [HR (95% CI) 0.48 (0.35–0.66), $P < 0.001$; $n = 303$] of the patients in the EARLY-AF trial, 26% vs. 55% ($P < 0.0001$; $n = 203$) of the patients in the STOP-AF trial, and 18% vs. 32% [HR (95% CI) 0.48 (0.26–0.86), $P = 0.013$; $n = 218$] in the Cryo-FIRST trial had AA recurrence. The differences in the absolute number of primary endpoints between the trials are mainly explained by different AF screening modalities ranging from continuous rhythm monitoring by implantable loop recorders in the EARLY-AF trial to intermittent monitoring in the other two trials. In all three trials, there were no differences in adverse safety outcomes between the CA and the AAD groups.[6–8]

Compared with Cryoballoon-CA, the data on radiofrequency (RF) CA compared with AAD as an initial treatment in AF patients are more dated. Three trials, published between 2005 and 2014, have investigated this topic: the RAAFT (Radiofrequency Ablation vs. Antiarrhythmic Drugs as First-line Treatment of Symptomatic Atrial Fibrillation) study, the RAAFT-2 (Radiofrequency Ablation vs. Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation) study, and the MANTRA-PAF (Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation) study.[5,29,30] The results of these RF-CA trials need to be considered in the context of earlier study periods, in comparison with the Cryoballoon-CA trials, and the substantial technological improvement over the last 10–15 years in RF-CA for AF. Taken together, the three trials enrolled nearly 500 patients with a mean age ranging from ~54–55 years, 70–75% being male, and almost exclusively with paroxysmal AF. The RAAFT and the RAAFT-2 trials had a follow-up period of 1 year with the primary efficacy endpoint of time to first AA recurrence, assessed by intermittent monitoring. Both trials reported outcomes in favour of CA compared with AAD: 13% vs. 63% ($P < 0.0001$; $n = 70$) of the patients in the RAAFT trial had symptomatic AF recurrence and 55% vs. 72% [HR (95% CI) 0.56 (0.35–0.90), $P < 0.001$; $n = 127$] of the patients in the RAAFT-2 trial had any atrial arrhythmias >30 s after 1 year.[29,30] The MANTRA-PAF trial had a follow-up of 2 years with repeated 7 day Holter-ECGs and investigated a primary efficacy endpoint of AF burden overall and within each Holter-ECG. While the authors did not find a statistically significant difference between RF-CA and AAD in overall AF burden (90th percentile of arrhythmia burden, 13% vs. 19%, $P = 0.10$; $n = 294$), they reported a lower AF burden in the RF-CA group in the Holter-ECG at 24 months (90th percentile, 9% vs. 18%, $P = 0.007$).[5] Across the three trials, adverse events were low and comparable between the RF-CA and AAD arms.[5,29,30]

In summary, the optimal timing of CA for AF is still not defined, but evidence supports ERC. CA as an initial rhythm control strategy is superior to AAD in terms of arrhythmia recurrence with similar rates of adverse events.

Can we be too late?

The paradigm of rhythm management in AF patients has long been to treat early in order not to miss a certain ‘point of no return’, after which sinus rhythm maintenance may be difficult to achieve or not achievable at all. However, our traditional study endpoint of AF recurrence ‘yes vs. no’ is changing into a more quantitative endpoint of AF burden. Besides AF burden, AF progression from paroxysmal to persistent AF is another endpoint that has been recently evaluated. For example, the ATTEST (Atrial Fibrillation Progression Trial) study showed a significant reduction in AF progression by CA vs. AAD (2% vs. 18%, $P = 0.0009$; $n = 255$) after 3 years.[31] These results have been replicated in the EARLY-AF study with a 75% reduction in AF progression by CA vs. AAD [2% vs. 7%, HR (95% CI) 0.25 (0.09–0.70), $P < 0.001$] over the 3 year follow-up period.[32] Next to reduced AF progression, evidence is also accumulating on AF regression after CA. The CAPLA (Catheter Ablation for Persistent Atrial Fibrillation) study evaluated PVI vs. PVI plus posterior wall isolation in persistent AF patients and showed that the majority of AF recurrences was paroxysmal indicating regression from persistent to paroxysmal AF.[33] These results are supported by the Progress-AF study, which investigated substrate changes in the left atrium after PVI.[34] The authors described a regression of atrial substrate in ~40% of their patients after the first CA with increases in global left atrial voltage, reduction of low voltage zones, and decreases in left atrial activation time.[34] A long-term follow-up analysis of the CAMERA-MRI study has supplemented these findings by showing improvements in right atrial electrical and structural properties after CA for AF.[35]

Next to a primary electrical endpoint of AF recurrence, two studies have investigated the quality of life and psychological distress as their primary outcome.[3,36] The CAPTAF (Catheter Ablation Compared with Pharmacological Therapy for Atrial Fibrillation) study randomized 155 patients with a mean age of 56 years, 77% being male, and a median AF duration of 3.5–5.6 years to CA or AAD for rhythm control. Patients in the CA group improved significantly more in their SF-36 General Health score [mean treatment difference of 8.9 points, (95% CI) 3.1–14.7; $P = 0.003$].[3] The REMEDIAL (Randomized Evaluation of the Impact of Catheter Ablation on Psychological Distress in Atrial Fibrillation) study analysed 96 AF patients with a mean age of ~59 years, 68% being male, and 46% having persistent AF, that were randomized to CA or AAD. Patients in the CA group had less psychological distress, measured by the HADS score, after 6 [11.9 (7.2) vs. 8.2 (5.4) points, $P = 0.006$] and 12 months [11.8 (8.6) vs. 7.6 (5.3) points, $P = 0.005$].[36]

Certain patient groups were previously considered too sick or too old to benefit from rhythm control, especially by CA due to a potentially increased complication risk. However, several CA studies in sicker patient populations have now shown larger reductions in a variety of adverse outcomes, compared with younger AF populations with less comorbidities despite a higher AF recurrence rate. These trials include the AATAC (Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRTD) study,[37] the CASTLE-AF (Catheter Ablation vs. Standard

Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) study,[38] the CABANA (Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation)-HF substudy,[4] the RAFT-AF (Rhythm Control—Catheter Ablation with or without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm vs. Rate Control with Medical Therapy and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for Atrial Fibrillation) study,[39] and the CASTLE-HTx (Catheter Ablation for Atrial Fibrillation in Patients with End-Stage Heart Failure and Eligibility for Heart Transplantation) study.[40]

Across all these trials, nearly 2000 patients with HF and AF were enrolled and randomized to CA or medical rhythm/rate control therapy. Patients could have HF with both preserved and reduced ejection fraction, mainly persistent or long-standing persistent AF, and a duration of AF ranging from 8 months up to 4 years. While the AF recurrence rates were unsurprisingly higher compared with the aforementioned CA studies in paroxysmal AF patients, consistent improvements in adverse cardiovascular outcomes were reported. In the AATAC trial, the composite endpoint of unplanned hospitalization or death over 2 years was reduced by 45% [32% vs. 58%, RR (95% CI) 0.55 (0.39–0.76), $P < 0.001$; $n = 203$].[37] A similar endpoint of hospitalization for HF or death over 60 months was reduced by 38% [29% vs. 45%, HR (95% CI) 0.62 (0.43–0.87), $P = 0.007$; $n = 363$] in the CASTLE-AF study[38] and a broader endpoint of death, disabling stroke, serious bleeding, or cardiac arrest by 36% [9% vs. 12%, HR (95% CI) 0.64 (0.41–0.99); $n = 778$] in the CABANA-HF substudy.[4] The RAFT-AF trial was terminated early and could not show a statistical difference between the two study arms of CA rhythm control vs. rate control in the primary endpoint of all-cause death or HF event but showed a trend in a similar direction as the other trials [23% vs. 33%, HR (95% CI) 0.71 (0.49–1.03), $P = 0.066$; $n = 411$]. The latest trial, the CASTLE-HTx study, enrolled the patients with the most comorbidities that were evaluated for heart transplantation and showed a large reduction of 76% [8% vs. 30%, HR (95% CI) 0.24 (0.11–0.52), $P < 0.001$; $n = 194$] in the primary endpoint of all-cause death, implantation of a left ventricular assist device, or urgent heart transplantation.[40] Besides their respective composite endpoints, all studies pointed in the same direction regarding all-cause mortality with varying reductions by CA: 56% [RR (95% CI) 0.44 (−0.20–0.96)] in ATTAC,[37] 47% [HR (95% CI) 0.53 (0.32–0.86), $P = 0.009$] in CASTLE-AF,[38] 43% [HR (95% CI) 0.57 (0.33–0.96)] in CABANA-HF,[4] 21% [HR (95% CI) 0.79 (0.48–1.30), $P = 0.35$] in RAFT-AF,[39] and 71% [HR (95% CI) 0.29 (0.12–0.72)] in CASTLE-HTx.[40]

Evidence on CA for AF in elderly patients is available from sub-analyses of randomized trials and from observational studies. In a CABANA substudy, the authors reported similar reductions in AF burden and low CA complication rates across all age strata, but no benefit for the primary outcome (death, disabling stroke, serious bleeding, or cardiac arrest) in patients >75 years.[41] In a meta-analysis of observational data, including ∼360.000 patients undergoing CA, patients aged >75 years compared with younger patients had similar success rates but higher complication rates, which were mainly found in the RF group but not in the cryoablation group.[42] These results were supported by an analysis from the Cryo Global Registry, which showed similar success and complication rates in patients aged >80 and <80 years undergoing cryoballoon ablation.[43]

In summary, in patients with longer AF duration or more comorbidities, a qualitative endpoint of AF recurrences 'yes vs. no' after CA is insufficient. We should rather aim for AF burden reduction and AF regression. Patients with concomitant HF derive benefits in adverse cardiovascular outcome reductions by CA, most likely because of reductions of AF burden. Treating physicians should recommend CA in appropriate patients with a low threshold. Elderly patients gain similar benefits compared with younger patients in AF burden reduction and have comparable complication rates.

Final remarks

Over the last 20 years, we have gained important insights on ERC in patients with AF. An ERC strategy with comprehensive patient care was shown to benefit patients with recently diagnosed AF. Several randomized studies support CA as an initial rhythm control strategy in patient populations with more comorbidities, especially HF. Future trials will investigate newer CA technologies and strategies, anticoagulation management after CA, and alternative rhythm control therapies.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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