

Table 1. Characteristics of included studies

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Ang 2018 Cryo vs RF	RCT	UK	Jul 2009– Dec 2012	203	≥18	CBA vs RFA vs CBA + RFA	90	>18 years, documented PAF on at least 2 occasions and accepted for catheter ablation for AF	Severe left atrial dilatation (>50mm), severe valvular disease, previous left atrial ablation, persistent AF, potentially reversible cause of AF, any contraindication to ablation
Buist 2018	RCT	Netherlands	NR	269	12	CBA vs RFA	90	Suitable for primo PVI for drug-refractory paroxysmal or early persistent AF	Procedures in which additional ablation strategies (e.g. complex fractionated atrial electrograms, linear ablations, right atrium ablations) were applied
Kuck 2018 FIRE AND ICE	RCT	8 countries	Jan 2012– Jan 2015	750	12	CBA vs RFA	90	18–75 years, symptomatic PAF with at least 2 episodes and at least one episode documented (30 seconds length, documented by ECG within last 12 months) that was refractory to class I or class III AADs or beta blockers	Life expectancy <1 year, pregnant or breastfeeding women, active systemic infection, cryoglobulinaemia, cardiac surgery/PCI/myocardial infarction in preceding 3 months, unstable angina pectoris, contraindication to chronic anticoagulation, NYHA class III-IV heart failure, LVEF <35%, mitral prosthesis, intracardiac thrombus
Andrade 2019/ Larsen 2020 CIRCA DOSE	RCT	Canada	Sep 2014– Jul 2017	346	12	CBA vs RFA	90	>18 years, PAF refractory to at least one class I or class III AAD	Previous left atrial ablation or surgery, AF due to reversible cause, intracardiac thrombus, cardiac valve prosthesis, contraindication to anticoagulation, clinically significant mitral valve regurgitation or stenosis, NYHA class III-IV heart failure, pregnancy, stroke/TIA in preceding 6 months, LVEF <35%
Pak 2021 CRAFT	RCT	South Korea	NR	312	12	CBA vs RFA	90	Patients who underwent catheter ablation for symptomatic and drug-refractory non-valvular PAF	Persistent or permanent AF, rheumatic valvular disease, significant structural heart disease other than left ventricular hypertrophy, left atrial diameter ≥55mm, history of AF ablation or cardiac surgery
Perez- Castellano 2014 COR	RCT	Spain	Jul 2009– Mar 2011	50	12	CBA vs RFA	90	18–75 years, symptomatic recurrent PAF (42 episodes in the last 6 months) refractory to ≥1 AADs (class I or III) and an anatomical pattern consisting of 4 single pulmonary veins	Prior AF ablation, prior cardiac surgery, moderate to severe valvular heart disease, anteroposterior left atrial diameter >50mm, hyperthyroidism, intracardiac thrombus, contraindications for anticoagulant therapy, concomitant acute illness, pregnancy, unavailability for follow-up for at least 1 year

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Ikenouchi 2018	PSM	Japan	Jan 2012–Aug 2017	198	12	CBA vs RFA	90	Consecutive patients >75 years with PAF or persistent atrial fibrillation undergoing first PVI ^a	Left atrial thrombus, abnormal thyroid function, severe frailty, long-standing AF (>1 year), severe valvular heart disease, contraindications for the procedure
Knecht 2014 BEAT-AF	PSM	Switzerland	NR	142	12	CBA vs RFA	90	Consecutive patients with documented episodes of AF	Persistent or permanent AF, history of any previous left atrial procedure (surgical or percutaneous), use of a magnetic navigation system
Matta 2018	PSM	Italy	NR	92	12	CBA vs RFA	90	Consecutive patients suffering from paroxysmal atrial fibrillation treated with CBA or RFA	NR
Tokuda 2016	PSM	Japan	NR	246	12	CBA vs RFA	90	414 consecutive patients who had undergone an initial catheter ablation procedure for PAF	NR
Andrade 2020 EARLY AF	RCT	Canada	Jan 2017–Dec 2018	303	12	CBA vs AAD	90	>18 years with symptomatic AF and ≥1 episode of AF detected on ECG within 24 months before randomisation	History of daily use of a class I or class III AAD at therapeutic doses
Kuniss 2021 Cryo FIRST	RCT	20 sites worldwide	Apr 2014–Oct 2018	218	12	CBA vs AAD	90	18–75 years with a normal ECG, LVEF ≥50%, thickness of the inter-ventricular septum ≤12mm, left atrium diameter (short axis) <46mm, recurrent symptomatic PAF, drug naive (had not previously received a Class I or III AAD for >48 hours)	Persistent AF, previous left atrial ablation or cardiac surgery, documented typical atrial flutter, previous TIA or stroke, intracardiac thrombus, hypertrophic cardiomyopathy
Wazni 2020 STOP AF	RCT	US	Jun 2017–May 2019	203	12	CBA vs AAD	90	18–80 years with recurrent symptomatic PAF	Previous AAD treatment (class I or III) for ≥7 days, enlarged left atrial diameter (>5cm), previous left atrial ablation or left atrial surgical procedure
Kuck 2021 ATTEST	RCT	29 sites worldwide	Feb 2012–May 2018	255	36	RFA vs AAD	90	≥60 years of age with PAF for ≥2 years and with ≥2 episodes over the 6 months preceding enrolment	Reversible AF, previous diagnosis of persistent/permanent AF/AT, cardioversion >48 hours after onset of AF/AT, recent cardiovascular events

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Morillo 2014 RAAFT-2	RCT	16 sites worldwide	Jul 2006– Jan 2010	127	24	RFA vs AAD	90	18–75 years, symptomatic with recurrent PAF lasting > 30 seconds (≤ 4 episodes within the prior 6 months); experienced at least 1 episode that was documented by surface ECG, 6 months before randomisation; and had no previous AADs	Previous AAD treatment, LVEF <40%, left atrial diameter >5.5 cm; moderate-to-severe left ventricular hypertrophy (wall thickness >1.5cm), valvular disease, coronary artery disease, or postcardiac surgery within 6 months; left heart ablation procedure, complete contraindication to use of heparin, warfarin, or both
Pappone 2011 APAF	RCT	Italy	Jan 2005– May 2005	198	48	RFA vs AAD	42	18–70 years, creatinine concentration <1.5mg/dL, AF history >6 months, AF burden >2 episodes/month in the last 6 months	AF secondary to transient or correctable abnormality, intra-atrial thrombus, tumour precluding catheter insertion, LA diameter >65mm, LVEF <35%, heart failure >NYHA functional class II, prior AAD therapy with amiodarone, flecainide, and sotalol, contraindication to beta-blocking therapy
Wazni 2005	RCT	3 countries	Dec 2001– Jul 2002	70	12	RFA vs AAD	None	18–75 years, monthly symptomatic AF episodes for at least 3 months	Previous history of atrial flutter or AF ablation, previous open-heart surgery, previous treatment with AAD, contraindication to long-term anticoagulation
Wilber 2010	RCT	19 sites worldwide	Oct 2004– Oct 2007	167	9	RFA vs AAD	90	3 symptomatic AF episodes (≥ 1 episode verified by ECG) within the 6 months before randomisation, not responding to ≥ 1 AAD (class I, class III, or atrioventricular nodal blocker)	AF ≥ 30 days in duration, age <18 years, LVEF <40%, previous ablation for AF, documented left atrial thrombus, amiodarone therapy in the previous 6 months, NYHA class III or IV, myocardial infarction within the previous 2 months, CABG in previous 6 months, thromboembolic event in previous 12 months, severe pulmonary disease, implanted ICD, contraindication to AAD or anticoagulants
Suruga 2021	PSM	Japan	Oct 2016– Aug 2017	60	12	HBA vs CBA	90	Consecutive HBA patients and PSM CBA patients	NR

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Sohara 2016	RCT	Japan	NR	143	9	HBA vs AAD	84	20–75 years, refractory to ≥ 1 class I to IV AADs	Previous left atrial ablation or surgery for AF, refractory to selected AADs, NYHA class III–IV, myocardial infarction or unstable angina pectoris during the previous 6 months, comorbid severe ischaemic heart disease, valvular disorder, severe pulmonary hypertension, carotid occlusion, deep-vein thrombosis, history of cerebral infarction or intracerebral bleeding with apparent neurological symptoms during the previous 6 months
Chun 2021	RCT	Germany	Apr 2017–Apr 2019	200	12	LBA vs CBA	90	18–80 years, symptomatic PAF or persistent AF refractory to ≥ 1 AAD, including beta-blockers (class I–III) ^a	Previous PVI attempts. ineligible for treatment with oral anticoagulation, presence of an intracardiac thrombus, moderate or severe mitral valve disease
Yano 2021	PSM	Japan	Apr 2019–Jul 2020	74	3	LBA vs CBA	None	Consecutive PAF patients undergoing primary PVI with CBA or LBA	NR
Gal 2014	RCT	Netherlands	NR	460	43	PVAC vs RFA	90	Consecutive patients with symptomatic AF	NR
McCready 2014	RCT	UK	Sep 2007–Mar 2012	188	12	PVAC vs RFA	90	Patients with PAF who had failed at least one AAD who had been listed for a planned PVI procedure	Patient objection, prior AF ablation, left atrial size >60 mm, mechanical prosthetic mitral valve replacement, hypertrophic cardiomyopathy, contraindications to anticoagulation, pregnancy

^aAlthough persistent AF was included in the trial, only the paroxysmal AF subgroup was included in subsequent analysis.

AAD: antiarrhythmic drugs; AF: atrial fibrillation; AT: atrial tachycardia; CABG: coronary artery bypass graft; CBA: cryoballoon ablation; CBA+RFA: combined cryoballoon plus radiofrequency ablation; ECG: electrocardiogram; HBA: hot balloon ablation; ICD: implantable cardioverter-defibrillator; LA: left atrial; LBA: laser balloon ablation; LVEF: left ventricular ejection fraction; NR: not reported; NYHA: New York Heart Association; PAF: paroxysmal atrial fibrillation; PSM: propensity-score matched study; PVAC: pulmonary vein ablation catheter; PVI: pulmonary vein isolation; RCT: randomised controlled trial; RFA: radiofrequency ablation; TIA: transient ischaemic attack