

Transforming atrial fibrillation management by targeting comorbidities and reducing atrial fibrillation burden: the 10th AFNET/EHRA consensus conference

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Atrial fibrillation (AF) is a growing unmet medical need. To reduce its impact on patients' lives, improvements in stroke prevention therapy, treatment of concomitant conditions, and rhythm control therapy are actively developed: Innovations in anti-thrombotic agents, new anti-arrhythmic drugs (AADs), and novel interventional rhythm control therapies emerge alongside AF-reducing effects of general cardiometabolic therapies. Simple risk scores are slowly replaced by personalized AF risk estimation using quantifiable features. These developments were discussed by over 80 experts from academia and industry during the 10th Atrial Fibrillation NETWORK /European Heart Rhythm Association consensus conference from 5 to 7 May 2025. The emerging consensus, described here, is multi-domain therapy combining stroke prevention, rhythm control, and therapy of concomitant cardiovascular conditions. This combines anti-coagulants, AADs, and AF ablation with old and new cardiometabolic drugs that can reduce AF risk, AF burden, and AF-related complications at scale. The paper furthermore describes quantitative traits that may enable a shift towards risk-driven therapy based on AF phenotypes. These can enable adjusted therapy strategies that are safe, accessible, and patient-centred. Applying modern data science and artificial intelligence methods to quantitative phenotypic and genetic features can further improve risk estimation and personalized therapy selection. At the same time, translational and clinical research into reversing the drivers of AF and into improved stroke

prevention through new drugs and through combination therapies is needed. Together, these efforts offer pathways towards personalized, patient-centred, multi-modal, and accessible AF management that integrates rhythm control, stroke prevention, and therapy of concomitant conditions to bridge today's practical needs with tomorrow's therapeutic innovation.

Keywords

Atrial fibrillation • Rhythm control • Stroke prevention • Ablation • Atrial fibrillation burden • Heart failure • Antiarrhythmic drugs • Artificial intelligence • Integrated care

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Introduction

The landscape of atrial fibrillation (AF) management is undergoing considerable shift. While stroke prevention has long been the cornerstone of AF treatment, supported by well-established risk stratification schemes and effective oral anti-coagulant therapies, recent ESC guidelines emphasize the importance of managing comorbidities as a core component of AF-CARE.^{1,2} In addition, large-scale trials, such as EAST-Atrial Fibrillation NETwork (AFNET 4)³ and the earlier ATHENA trial,⁴ underscore the prognostic relevance of early and safe rhythm control to prevent cardiovascular events⁵ including reductions in stroke and the potential to delay heart failure development and improve quality of life.^{3,6} Rhythm control strategies were also associated with a favourable cost-effectiveness profile.⁷

The low stroke risk in patients with low-burden AF challenges the current binary diagnostic model of AF, where one documented episode defines a lifelong diagnosis.^{8–10} A shift in treatment from an exclusive focus on stroke prevention to management of concomitant comorbidities and AF burden reduction is emerging.¹¹ Both rhythm control and therapy of coexisting conditions remain underused, and patients with AF continue to experience poor outcomes with associated high health-care costs. This underscores the need for streamlined treatment to target risk factors, AF burden and rhythm. While rhythm control therapy evolves into the default treatment for many patients with AF, new technologies for restoration and maintenance of sinus rhythm are being developed: simplified ablation pathways, individualized anti-arrhythmic drug (AAD) use, new AADs, and emerging tools for AF burden monitoring offer opportunities to improve care.

Anti-thrombotic therapy also continues to evolve. Direct oral anti-coagulants are now the standard anti-coagulation therapy. Left atrial appendage occlusion is undergoing evaluation in large outcome trials.^{12,13} New, safer agents, such as factor XI and factor XIa inhibitors are being evaluated for efficacy in patients with AF.¹⁴ Promising safety data contrast with weaker-than-expected stroke preventing effects with asundexian in the published trials.^{15,16}

This paper describes the main outcomes of the 10th AFNET/European Heart Rhythm Association (EHRA) consensus conference. Over 80 experts from academia and industry, invited by the AFNET and the EHRA, met from 5 to 7 May 2025 to align contemporary

and evolving evidence, identify evidence gaps, and develop perspectives for better care. The emerging consensus is a shift towards risk-driven management and dynamic rhythm control strategies that are safe, accessible, and patient-centred.

Comorbidities in atrial fibrillation: a call for quantification

AF typically develops due to a combination of modifiable and non-modifiable risk factors that promote AF development, disease progression, and outcomes.¹ The genetic make-up of AF, consisting of common and rare variants that confer AF risk,^{17–19} sex, and older age²⁰ are among the best-defined non-modifiable risk factors. Treatment of modifiable conditions such as hypertension, heart failure, obesity, diabetes, and excess alcohol consumption show beneficial effects on reduction of AF recurrence.²¹ Additional comorbidities, including pulmonary hypertension, sleep apnoea, valvular heart disease, chronic kidney disease (CKD), and thyroid dysfunction, as well as environmental exposures ('exposome') contribute to AF and to AF-related morbidity and mortality in patients with AF.^{22,23}

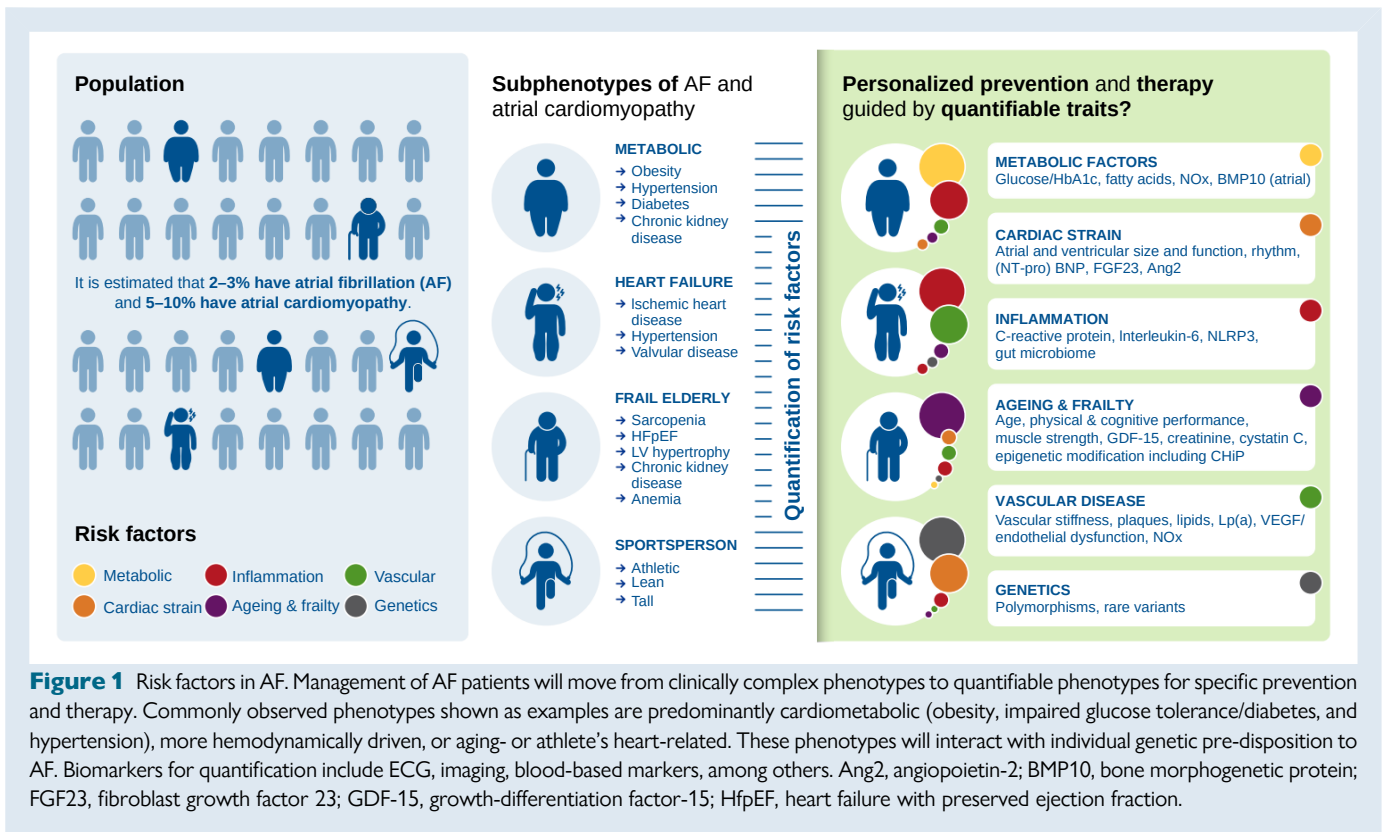
Risk factors and comorbidities tend to cluster, producing discernible patient phenotypes with prognostic and therapeutic implications, *Figure 1*.^{24–26} Risk factors are often determined at baseline and only in a dichotomized fashion ('yes/no').^{27,28} Quantifying the severity of comorbidities may help integrate risk profiles into clinical care.²⁹ While some have clear metrics (e.g. blood pressure, creatinine clearance, or glycosylated haemoglobin), others lack accepted quantitative measures. Furthermore, risk factor quantification requires multi-dimensionality, integrating clinical features, ECG-parameters, imaging, blood components, behavioural, and environmental factors. Moreover, risk is dynamic, shaped not only by evolving comorbidities and environmental exposures, but also by rhythm variability and patient self-management.³⁰ Protective or resilience factors may mitigate this risk. Non-modifiable risk factors such as racial differences and genetic predisposition may be modulated during life by epigenetic changes, changes in reading and expression profiles e.g. of PITX2, or clonal haematopoiesis, thereby affecting AF and AF-related outcomes.^{17,31–40}

Holistic, integrated management of comorbidities with the aim to reduce modifiable risk factors⁴¹ is complex, yet improves outcomes.^{42,43}

Although each person suffering from AF is unique, a few AF phenotypes appear frequent in the clinical setting, *Figure 1*, for example:

- An elderly frail female with CKD, cognitive impairment, and heart failure with preserved ejection fraction (HFpEF).
- A metabolically unhealthy obese individual with hypertension, diabetes, and fatty liver disease,⁴⁴ or
- An endurance runner with an athlete's heart.

Risk factors and comorbidities can be quantified using biometric data (e.g. weight, age, and body size), imaging findings, ECG characteristics, circulating biomarkers,^{45,46} and other parameters (*Figure 1*).⁴⁷ Imaging biomarkers, such as left atrial fibrosis and epicardial fat (via cardiac MRI or via CT scan), or atrial function markers like atrial strain (via echocardiography), predict AF progression and incident heart failure and are linked with stroke and cognitive decline.^{48–52} Blood



biomarkers representing cardiac strain (e.g. N-terminal pro B-type natriuretic peptide) and cardiomyocyte damage (high-sensitivity troponin), kidney disease (estimated glomerular filtration rate, cystatin C), thrombo-inflammation (D-dimer, C-reactive protein, and interleukin-6), oxidative stress (growth-differentiation factor-15), activation of endothelial cells (angiopoietin 2), and fibroblasts (fibroblast growth factor 23, galectin 3), or atrial dysfunction (bone morphogenetic protein 10), predict AF and/or AF-related outcomes such as stroke, heart failure, and bleeding, several of which are included in biomarker-based risk scores in AF.^{53–58} ECG features such as P wave duration, amplitude or area, or AF burden, can be quantified and allow prediction of incident AF, recurrent AF, and risk of cardiovascular complications.^{59–61}

Artificial intelligence (AI) may be well suited to define clusters of risk factors that contribute to AF, particularly those with complex or poorly understood pathophysiology, an area that remains a focus of ongoing research. This can lead to patient clusters that may form a basis for personalized therapy. The development of digital twins (computational models that simulate the structural, electrical, and physiological characteristics of individual patients) offers a novel approach to refine the discovery and validation of mechanistically distinct AF phenotypes.⁶² This is explored in current studies (TARGET, ARISTOTELES, Research - Maestria H2020).^{63–66}

This group suggests that quantification of comorbidities and disease processes using multi-modal biomarker strategies can tailor therapy of comorbidities and improve prevention of AF-related complications.⁶⁷

Cognitive function and atrial fibrillation

Cognitive impairment is a frequent comorbidity that can render AF management more difficult. Cognitive decline is also a potential adverse

outcome of AF. Mild cognitive impairment or dementia are observed in up to 40% of older adults with AF, and AF itself is associated with a heightened risk of both developing cognitive impairment and progressing from mild cognitive impairment to dementia, even in the absence of stroke.^{68–72} Old age, frailty, and cognitive decline often coexist and increase vulnerability in older adults.⁷³ As the global population ages, the need to prevent or slow the development of cognitive dysfunction becomes more imperative to preserve functional independence and quality of life.⁷⁴

To diagnose cognitive impairment, several cognitive, screening, and diagnostic tests exist, each with their own limitations, *Table 1*. The mini-mental score examination (MMSE) and Montreal cognitive assessment (MoCA) are the most widely used tools to quantify overall cognitive function in both research and clinical practice. They allow for a quick assessment of global cognition and brief evaluations of attention, language, memory, and visuospatial/executive functions but show learning and ceiling effects.^{82,83} The MoCA is more sensitive than the MMSE for mild cognitive deficits. A more precise assessment of cognitive function requires a battery of tests administered by a trained professional. This is the accepted method to diagnose cognitive impairment and dementia but requires skills, time, and resources. Self-administered or on-site on-line tests (e.g. Cogniciti⁸⁴ and Creyos⁸¹) may be useful alternatives but await validation.

Several studies reported a possible association between AF burden and cognitive impairment. That link appears accentuated in patients with persistent or permanent AF.^{85,86} Patients with AF have a higher rate of brain lesions, detected by cerebral imaging, infarcts and white matter hyperintensities, and lower brain volume, compared to patients in sinus rhythm,⁸⁷ and may have cerebral hypoperfusion.^{88,89} The presence of brain lesions is associated with a higher risk of cognitive decline.⁹⁰

Several underlying mechanisms have been suggested to explain the association of AF and cognitive impairment: brain infarcts with or without accompanying symptoms of stroke, chronic inflammation of the

Table 1 Common test for cognitive function that have been used in patients with atrial fibrillation

To be performed by professionals	Test	Tested domains	Particularities	Time duration	Strengths	Weaknesses
	Screening tools MoCA ^{75,76}	Global cognition	Detection of MCI and dementia Add 1 point if education level ≤ 12 years T-MoCA could be done remotely Free for academic purposes	10 min	Validated in multiple large studies, including in AF patients Good diagnostic performance for MCI Available in >100 languages	Ceiling and learning effect
	MMSE ⁷⁶	Global cognition		10 min	Validated in multiple large studies Available in numerous languages Studied in AF patients	Ceiling and learning effect Less sensible than the MoCA
	Mini-Cog ^{77a}	Memory, visual, and executive functions	Detection of dementia	<5 min	Very quick Validated in multiple studies Studied in AF patients	Language, attention, orientation not assessed Smaller sample in validation studies Limited use in detecting MCI
	SLUMS ^{78a}	Global cognition	Scoring threshold depends on education levels	5–10 min	Initially developed for geriatric veterans	Less used and studied Lack of sufficient normative data
	CDT ^{79a}	Visuospatial skills, executive functions, and language comprehension	Detection of dementia	<5 min		Limited use in detecting MCI
Self-assessment	Cognitive brain health assessment ^{80a}		Online test English and French	20–30 min	No ceiling effect	Not validated in AF patients
	Creyos ⁸¹		Online test English, Spanish, and French	40 min	No ceiling effect	Not validated in AF patients

MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; CDT, clock drawing test; CAMCOG, Cambridge cognition examination; TMT, trail making test and B; VCI, vascular cognitive impairment.

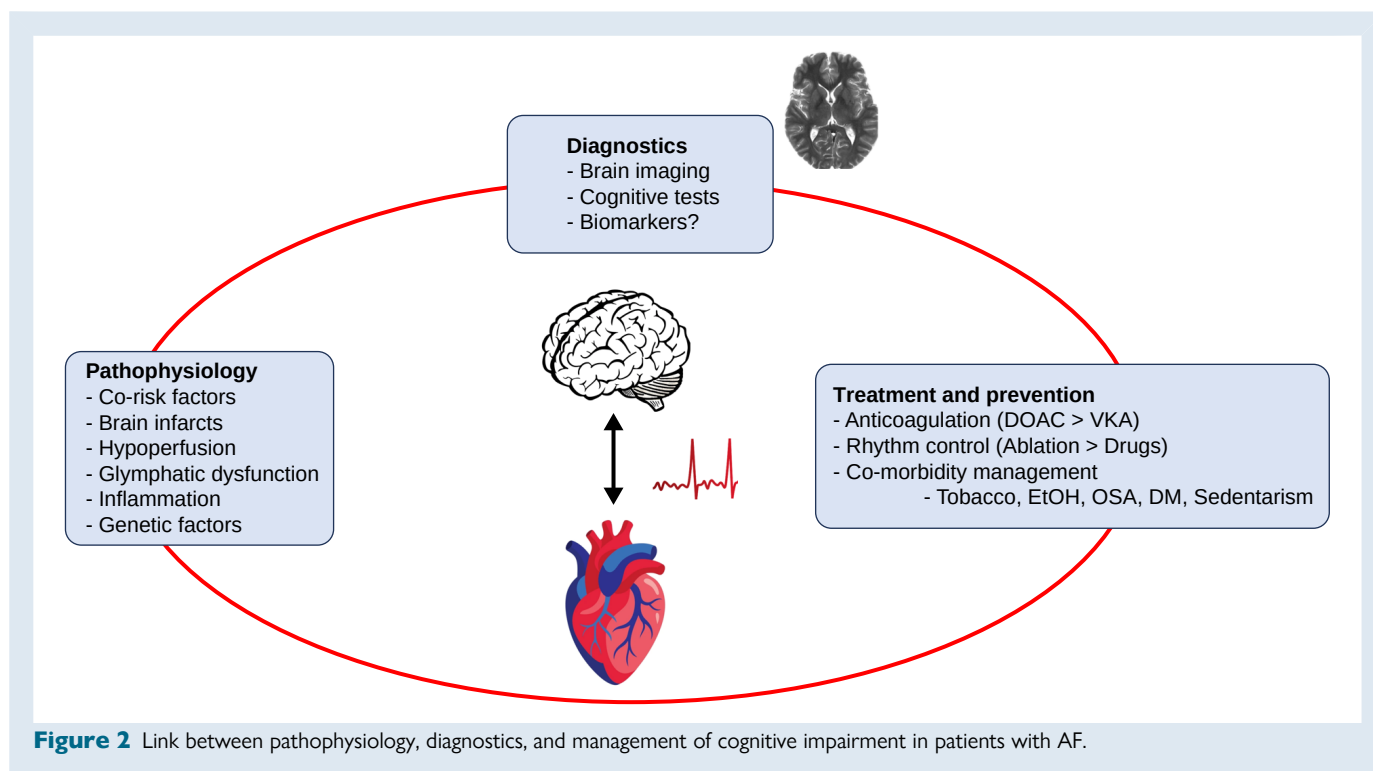
^aFree of charge.

brain, cerebral micro-bleeds, genetic pre-disposition, and cerebral hypoperfusion, Figure 2.^{72,91,92} More recently, impairment of the glymphatic system (a brain-wide network that enables physiological flow of cerebrospinal and interstitial fluid and is required for metabolic balance in the brain) has been proposed as an additional mechanism contributing to cognitive decline in AF patients.^{93,94}

The pattern of cognitive deficits may vary by underlying cause. In patients with AF, impairment is often observed across multiple cognitive domains, with a particular vulnerability in executive function, which includes planning, task-switching, focus, and working memory. This contrasts with the predominantly memory-based deficits characteristic of

Alzheimer's disease. As such, cognitive screening in AF may benefit from a stronger emphasis on tools that specifically assess executive dysfunction.

Identifying causal links between AF and cognitive decline, as well as effective strategies to slow cognitive decline and prevent dementia, is of major importance. A multi-disciplinary approach is recommended to slow cognitive decline and prevent dementia.^{95,96} Oral anti-coagulation,^{97,98} anti-hypertensive therapy, potentially with low blood pressure targets,⁹⁹ diabetes control, sleep apnoea management, reduction of alcohol and tobacco consumption, good nutrition, social inclusion, and physical activity form the basis of preventive



treatment.^{100,101} Rhythm control using AF ablation is associated with preservation of cognitive function in non-randomized datasets, a meta-analysis, and small randomized controlled trials, again pointing to a potential role of AF burden reduction for cognitive function.^{102–104} While these associations are promising, they remain hypothesis-generating and require confirmation in prospective and larger trials.

Atrial fibrillation burden

AF burden is defined as the proportion of time that a patient is in AF.¹⁰⁵ In simple terms, AF burden can be estimated as the time in AF divided by the monitored time. Rather than the binary information that creates a lifelong diagnosis of AF based on a single ECG with AF in current clinical practice, or the broad categorization of AF patterns that is used in current AF guidelines (e.g. paroxysmal or persistent AF), AF burden is measured on a continuous scale and provides quantitative information. A high AF burden has been associated with lower quality-of-life, more healthcare utilization, adverse cardiovascular outcomes (stroke, heart failure hospitalization, and death), and higher cost of care.^{106–120} The association between AF burden and stroke risk is evident across cohorts and trials.⁶⁰ Recent guidelines recognize AF burden as a potentially actionable metric, and AF burden reduction as a potential therapeutic target, while noting evidence gaps.^{1,105,121} Pending further validation of its association with outcomes, AF burden has the potential to assist clinical decision making, evaluate treatment success, and prognosticate outcomes in the future.

The most accurate estimation of AF burden is captured through continuous monitoring e.g. with implantable devices (CIEDs and ICMs). In practice, most patients undergo intermittent monitoring, which offers a less accurate estimate of true burden. Shorter monitoring durations have lower sensitivity to detect AF but can also overestimate AF burden in those with a low AF burden, when compared to continuous rhythm monitoring. As AF monitoring frequency or duration increase the sensitivity and accuracy of non-invasive AF burden assessment

improves.¹²² Furthermore, the precision of AF burden estimates increases with higher underlying AF burden.¹¹⁹

Although evidence remains limited, available data suggest that AF burden is associated with outcomes in a dose-dependent manner: patients with an AF burden below 0.1% after AF ablation generally have a low risk of stroke and cardiovascular events. Low rates of stroke are also reported in patients with device-detected AF without ECG-documented AF^{123,124} and after AF ablation.^{12,125} On the other hand, an AF burden >5% has been linked to progressively increased rates of adverse cardiovascular outcomes and healthcare utilization in device-detected, population-based studies.^{60,113–115,117,126,127} In the recently published EAST-AFNET 4 AF burden sub-analysis, an AF burden <5–6% on therapy was associated with lower cardiovascular event rates, with lower AF burden potentially resulting in even lower event rates.¹¹⁹ In patients with AF and heart failure with reduced ejection fraction (HFrEF) in the CASTLE-AF and CASTLE-HTx trials, a median AF burden of 50% with medical therapy was reduced to a median burden 20% with AF ablation, and was associated with less heart failure events and better survival.^{111,128} The relationship between AF burden and outcomes in CASTLE-AF suggests that event rates drop with AF burden below 15–20%. Based on these hypothesis-generating data, an accurate estimate of the baseline AF burden may in the future influence therapeutic decisions for rhythm control and potentially for anti-coagulation. Measurable proxies of AF burden load like ECG-parameters or blood biomarkers that are associated with recurrent AF^{46,129} and with cardiovascular events^{45,58,130} in patients with AF should be further developed. To summarize, different AF burden levels will have different effects on AF-related outcomes such as cardiovascular death, stroke, heart failure, cognitive function, and quality of life. Further research will be needed to describe these AF burden levels, and potentially to define AF burden thresholds. Additionally, future studies should be targeted to better assess the relationship between AF burden and the underlying atrial cardiomyopathy.^{131,132}

While associations between low AF burden and better outcomes are robust, causality remains unproven (with the exception of exploratory

Table 2 Ongoing or future randomized clinical trials on rhythm control for AF with expected sample size >100 subjects

Trial (clinicaltrials.gov)	Target size, N	Follow-up	Estimated start	Estimated completion	Population	Intervention	Control	Primary end point(s)
EMOTICON (NCT04942171)	320	1 year	June 2021	2026	AF, age 20–80 years, LA diameter <55 mm	AF catheter ablation	Medical therapy (AAD, rate control)	Change in cognitive function (MOCA), depression (CES-D), anxiety (GAD-7)
RAAF-3 (NCT04037397)	120	18 months	September 2019	2025	Symptomatic persistent AF	First-line, early RF catheter ablation/PVI (2:1)	First-line AAD	Time to first recurrence of AF/AF/AT >30 s after 3 month blanking period
ABLATE vs. PACE (NCT04906668)	196	36 months	May 2021	2027	Persistent AF, age ≥ 75 years	Cryoballoon PVI	AVN ablation with dual chamber pacemaker	Hospitalization for AF/AF/AT or cardiac decompensation; recurrent AF/AT/AF/AT requiring repeat ablation or cardioversion after blanking period; CRT upgrade due to reduced LVEF $\leq 35\%$ in ablate/pace group
RACE-X (NCT06200311)	604	30 months	July 2024	J2029	AF, Age 65–80 years and atrial cardiomyopathy (LAVi >34 mL/m ²)	AF catheter ablation (PVI)	Medical therapy (1st line rate control; 2nd line pharmacological rhythm management; 3rd line AF ablation)	Composite CV death and CV hospitalization/urgent visit
RACE 9 OBSERVE-AF (NCT04612335)	490	4 weeks	November 2020	2025	Early paroxysmal AF (<36 h)	Early Cardioversion (pharmacological or electrical) within 48 h	Watch and wait, rate control	Sinus rhythm after 4 weeks
EAST ^{high} -AFNET 11 (NCT06324188)	2312	Event-driven	October 2024	2030	AF diagnosed within 2 years, CHA ₂ DS ₂ -VASc ≥ 4	Early PVI	Usual care/optimal medical therapy	Composite of CV complications related to AF (CV death, stroke, heart failure hospitalization); composite of all-cause death and serious complications of AF therapy
EAST STROKE (NCT05293080)	1746	Event-driven	November 2025	2030	Ischaemic stroke within 4 weeks; AF 1st detected ≤ 1 year	Early Rhythm Control (AAD, electrical cardioversion, ablation)	Usual care (primarily rate control drugs)	Time to 1st recurrent stroke, CV death, hospitalization due to worsening HF or ACS.
EMERGE Cryo (NCT05294445)	350	12 months	December 2021	2028	AF (longest duration < 6 month, recent onset ≤ 1 yr), presenting at the ED or outpatient clinic within last 2 weeks due to AF	AF ablation (Cryo PVI)	Usual care	AF/AF/AT (>30 s) through 3–12 months

Continued

Table 2 Continued

Trial (clinicaltrials.gov)	Target size, N	Follow-up	Estimated start	Estimated completion	Population	Intervention	Control	Primary end point(s)
CRAAFT AF (NCT06505798)	1200	2 to 5.5 years	September 2024	2031	HFpEF (LVEF < 50%) and AF	AF catheter ablation	Optimal medical therapy	Time to all cause mortality, urgent CV hospitalization
DAN-Ablate HF (NCT06560047)	1616	12 months	August 2024	2029	HFpEF (LVEF < 50%) and AF within past 1 year, age 18–80 years	AF catheter ablation	Standard therapy	Time to hospitalization for worsening HF or CV death
CABA+HFPEF (NCT05508256)	1548	12–48 months	March 2023	2029	HFpEF or HFmrEF (LVEF > / $\leq$ 40%) and paroxysmal or persistent AF (< 24 months)	Early AF catheter ablation	Usual medical care	Composite of CV death, stroke, unplanned hospitalization for HF or ACS
STABLE-SR IV (NCT06125925)	436	to 36 months	November 2023	2026	HFpEF (LVEF > / $\leq$ 50%), paroxysmal or persistent AF, CHA2DS2-VASc > / $\leq$ 2	RF catheter ablation	Medical therapy	Time to composite endpoint of hospitalization or urgent visit for worsening HF and CV death
CAPHF-AF (NCT06740539)	304	24 months	December 2024	2027	HFpEF, paroxysmal or persistent AF	AF catheter ablation	Medical therapy—HF treatment and rate control	Composite all-cause death or rehospitalization for worsening HF
CryoStopPersAF (NCT05939076)	220	12 months	August 2023	2029	Non-long-standing persistent AF, age 18–75 years, LVEF > 40%	AF ablation (Cryoballoon PVI)	AAD (Dronedaron, flecainide, propafenone or sotalol)	Atrial tachyarrhythmia recurrence > / $\leq$ 6 min on ILR (3–12 months)
AVANT GUARD (NCT06096337)	484	12 to 36 months	December 2023	2028	Symptomatic persistent AF	PFA for isolation of PVs and posterior wall	AAD (Flecainide, Sotalol, Propafenone, Dofetilide, Dronedaron)	Treatment success: freedom from (> / $\leq$ 1 h asymptomatic, 30 s asymptomatic AF/AT/AFL by ILR), electrical cardioversion, ablation, and in ablation arm AAD use at 12 months; composite adverse events
EDearly AF (NCT06322017)	294	2 years	April 2024	2030	Age > / $\leq$ 75 with paroxysmal or persistent AF diagnosed < 12 months	Early PVI	Medical therapy: AAD (flecainide, sotalol, amiodarone) or rate control drugs	Time to CV death, all cause hospitalization, stroke
TAP-CHF phase 1 (NCT04160000)	100	12 months	July 2020	2025	HFpEF (LVEF > 45%), paroxysmal or persistent AF	AF catheter ablation	AAD or rate control	Time to HFH and/or CV mortality
PVI-SHAM-AF (NCT05119231)	260	1 year	November 2021	2026	Symptomatic AF	AF catheter ablation—PVI	Sham PVI	Change in AFEQT sum scores at 6 months

Continued

Table 2 Continued								
Trial (clinicaltrials.gov)	Target size, N	Follow-up	Estimated start	Estimated completion	Population	Intervention	Control	Primary end point(s)
OPTIMAL AFHF	1056	5 years	2025	2032	HFrEF (LVEF < 40%) and AF	PVI	Medical therapy or AVN ablation	Death, stroke, and HFH
BoxX-NoAF NCT06989775	1440	NA	2026	2028	No AF; undergoing cardiac surgery; CHA ₂ DS ₂ -VASc = > 3 and Age = > 65 years or CHA ₂ DS ₂ -VASc = > 2 and Age = > 65 and enlarged left atrium (≥4.5 cm)	Prophylactic PVI ablation using encompass isolator clamp and LAA exclusion using the AtriClip; implant of an implantable cardiac rhythm monitor	No intervention; implant of an implantable cardiac rhythm monitor	Phase 1—Postop AF at 30 days. Phase 2—Clinical AF over long-term

AF burden analyses of rhythm control trials).^{111,118,119} Demonstrating that reducing burden improves clinical endpoints is critical, see *Table 2*. Populations in need of further study

- (1) Patients undergoing screening for AF
- (2) Patients with device-detected AF
- (3) Patients undergoing monitoring for AF following a stroke
- (4) Patients with known AF who are naïve to rhythm control therapy
- (5) Patients on rhythm control therapy with AADs and AF ablation
- (6) Patients with structural heart disease or cardiomyopathy

It is possible that the outcome-relevant AF burden threshold may differ across these populations and in all these settings the independent role of an underlying atrial cardiomyopathy, of variable severity, should be defined.¹³¹

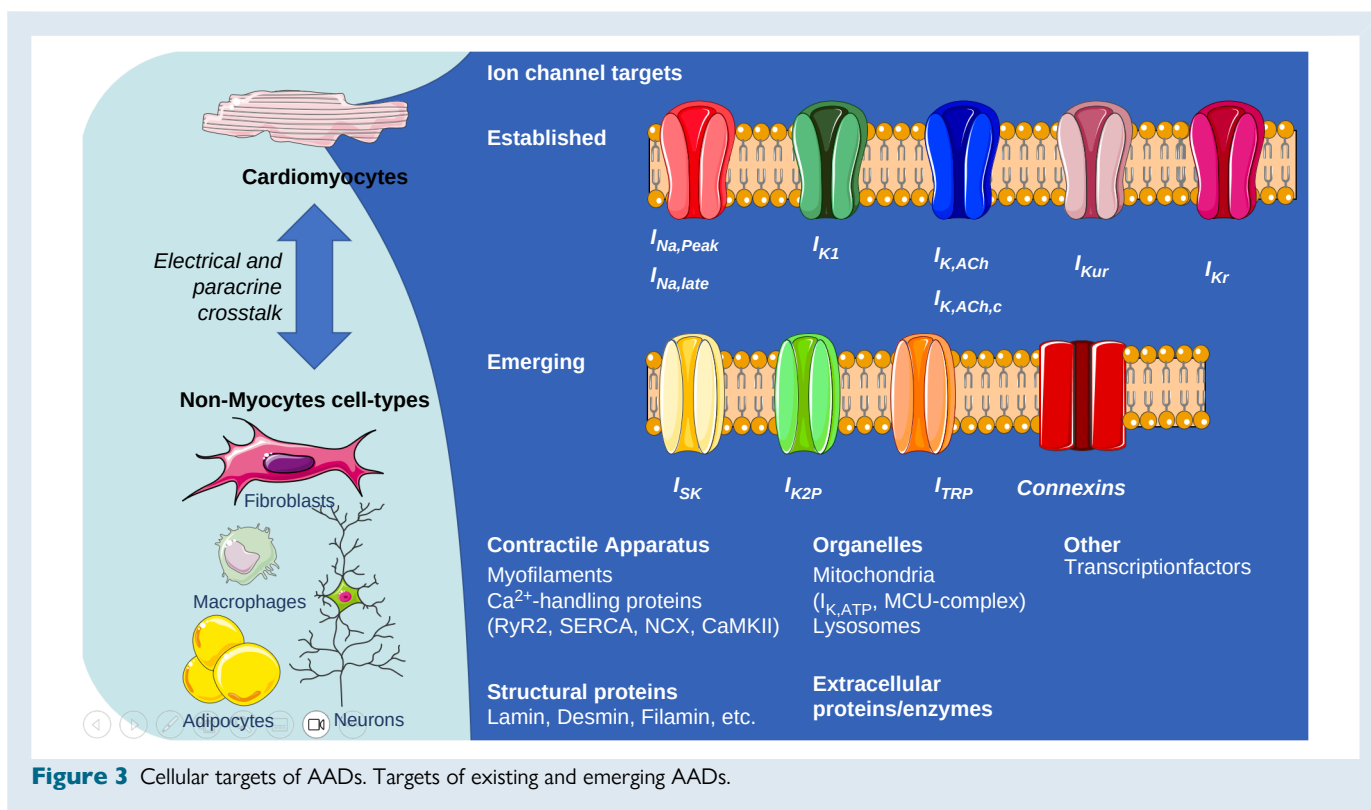
Until then, there is good evidence that a very low AF burden, possibly below 1–3%,⁶⁰ is associated with a low risk of stroke. Pooling existing data sets combining AF burden information and outcomes could go a long way to define meaningful AF burden thresholds or ranges. While AF burden is best assessed with an invasive continuous cardiac monitor device (ICM or CIED), serial non-invasive monitors of 7- to 14-day duration applied every 3–6 months over a period of 12 months for total monitoring duration of 21–28 days provides a relatively accurate assessment of AF burden.¹³³ Standards of AF burden quantification across devices and manufacturers are needed to advance research in the field. The concept of reducing AF burden was already explored in trials such as ANTIPAF,¹³⁴ but has gained renewed attention following recent outcome trials that demonstrate that rhythm control reduces heart failure, stroke, and cardiovascular mortality.^{3,4,135–138} These findings renewed interest in developing AADs and better AF ablation technologies. Ongoing research will further quantify the effect of these therapies on AF burden.

New anti-arrhythmic drugs and expanded use of current drugs

Catheter ablation has become an increasingly utilized rhythm control strategy; yet, it remains inaccessible to the vast majority of patients with AF. Data from 27 European countries show that ~172 000 AF ablation procedures are performed annually,¹³⁹ a modest number when compared to the more than 11 million individuals living with AF in Europe. Reflecting the heterogeneity of the disease, not all patients are ideal candidates for invasive procedures. Furthermore, access to specialized care is often limited. Even after undergoing ablation, many patients require long-term therapy with AADs, underscoring the continuing importance of pharmacological rhythm control.¹⁴⁰ The increasing focus on early rhythm intervention and AF burden as a therapeutic target further supports the use of AADs preceding, enhancing or replacing AF ablation therapy.³

Continued use of existing AADs remains essential in clinical care,¹⁴⁰ while current work aims to develop safer, more targeted anti-arrhythmic therapies grounded in mechanistic insights. Ongoing research aim to identify novel molecular and cellular targets and refine pathways to develop agents with improved efficacy and safety profiles. Important unmet needs for AADs remain in patients with AF and heart failure, those with recurrent AF despite current AAD therapy, and in patients intolerant to amiodarone.

The continued use of AADs is supported by their well-established efficacy and acceptable safety in light of the unmet need.^{140–142} Drugs like amiodarone, dronedarone, flecainide, and propafenone, introduced decades ago, have demonstrated good efficacy and acceptable safety when used in suitable patients,^{1,142,143} often without specific approval as AADs for AF.¹⁴⁴ Amiodarone, for example, was initially approved as an anti-anginal drug, and flecainide and propafenone were approved for the treatment of other arrhythmias.¹⁴⁵ Clinical guidelines, mainly based on post-approval trials and observational data, integrate



these drugs into treatment algorithms in patients with AF.^{140,146} The safety concerns that arose after the unexpected outcomes of the CAST trials still shape concerns regarding approval of AADs, illustrated by the amount of data that was required to approve dronedarone.^{4,144,147,148} Despite long-standing concerns about pulmonary toxicity, recent nationwide data suggest that long-term low-dose amiodarone is associated with minimal risk of interstitial lung disease and no increase in mortality, potentially supporting its broader use in rhythm control for AF.¹⁴⁹ AADs also retain their effectiveness after AF ablation and are commonly used after the procedure to reduce recurrences.^{150,151} Importantly, the beneficial effects of rhythm control on clinical outcomes can be observed within the first few weeks after therapy initiation¹⁵² and justifies a small risk of severe side effects, changing the balance between safety and efficacy requirements for AADs.³

Characterizing the limitations and side effects of existing drugs, including pro-arrhythmia and extracardiac toxicity, may help define key targets for improvement in future therapies. A recent example is SGLT2 inhibitors, which have been shown to reduce incident AF by 10–20%.^{153,154} Whether these anti-arrhythmic effects persist in patients with established AF, such as after cardioversion or ablation, remains uncertain. Similarly, it is unclear whether the observed benefits are driven by metabolic effects or by interactions with cardiac ion channels.^{40,155,156}

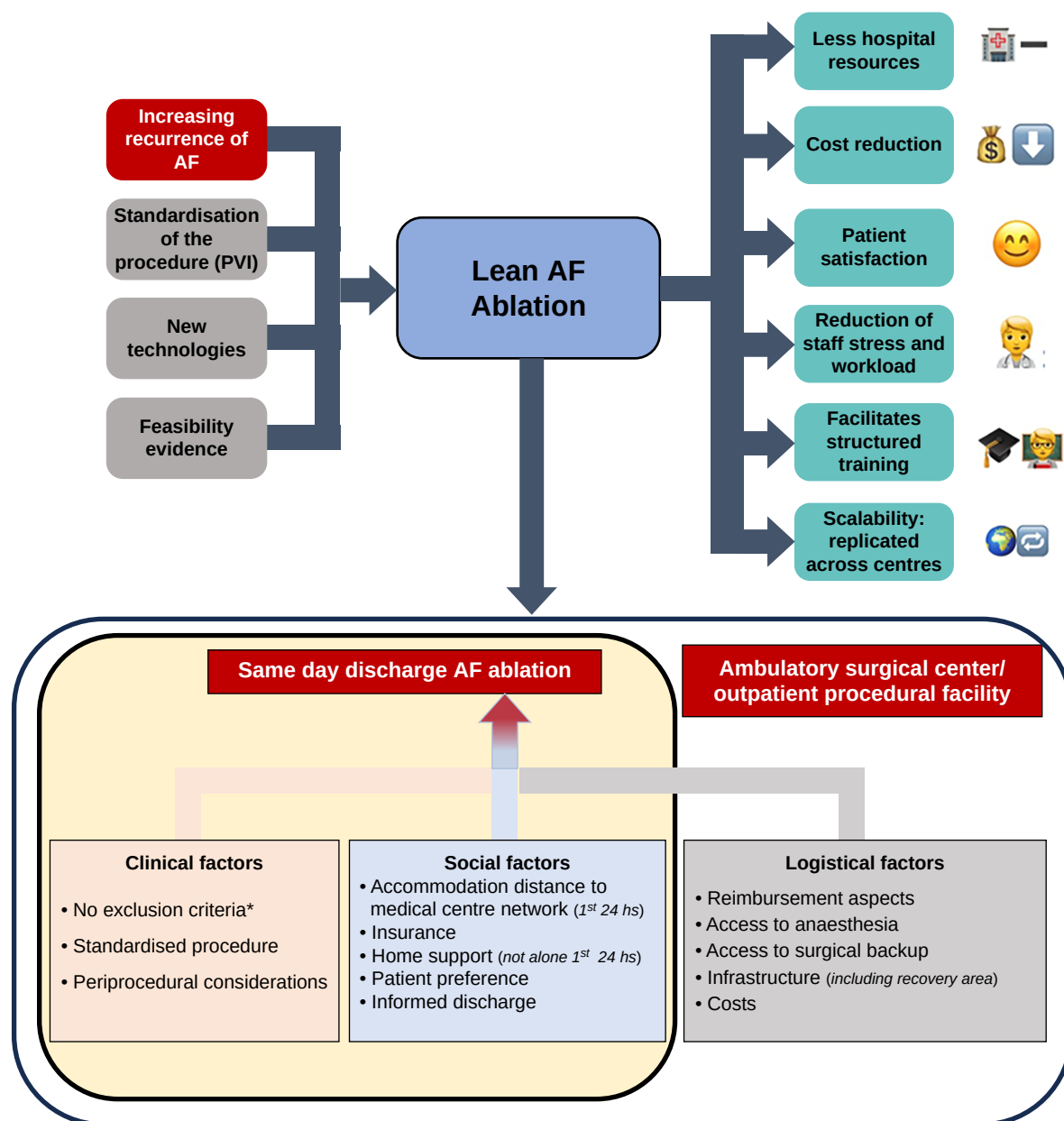
Promising emerging agents include the SK-channel blocker AP30663, which has completed phase 2 for acute cardioversion,¹⁵⁷ the SK-channel blocker AP31969 for SR maintenance, currently in early clinical development (NCT06066099), the TASK-1 blocker doxapram, currently in phase 2,¹⁵⁸ the multi-channel blockers budiardone¹⁵⁹ and antazoline,¹⁶⁰ TRP channel blockers,¹⁶¹ connexin activators,^{162,163} or the histone deacetylase 6 inhibitor PKN605 (NCT07217067).

Further therapeutic perspectives have emerged from genome-wide association studies, highlighting the importance of atrial resting membrane potential and atrial cardiomyocyte metabolism as potential

targets for rhythm control therapy.^{40,57,164,165} AI tools like AlphaFold, Rosetta, and others are already accelerating the discovery and structural characterization of lead compounds. Going forward, the availability of new experimental approaches like induced pluripotent stem cell-derived cardiomyocytes, digital twins, crystallography, and AI-driven structural biology may accelerate the pre-clinical characterization of discovery of new potential anti-fibrillatory targets in the atrial cardiomyocytes such as calcium handling proteins (RyR2, SERCA, and NCX), contractile proteins (titin, myosin, actin, and tropomyosin),¹⁶⁶ or structural proteins (lamin, desmin, and filamin). Similar tools may be utilized to explore potential novel anti-AF targets in non-cardiomyocytes like atrial fibroblasts, macrophages, adipocytes, neurons, and ganglionated plexus.^{167,168} These processes already led to several new AADs that are currently in clinical development with further compounds in pre-clinical and early clinical development, Figure 3.

The availability of non-invasive and invasive long-term rhythm monitors simplifies assessment of efficacy (AF burden reduction) and safety (pro-arrhythmic) in clinical trials.^{127,169} This can accelerate early clinical development and may provide opportunities for approval of a drug paired with a rhythm monitor, e.g. to enhance safety.^{170,171} To meet the medical need, clinical trials for AADs should be streamlined by removing unnecessary bureaucratic hurdles, while preserving the high standards required for regulatory approval. There is an emerging consensus that the historic outcome of time to first recurrent AF is not meaningful clinically. AF burden may replace this, enabling quantification of effectiveness. More data are needed to substantiate this concept.

In conclusion, better use of current AADs and new AADs are needed to address the unmet medical need in pharmacological rhythm control therapy. As science progresses towards more targeted approaches, the practical, accessible, and evidence-based use of current AADs ensures that care for patients with AF continues to evolve in both effectiveness and inclusivity, independent of the patient's sex.¹⁷²



*Exclusión criteria: BMI ≥ 40 , severe lung disorders, HFrEF, severe critical organ disease, previous ablation adverse event

Figure 4 Patient-centred strategies to deliver AF ablation. Top panel. Requirements for the development of lean AF ablation strategies, and potential benefits of lean AF ablations. Lower panel. Clinical and social factors needed for same-day discharge of AF ablation patients.

AF ablation: optimizing procedural efficiency through same-day procedures and same-day discharge

Efficient, standardized, and patient-centred models to deliver AF ablation have been instrumental in providing this therapy for many patients, Figure 4 (upper panel). A core feature of this model is the shortening of hospital stay through same-day procedures (SDP), where both the intervention and discharge occur on the same day with or without discharge on the same day, and/or same-day discharge (SDD), in which

patients are discharged on the day of their procedure.^{173–176} SDD for AF ablation is the norm in ambulatory surgical centres that offer AF ablation. Ambulatory surgical centres are independent outpatient facilities (increasingly common in the US); those that perform AF ablation require additional infrastructure to manage complications and favour treating low risk patients. SDP and SDD can occur embedded within hospitals, thus offering broader accessibility and operational continuity.¹⁷⁷ When implemented with careful selection and planning, SDP and SDD can reduce costs, improve patient satisfaction, and alleviate staff workload, while maintaining safety and outcomes.^{173,177–180}

Careful patient selection is central to the safe implementation of SDP and SDD protocols, Figure 4 (lower panel). Social criteria include the

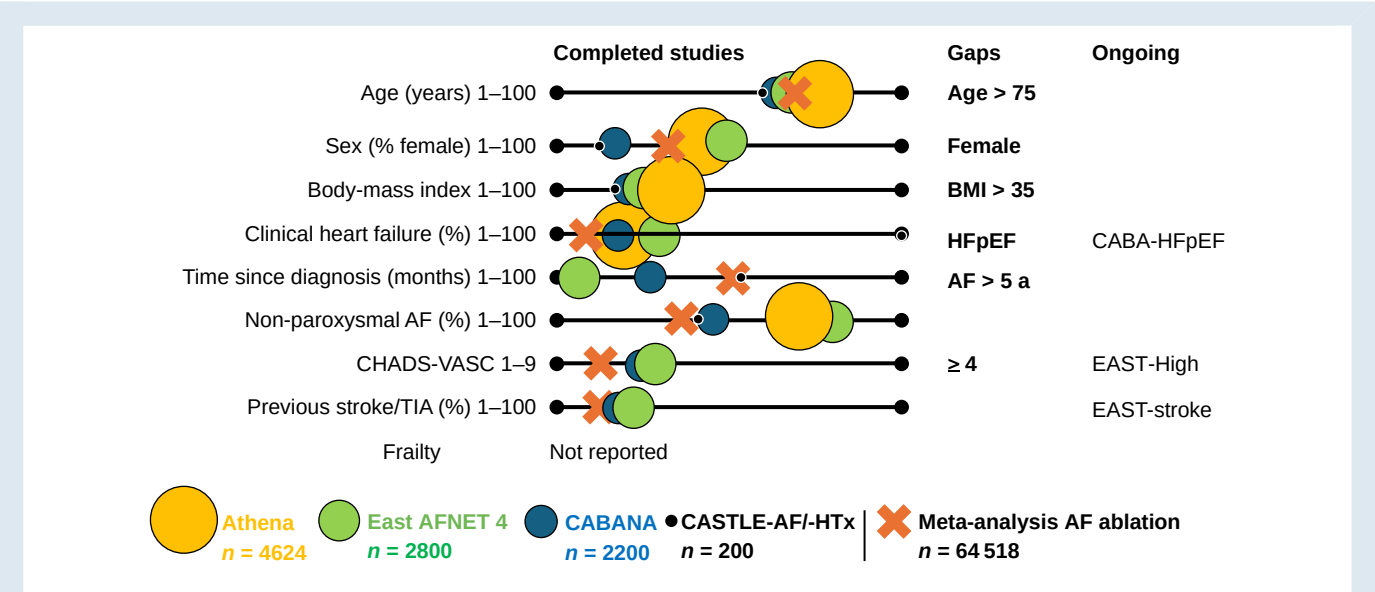


Figure 5 Demographic features of published rhythm control outcome studies. Recent clinical trials showing that rhythm control therapy using dronedarone (ATHENA), early rhythm control (EAST-AFNET 4), or AF ablation (CASTLE-HTx and CASTLE-AF) reduces cardiovascular events including cardiovascular death, stroke, and unplanned hospital admissions. Notable gaps in knowledge include female patients, patients with AF duration more than 5 years, elderly, frail patients and patients with multiple comorbidities.

presence of a caregiver for at least 24 h after discharge from hospital and access to emergency care within acceptable distance of their home. Use of ultrasound-guided venous access,¹⁸¹ venous closure devices,^{178,182} or vascular sutures and refined workflows have extended the scope of eligibility for SDD by reducing vascular complications and time to mobilization.¹⁸³ Clinically, patients with more complex comorbidity phenotypes, including elderly frail patients⁷³ but also patients with high or very low BMI, heart failure with reduced ejection fraction, advanced COPD, or history of severe procedural complications often require in-hospital care before and after an AF ablation.^{176,184} Reimbursement practices are quite heterogeneous across different countries, but should be updated, by offering a value to SDD.¹⁸⁵

Modern AF care begins well before the ablation, *Figure 4*. On the waiting list, patients should receive education on symptom management, lifestyle and risk factor modification, and procedural expectations. This engagement is critical to empower patients and reduce peri-procedural anxiety. Moreover, the implementation of structured decision-making tools and algorithms may further streamline eligibility for early rhythm-control strategies and SDD,¹⁸⁶ which may have prognostic implications.³

A standardized procedural workflow is essential to support SDD implementation. Single-shot techniques such as cryoballoon and pulsed field ablation (PFA), enable consistent pulmonary vein isolation with short procedure times and reproducible results across operators, albeit no formal comparison with radiofrequency ablation in this field has been done.^{187–190} Major complications are rare and mostly occur within the first few hours post-procedure.^{184,191}

The post-procedure phase in an SDD workflow requires focused observation protocols. Hemodynamic stability, groin site integrity, rhythm assessment, and pain control must all meet pre-defined discharge criteria.^{176,179} Most complications occur within the first 6 h, supporting early discharge for low-risk patients.^{182–184,186} At discharge, patients should receive clear instructions on warning signs and when to seek care. Follow-up should include timely clinical contact, medication review, and rhythm monitoring planning.¹⁴⁶

Implementing an SDD-based AF ablation model requires specialized training and infrastructure. Physicians must be EP-certified and trained in lean procedural management and complication handling with already passed learning curve.^{192,193} Allied professionals should be skilled in the full peri-procedural workflow.¹⁹² Institutional and facility infrastructure should include a standard EP lab, recovery area with rhythm and hemodynamic monitoring, and emergency escalation protocols.¹⁹³ EHRA surveys support team-based protocols and clear pathways to ensure quality across centres.^{22,176}

Modern quality indicators for AF ablation include rhythm outcomes, AF burden after ablation, complication rates, 30-day readmission, patient satisfaction, and cost-effectiveness. Health economic evaluations show that well-implemented SDP and SDD maintain safety while reducing cost.¹⁸⁰ Real-world data from high-volume registries, including EU-PORIA, the PROFA trial^{184,187} and EHRA meta-analysis¹⁷⁶ support the safety and efficacy of such protocols. As new technologies evolve, these indicators will be critical to benchmarking and continuous improvement.²

Ongoing trials on rhythm control

Recent outcome trials testing rhythm control interventions (dronedarone, early rhythm control, and AF ablation) show a welcome shift away from evaluating new therapies in relatively young, healthy patients with AF towards studying patients within the typical age groups and with typical comorbidities of general AF patients, *Figure 5*.

The signals that rhythm control therapy can reduce cardiovascular events are clear but additional evidence to define the role of rhythm control for every patient with AF is still needed. Fortunately, several trials are ongoing, *Figure 5*. Additional trials not listed here can be expected to assess newer AADs and ablation techniques, clarify how AF burden reduction impacts outcomes, and extend evidence to under-studied populations.

Ongoing rhythm control trials testing effects on cardiovascular events

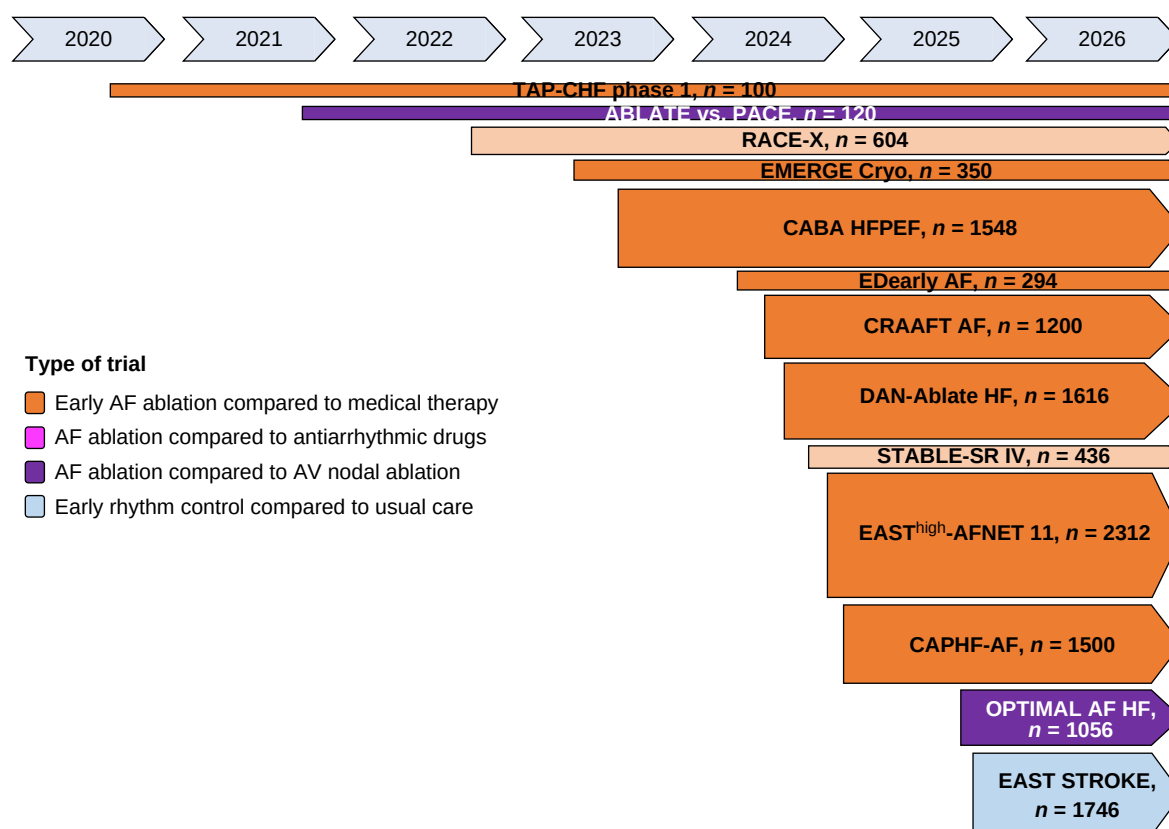


Figure 6 Ongoing clinical trials on rhythm control therapy. This timeline illustrates ongoing randomized clinical trials investigating the effect of different rhythm control therapies on cardiovascular outcomes. Trials are categorized by type of intervention and comparator. Notably, several large-scale studies address key evidence gaps in patients with heart failure, cognitive decline, and post-ablation therapy.

Ongoing and desirable trials

Trials evaluating rhythm control therapy innovations have typically studied relatively young, predominantly male patients with AF and few comorbidities. Even the published rhythm control trials that were designed to detect effects on cardiovascular events enrolled patients with relatively recent-onset AF and moderate comorbidity (average age 65–71 years, CHA₂DS₂-VASc 3; Figure 5). Only a few patients with long-standing persistent AF, marked atrial enlargement, or severe obesity were enrolled. A recent sub-analysis of EAST-AFNET 4 is one of the few data sets providing information on the effectiveness and safety of rhythm control in obese patients.¹⁹⁴ More detailed anthropometric measurements and quantification of epicardial fat could help better understand the management of patients with obesity, and careful selection of patients with HFpEF using validated criteria is essential. While some studies show benefit of AF ablation in patients with AF and advanced HFpEF, further data are needed for HFpEF.^{137,138,195} Critically, very elderly and frail individuals have been excluded from most earlier rhythm control trials.^{196,197} Multi-morbidity is usually defined as the coexistence of two or more health conditions¹⁹⁸ and can be quantified using tools like the Charlson comorbidity index.¹⁹⁹ Frailty is a loss of functionality usually described by the physical phenotype (measured by walking speed and grip strength) and the cumulative deficit model (measured with tools such as the Edmonton Frail scale²⁰⁰). Testing rhythm control in frail and multi-morbid patients seems warranted. Several less common but clinically relevant

conditions—such as advanced lung disease, pulmonary hypertension, valvular heart disease, cancer, hypertrophic cardiomyopathy, and amyloidosis—may also warrant dedicated outcome trials. Additional gaps remain with respect to the inclusion of racial and ethnic minorities, individuals with low health literacy, and those from underserved backgrounds.

Outcomes

Until AF burden is sufficiently evaluated, outcome trials remain relevant to define the clinical use of rhythm control therapy. Although stroke remains important heart failure is a relevant cause of death and hospitalization in patients with AF. All-cause cardiovascular hospitalization captures admissions for AF or complications of its therapy. Cardiovascular mortality is generally preferred to all-cause mortality to measure outcomes of cardiovascular interventions. Given the advanced age of some patient groups, adjustment for competing hazards is advisable. In addition to these ‘harder’ clinical outcomes, patient-reported outcomes, quality of life, and economic data will be essential for understanding the impact of therapy and for its implementation.²⁰¹ Finally, AF rhythm control research would benefit from standardized methods to measure and report AF burden and its relationship to major clinical outcomes.¹⁰⁵ Outcome assessments should also account for the lack of blinding in ablation trials, e.g. by blind adjudication of outcome events.

Table 3 Unanswered key questions and knowledge gaps in atrial fibrillation**Key Questions and Knowledge Gaps**

Comorbidities

- What is the optimal mode of quantification of risk factors and comorbidities over time?
- How can the identification of novel biomarkers—beyond established ones—help characterize clinically complex AF phenotypes, and how do dynamic changes in these biomarkers relate to outcomes and exposome-related influences?
- How can we individualize and effectively manage dynamic risk factors over time

Cognitive function

- What is the best cognitive test for AF patients in both clinical and research settings? When and how often should cognitive function be assessed in individuals with AF? Should AF patients be screened for cognitive decline?
- Is there a quantitative relationship between AF burden and cognitive decline? How much reduction in AF burden would have an impact on slowing cognitive decline?
- What is the role of AF ablation or AAD therapy in preventing cognitive decline?
- What is the role of biomarkers?
- What is the role of brain MRI imaging in screening and follow-up?

AF burden

- What amount of AF burden reduction is needed to improve outcomes?
- What is the relationship between method of AF detection and AF burden?
- What duration of rhythm monitoring is required to reliably estimate AF burden using ECG patches or wearable cardiac devices in populations with different AF burdens and episode durations and frequencies?
- Can ECG markers or blood biomarkers (like NT-proBNP, BMP10, Angiotensin2, and FGF23) be used as proxies for AF burden and for burden-related outcomes.
- Does the threshold or threshold range of AF Burden differ for different clinical outcomes
 - (a) Stroke
 - (b) Heart failure hospitalization
 - (c) Cardiovascular death
 - (d) Cardiac (left ventricular) function
 - (e) Cognitive function
 - (f) Quality of life
- Does the context of AF detection affect the relation between AF burden and outcomes? (Screening-detected AF, device-detected AF, AF detection post-stroke, treatment naïve, ECG-diagnosed AF, and patients already on rhythm control therapy)

AF burden reduction

Anti-arrhythmic drugs

- Which clinical and biological phenotypes best predict response to specific anti-arrhythmic drug therapies?
- How can AF burden be standardized to be used as a primary outcome measure for evaluating anti-arrhythmic drugs?
- Which patient groups have the greatest unmet medical need for new anti-arrhythmic drugs?
- Is the outcome-reducing effect of drug-based early rhythm control linked to AF burden reduction?
- Can dosing strategies or combination approaches improve the risk–benefit profiles of anti-arrhythmic drugs?
- Which novel molecular targets—identified through omics, AI, or advanced *in vitro/in vivo* models—hold the greatest promise for developing safer, mechanism-based anti-arrhythmic therapies, and how can early translational tools accelerate their clinical development?

AF Ablation

- Which patient populations derive the greatest long-term benefit from catheter ablation, and how can we refine patient selection across diverse clinical phenotypes—including elderly, frail, or multi-morbid individuals?
- What are the barriers—clinical, geographic, systemic—to equitable access to catheter ablation, and how can healthcare systems ensure broader availability without compromising quality?
- How should AF burden, quality of life, and cardiovascular outcomes be integrated into the assessment of catheter ablation success, both in clinical practice and research?

Outcome trials on rhythm control

- What are the benefits of specific rhythm control strategies—such as anti-arrhythmic drug therapy, catheter ablation—in distinct patient populations, including the very elderly (>75 years), women, individuals with severe obesity (BMI > 35 kg/m²), valvular disease, advanced pulmonary and kidney disease, and those with multiple comorbidities (high CHADSVA score)?

Continued

Table 3 Continued**Key Questions and Knowledge Gaps**

- Do patients with rare and complex comorbidities such as hypertrophic cardiomyopathy and other inherited conditions, amyloidosis, pulmonary hypertension, cancer, or multiple coexisting conditions require specific rhythm control plans?
- How effective are rhythm control strategies in patients with heart failure with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF)?
- How effective and safe is rhythm control in elderly and frail patients with multiple comorbidities?
- What is the role of device-based rate control ('pace and ablate') for outcome reduction?

In the coming 5 years, multiple large AF outcome trials will address key evidence gaps, *Figure 6* and *Table 2*. These include studies in patients with heart failure (with and without reduced EF), older adults, individuals with a high comorbidity burden, those with newly diagnosed AF, and trials including pace-and-ablate as a control strategy. At least one large, randomized trial of a new AAD is also expected. Together, these studies will provide detailed, high-quality data to help guide rhythm control strategies in a broader and more representative group of patients with AF. Additional outcome trials could target key under-represented populations: frail patients, patients with severe obesity (BMI >35 kg/m²), patients with valvular heart disease, and those with long-standing persistent AF. Such trials may be suitable for combined interventions, e.g. in a factorial design.

Conclusion

AF therapy remains a large unmet global medical need. The growing role of rhythm control as a treatment with the potential to modify the course of disease by reducing AF burden and to reduce cardiovascular events creates a new unmet medical need for simple, safe, and effective rhythm control therapy. While catheter ablation continues to expand, most patients with AF will rely on pharmacological therapies, either as a primary or adjunctive approach. Optimizing the use of existing AADs, through better patient selection and tailored treatment strategies, remains a clinical imperative. At the same time, new AADs are being developed, based on mechanistic insights, advanced modelling, and AI-assisted compound screening, and more efficient ablation methods are emerging at a rapid pace. These innovations offer opportunities to develop safer, more targeted rhythm control therapies.

Incorporating meaningful outcomes such as AF burden and patient-reported outcomes can strengthen the design and relevance of future trials.

To advance the field, action on the key research priorities and knowledge gaps outlined in *Table 3* is needed, necessitating the need for translational, clinical, and regulatory collaboration. Accelerating both innovation and implementation will be essential to deliver equitable, effective rhythm control for all patients with AF.

Together, these efforts offer a path towards more personalized, effective, and accessible rhythm control—bridging today's practical needs with tomorrow's therapeutic innovation.

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Data availability

This review article does not contain original data.

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