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CLINICAL RESEARCH

Longer and better lives for patients with atrial fibrillation: the 9th AFNET/EHRA consensus conference

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Aims

Recent trial data demonstrate beneficial effects of active rhythm management in patients with atrial fibrillation (AF) and support the concept that a low arrhythmia burden is associated with a low risk of AF-related complications. The aim of this document is to summarize the key outcomes of the 9th AFNET/EHRA Consensus Conference of the Atrial Fibrillation NETwork (AFNET) and the European Heart Rhythm Association (EHRA).

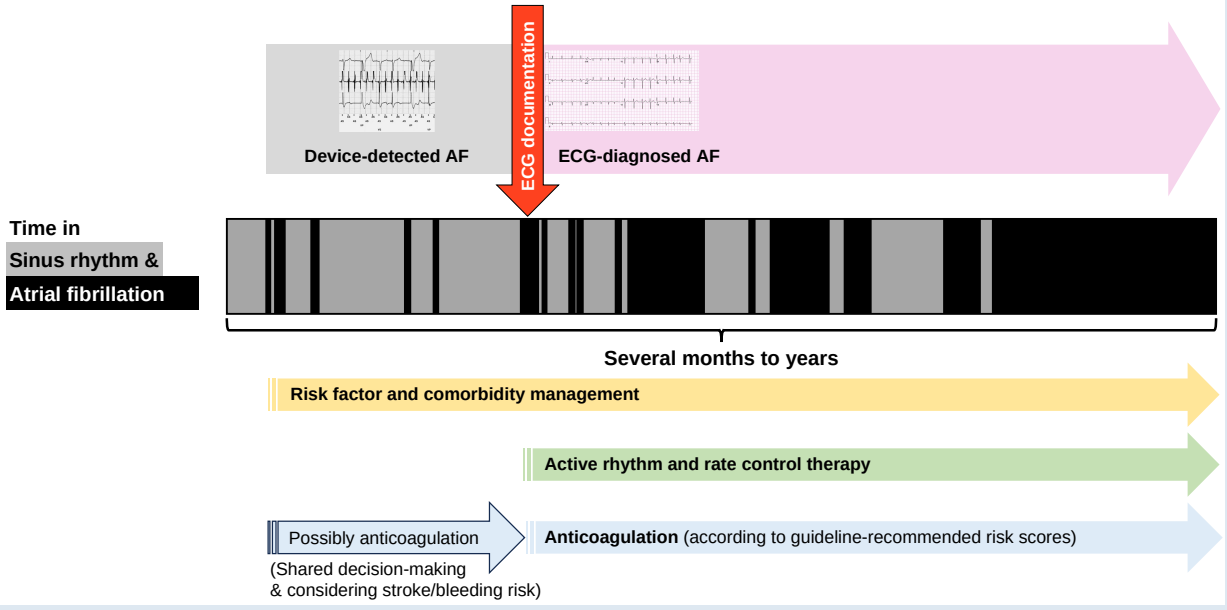
Methods and results

Eighty-three international experts met in Münster for 2 days in September 2023. Key findings are as follows: (i) Active rhythm management should be part of the default initial treatment for all suitable patients with AF. (ii) Patients with device-detected AF have a low burden of AF and a low risk of stroke. Anticoagulation prevents some strokes and also increases major but non-lethal bleeding. (iii) More research is needed to improve stroke risk prediction in patients with AF, especially in those with a low AF burden. Biomolecules, genetics, and imaging can support this. (iv) The presence of AF should trigger systematic workup and comprehensive treatment of concomitant cardiovascular conditions. (v) Machine learning algorithms have been used to improve detection or likely development of AF. Cooperation between clinicians and data scientists is needed to leverage the potential of data science applications for patients with AF.

Conclusions

Patients with AF and a low arrhythmia burden have a lower risk of stroke and other cardiovascular events than those with a high arrhythmia burden. Combining active rhythm control, anticoagulation, rate control, and therapy of concomitant cardiovascular conditions can improve the lives of patients with AF.

Graphical Abstract



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What's new?

Recent evidence suggests important improvements to the management of patients with one atrial fibrillation (AF).

(1) Active rhythm management should be part of the default initial treatment for patients with AF.
(2) Patients with device-detected AF have a low burden of AF and a low risk of stroke. Anticoagulation prevents some strokes and also increases major but non-lethal bleeding.
(3) More research is needed to improve stroke risk prediction in patients with AF, especially in those with a low AF burden. Biomolecules, genetics, and imaging can support this.

In summary, combining active rhythm control, anticoagulation, rate control, and therapy of concomitant cardiovascular conditions can improve the lives of patients with AF.

Introduction

The year 2023 is the first year since 2011 in which three hot line presentations of clinical trials in patients with atrial fibrillation (AF) were presented at the annual congress of the European Society of Cardiology (ESC) and simultaneously published in the *New England Journal of Medicine* (CASTLE-HTx, ADVENT, and NOAH-AFNET 6).[1–3] In November 2023, ARTESiA was presented and published.[4] Unlike in 2011, when the focus was on anticoagulation,[5–7] two of the trials presented at ESC evaluated AF ablation,[2,3] the most effective method for active rhythm management. The two other large trials, although primarily assessing the efficacy and safety of anticoagulation in patients with device-detected AF, found a low stroke risk in a population with risk factors and a very low AF burden, highlighting the possible role of arrhythmia burden for stroke risk.[1,4] This shift from evaluating the effect of anticoagulation towards evaluating active rhythm control management in clinical trials highlights the recent growth in this clinical area (*Figure 1*). From 11–13 September 2023, experts from academia and industry met for the 9th AFNET/EHRA consensus conference of the Atrial Fibrillation NETwork (AFNET) and the European Heart Rhythm Association (EHRA) to discuss these recent findings. To acknowledge the 20th anniversary of AFNET, the 9th AFNET/EHRA consensus conference was held in Münster, Germany, the home of AFNET.

Methods

The 9th AFNET/EHRA consensus conference brought together 83 international interdisciplinary experts including arrhythmia and heart failure specialists, pharmacologists, basic and translational scientists, general practitioners, neurologists, nurse practitioners, epidemiologists, clinical trialists, and health economists in Münster, Germany on 11–13 September 2023. The conference started with four sessions of expert talks summarizing recent developments in the field. Thereafter, the participants split into six breakout groups to discuss specific topics. Each break-out group summarized their thoughts and statements on posters and presented them to the plenary. These were discussed and adapted in poster walk-through sessions. The consensus summarized here integrates this iterative, intensive dialogue in each group and in the plenum, using formal and informal feedback. Refinement of the consensus and integration of new data[4,8,9] was done during the writing process. Details of the methodology have been described before.[10–13]

Active rhythm management: from symptom control to outcome reduction

Atrial fibrillation guidelines recommend active rhythm control to improve symptoms in patients with AF. Since the release of the 2020 ESC AF guidelines, new data indicate that patients with recent onset AF and stroke risk factors[14] and those with heart failure with reduced ejection fraction have better cardiovascular outcomes on rhythm control therapy.[3,15,16] This evidence supports the use of early rhythm control irrespective of symptoms. The trials do not show safety signals associated with rhythm control. The safety of modern rhythm control is confirmed in analyses of large electronic health records.[17–19] Furthermore, the risk of stroke is low in patients with risk factors and a very low burden of device-detected AF (see 'Atrial fibrillation burden in patients with electrocardiogram-diagnosed atrial fibrillation and in patients with device-detected atrial fibrillation' section). This suggests that a reduction in arrhythmia burden could explain the outcome-reducing effect of rhythm control therapy. The concept of AF burden reduction as a component of treating patients with AF has been highlighted in the recent 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of AF.[20] Taking this in context with earlier trials such as ATHENA,[21,22] the group sees a paradigm shift that moves rhythm control *from a symptom-improving 'lifestyle therapy' to an outcome-reducing treatment to reduce stroke, heart failure, and, to a lesser extent, acute coronary syndrome and cardiovascular death.*

Identification of patients suitable for rhythm control

Currently, only a small minority of patients with AF are treated with rhythm control therapy. Based on the outcome-reducing effects of early rhythm control and AF ablation, patients with AF should, by default, undergo at least one attempt of active rhythm control (*Figure 2*). This may include a 'diagnostic cardioversion' to unmask AF-related symptoms and arrhythmia-induced cardiomyopathy. Left ventricular dysfunction should probably encourage rhythm control.[3,15,16,23] Early rhythm control reduced outcomes in patients with heart failure.[23] Atrial fibrillation ablation reduced cardiovascular events compared with medical therapy in two randomized trials, CASTLE-AF and CASTLE-HTx,[3,15] and in a pre-specified subanalysis of the CABANA trial.[24] A few patients, who experience a good symptom control by rate control alone and in whom preventing cardiovascular events is no longer relevant (for example due to limited life expectancy or advanced age), may opt to not receive rhythm control therapy.

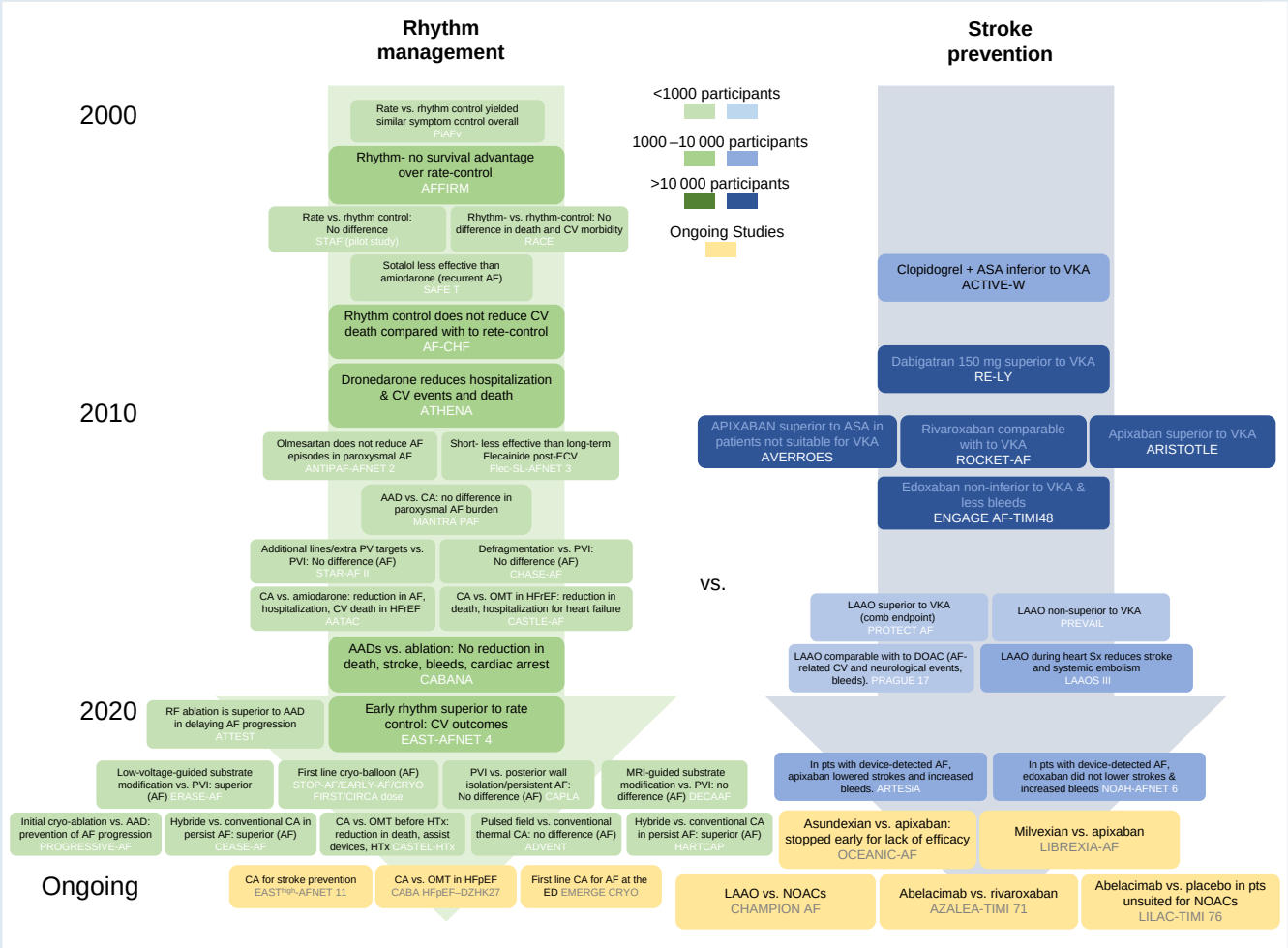

Figure 1 Timeline of landmark trials in atrial fibrillation management on active rhythm management (left) and stroke prevention (right) from 2000 until today. The studies are colour-coded based on their size (from light to dark: <1000, 1000–10 000, and >10 000 participants), and ongoing studies are shown in orange. AAD, antiarrhythmic drugs; AF, atrial fibrillation; CA, catheter ablation; CV, cardiovascular; ECV, electrical cardioversion; ED, emergency department; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; Htx, heart transplantation; LAAO, left atrial appendage occlusion; OMT, optimal medical treatment; NOACs, novel oral anticoagulant drugs; PVI, pulmonary vein isolation; VKA, vitamin K antagonist.

Role of atrial fibrillation ablation for delivering early rhythm control

The outcome-reducing effect of early rhythm control was achieved using antiarrhythmic drugs in most patients.[25] Attaining sinus rhythm was the main mediator of outcome reduction in EAST-AFNET 4.[26] The EAST-AFNET 4 trial also showed that early and systematic rhythm control is effective across AF patterns, including paroxysmal AF, persistent AF, and first-diagnosed AF.[27] Antiarrhythmic drugs remain a key component of rhythm control therapy. Atrial fibrillation ablation reduced symptoms,[28] psychological distress,[29] and arrhythmia burden[30] more than antiarrhythmic drug therapy. Ongoing and planned trials are evaluating whether AF ablation can also reduce cardiovascular events [CABA-HFPEF DZHK27 trial (NCT05508256), EAST^{high}-AFNET 11, and others].

Improving atrial fibrillation ablation

Pulmonary vein isolation (PVI) remains the main target for AF ablation. The STAR-AF II,[31] CAPLA,[32] and DECAAF II[33] studies showed that empiric placement of additional ablation lines or magnetic resonance–guided ablation of fibrotic areas does not improve AF rhythm outcome after AF ablation compared with PVI alone. Several smaller recent trials comparing additional AF ablation targets to PVI only, including ERASE-AF,[34] showed a mix of neutral outcomes and improved prevention of recurrent AF. Additional studies, such as COAST AF (NCT03347227) and STAR-AF III (NCT04428944), will further evaluate additional ablation strategies on top of PVI. Recent randomized trials evaluating hybrid AF ablation combining surgical and endocardial ablation approaches, including CEASE-AF[35] (71.6% vs. 39.2%) and HARTCAP[36] (89% vs. 41%), showed good sinus rhythm maintenance without increased procedural complications in patients with persistent AF who have more recurrences of AF after PVI.[37,38]

Pulsed field ablation (PFA), a non-thermal energy source, conceptually targets cardiomyocytes and may spare other cell types. This conceptual advantage does not translate into better rhythm control in the ADVENT trial.[2] So far, there are very few reports of oesophageal complications or phrenic nerve injuries persisting past hospital discharge, comparable with cryo-balloon-based PVI,[39] and major

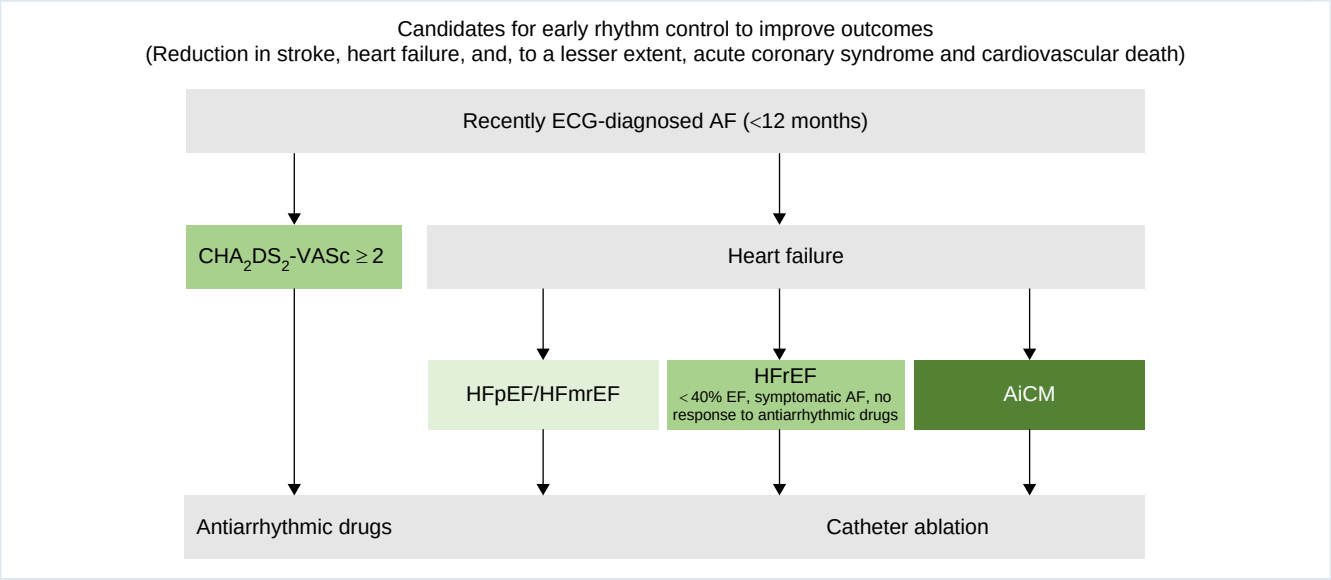

Figure 2 Candidates for early rhythm control to improve outcome. Colours represent the quality and availability of data (from dark for best quality and availability of data to light for the worst quality and availability of data). AF, atrial fibrillation; AiCM, arrhythmia induced cardiomyopathy; HFrEF, heart failure with reduced ejection fraction; HFpEF/HFmrEF, heart failure with preserved or mid-range ejection fraction; RF, risk factors.

complications (pericardial tamponade, stroke, and stroke resulting in death) appear low at 1.6%.[40] More data are collected to define the efficacy and safety of PFA as an energy source for AF ablation.

New antiarrhythmic drugs

Despite the advances in ablation therapy, there remains an unmet need for effective and safe antiarrhythmic drugs. Such compounds will need to demonstrate improvements compared with existing drugs that show good efficacy and safety when used in appropriate patients.[14] The development of antiarrhythmic agents has declined over the last decades,[41] but several promising compounds targeting ion channels are currently in clinical development (*Table 1*). Small conductance Ca^{2+}-activated K^+ (SK) channels are up-regulated in patients with AF.[42] In a Phase 2 proof-of-concept study, a relatively selective SK-channel blocker successfully met efficacy and safety endpoints for pharmacological cardioversion of patients with recent-onset AF.[43] A Phase 1 study for a second-generation oral lead compound (AP31969) for sinus rhythm maintenance is leading to the planning of a Phase 2 study in patients with implantable loop recorders. HSY244 is a novel antiarrhythmic drug with the undisclosed mechanism of action and has been evaluated concerning efficacy for cardioversion of AF. The programme was terminated in 2023 based on business decisions (NCT04582409). HBI-3000 is a multi-channel blocker, which was well tolerated in the Phase 1 clinical trial and is currently investigated in a Phase 2 trial for acute intravenous cardioversion of patients with recent-onset AF (NCT04680026). An oral multi-channel amiodarone analogue with a relatively short elimination half-life, known as budiodarone, was successfully investigated in PASCAL, a Phase 2 study in patients with recurrent AF documented with pacemakers, and awaits further development. Additional, ongoing work aims to develop inhalable formulations of antiarrhythmic drugs and the repurposing of drugs approved for other indications (e.g. oral doxapram, colchicine, and metformin and injection of botulinum toxin type A into epicardial fat pads) as antiarrhythmic drug therapy in patients with AF (*Table 1*). Ranolazine is approved as an antianginal agent in Europe, and in the USA, it is also approved for the management of long QT3 syndrome. It is a late sodium current inhibitor with a minor inhibitory effect on the HERG current. It is being used, often in combination with amiodarone, for the suppression of AF recurrences.

Rate control drugs and ablate and pace

Rate control therapy remains an important component of rate and rhythm management in patients with AF.[10] The concept of rate control, enabling better cardiac function by slowing and regularizing ventricular rate during episodes of AF, remains unchanged. Almost all rhythm control trials are conducted against a background therapy of rate control,[14] typically using beta-blockers, calcium channel antagonists, and digitalis glycosides.[44,45] Medical rate control therapy should be part of active rhythm management in patients with AF, considering the rate-controlling effects of several antiarrhythmic drugs, including amiodarone, dronedarone, propafenone, and sotalol. The recent APAF-CRT trial showed that there is a role for rate control using a pace-and-ablate strategy in symptomatic heart failure patients with permanent AF to improve clinical outcome.[46] Ablate-and-pace therapy should be considered when rhythm control therapy is unsuccessful.[47] After AV-node ablation, patients become pacemaker dependent, which may lead to pacing-induced cardiomyopathy.[48] Technical improvements increased the interest in conduction system pacing (CSP).[49] Conduction system pacing might be the most appropriate pacing mode for avoiding the development of pacing-induced cardiomyopathy[50] and is already used in patients treated with ablate-and-pace rate control.[51] Outcome studies are planned or ongoing (CONDUCT-AF, LBBAP-AFHF, RAFT-P&A, and others) and reviewed elsewhere.[52]

Practical considerations and summary

Most patients with AF should undergo at least one attempt of active rhythm management during the first year after AF is diagnosed. In patients with AF and concomitant heart failure with reduced ejection fraction, rhythm management should be introduced as a fifth pillar on top of the established 'fantastic 4' [an angiotensin receptor–neprilysin inhibitor, a beta-blocker, a mineralocorticoid receptor antagonist, and a sodium-glucose co-transporter (SGLT) 2 inhibitor] for comprehensive

Table 1 New antiarrhythmic drugs and new formulations of existing antiarrhythmic drugs in development

Novel antiarrhythmic agents

Agent (developer)	Main antiarrhythmic target	Indication	Formulation	Current clinical status
AP30663	Small conductance calcium-activated potassium (SK) channel blocker	Cardioversion of recent-onset AF	Intravenous	Phase 2 completed (NCT04571385)
AP31969	Small conductance calcium-activated potassium (SK) channel blocker	Sinus rhythm maintenance	Oral	Phase 1 ongoing
HSY244	Undisclosed	Cardioversion of recent-onset AF	Intravenous	Phase 2 terminated (business decision) (NCT04582409)
HBI-3000 (sulcardine)	Multi-channel blocker	Cardioversion of recent-onset AF (>2 and <72 h)	Intravenous	Phase 2 ongoing (NCT04680026)
Budiodarone	Multi-channel blocker	Sinus rhythm maintenance	Oral	Phase 2 completed (PASCAL)
Botulinum toxin A	Cholinergic neurotransmission blocker	Prevention of postoperative AF	Injection around ganglionated plexuses	Phase 2 (NCT01842529; NOVA)

Reformulation of already approved AADs

Antiarrhythmic drug	Main antiarrhythmic target	Indication	Reformulation	Current clinical status
Flecainide	Sodium channel blocker	Cardioversion of recent-onset symptomatic AF	Inhalation solution	Phase 2 terminated (NCT05039359; RESTORE-1) Phase 3 currently on hold (NCT03539302; INSTANT)

Repurposing of already approved medications

Agent (developer)	Main antiarrhythmic target	Indication	Formulation	Current clinical status
Bucindolol	Beta 1 adrenergic blockade and receptor reduction	Sinus rhythm maintenance	Oral	Phase 2 completed (NCT01970501; GENETIC-AF)
Doxapram	TASK 1 inhibitor	Cardioversion of recent-onset AF	Intravenous	Phase 2 ongoing (EudraCT 2018-002979-17; DOCTOS)
Ranolazine	Late sodium channel blocker with minor effect on HERG channel	Sinus rhythm maintenance following cardioversion Reduction in AF burden in paroxysmal AF: Ranolazine and dronedarone given alone and in combination	Oral Oral	Phase 2 completed (NCT01534962; RAFFAELLO) Phase 2 completed (NCT01522651)

Published results of completed studies are explained in more details, including references, in the text.

heart failure management strategies.[53] In light of the emerging role of AF therapy in heart failure patients, electrophysiologists with knowledge in rhythm control, AF ablation, and ablate-and-pace therapies should be an integral part of heart failure teams.

Knowledge gaps and opportunities

(1) Quantification of arrhythmia burden, number, and duration of recurrent episodes is needed to better understand the emerging link between AF burden and cardiovascular events. The outcome-reducing effects of rhythm control therapy may be mediated by reducing AF burden and attaining sinus rhythm. This questions the relevance of the primary outcome of older rhythm control trials and time to the first AF recurrence.[3,15,16]
(2) Antiarrhythmic drugs and AF ablation exert synergistic rhythm-controlling effects.[54,55] More research is needed evaluating the effectiveness of antiarrhythmic drugs in the context of AF ablation.
(3) Most of the clinical trials evaluating rhythm control therapy so far were conducted in relatively young patients with AF. The outcome-reducing effect of early rhythm control therapy, in contrast, was most pronounced in patients with AF and a high comorbidity burden (CHA_2DS_2-VASc score 4 or more).[23] There is a clear unmet need to evaluate rhythm control, including AF ablation, in patients with AF and a high comorbidity burden.
(4) More research is needed to define the best methodology to deliver rhythm control therapy for all, integrating innovations in antiarrhythmic drug therapy and AF ablation.
(5) Future research in the field of rate control should focus on patient selection and timing of ablate-and-pace therapy. Studies that include multiple arms with AF ablation compared with AV-node ablation with CSP are necessary to guide clinical practice.
(6) Quantification of AF burden in drug trials, especially in trials of heart failure and in trials of new antiarrhythmic drugs, is needed to determine their effect on the association of AF burden reduction and prevention of AF-related outcomes.

Atrial fibrillation burden in patients with electrocardiogram-diagnosed atrial fibrillation and in patients with device-detected atrial fibrillation

Longer rhythm monitoring durations lead to a higher likelihood of detecting rare and short AF episodes, thereby increasing the number of patients with AF.[56] This has been conceptually described in earlier iterations of the AFNET/EHRA consensus conference.[57] Intermittent electrocardiogram (ECG) recordings or 24-h ambulatory ECG monitors detect fewer patients with AF than continuous rhythm monitoring, mainly diagnosing AF in patients with a high arrhythmia burden.[56,58,59] The growing availability of consumer electronics capable of detecting and quantifying arrhythmia episodes will make such information more widely available in the near future.[60–62]

Device-detected atrial fibrillation and electrocardiogram-documented atrial fibrillation

This group, including investigators from NOAH-AFNET 6 and ARTESiA, recommends to use the term 'device-detected AF' in preference to 'atrial high-rate episodes' and 'sub-clinical AF'. This recommendation is based on the following observations: A careful, core-lab–based analysis of all episodes leading to inclusion into NOAH-AFNET 6 revealed that 97% of these episodes showed all signs of AF.[63] Despite small differences in sensitivity and specificity, the algorithms for recognition of device-detected AF are mature and have been validated and refined over time.[64] The differences in outcomes, e.g. the lower rate of stroke, between device-detected AF and ECG-documented AF is unlikely to be related to differences in the signals recorded during an episode. The term device-detected AF has been used by others after the publication of NOAH-AFNET 6 and ARTESiA[9,65] and can simplify thinking and discussion around this phenomenon.

It remains unclear which patient and what AF burden merits oral anticoagulation to prevent AF-related complications such as death, stroke, thromboembolism, and other morbidities or mortality. At present, the distinction between ECG-documented AF and device-detected AF draws a boundary that has developed historically. Electrocardiogram-documented AF selects patients with a high AF burden. In the absence of documented ECG-diagnosed AF, randomized clinical trials performed so far have failed to demonstrate a benefit of therapy with oral anticoagulation, including patients with embolic stroke of undetermined source,[66,67] patients with heart failure,[68,69] or patients with atrial cardiomyopathy, but without AF.[70] Existing evidence that shows the effectiveness of oral anticoagulation in patients with paroxysmal and persistent AF is based on trials enrolling patients with ECG-diagnosed AF (often requiring at least two AF ECG documentations within 1 year as an inclusion criterion, which likely represents a high AF burden). The STROKESTOP study randomized (1:1) > 75-year-olds to be invited to screening for AF by a handheld ECG 2×/day for 2 weeks or to a control group.[71] Treatment with oral anticoagulants upon ECG documentation of AF reduced the primary combined endpoint of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalization, and all-cause death {hazard ratio 0.96 [95% confidence interval (CI) 0.92–1.00]; $P = 0.045$}. Studies initiating anticoagulation based on AF detection by continuous rhythm monitoring by implantable cardiac monitors in the LOOP study[72] or based on device-detected AF found by 24/7 rhythm monitoring via implantable cardiac devices in NOAH-AFNET 6[1] and ARTESiA[4] found a low event rate without anticoagulation, including a rate of stroke of 1%/year.[9] A sub-analysis from NOAH-AFNET 6 suggests that the low rate of stroke without anticoagulation extends to patients with long episodes of only device-detected AF ≥ 24 h.[8] The absolute treatment effects were the prevention of three strokes and an increase of seven to 16 major bleeds per 1000 patient-years.[9] These effects are probably not sufficient to recommend anticoagulation in patients with device-detected AF. Refined classifications of AF patterns[73] and ideally AF burden should be incorporated in outcome trials investigating the efficacy of modern rhythm control strategies.

Continuous (e.g. by implantable loop recorders) or semi-continuous (e.g. by wearable digital devices) long-term rhythm monitoring can provide information on AF burden, number of AF episodes, and duration of longest AF episode.[74] The average burden of device-detected AF in the absence of ECG-documented AF is low in patients with multiple comorbidities (0.13% median AF burden in LOOP[75]). Recent data from the RACE V registry suggest that paroxysmal AF has a higher burden that can be further differentiated into subgroups.[76,77] While continuous rhythm monitoring is the preferred method to evaluate AF burden, serial longer-term monitor[10,78] or even long-term intermittent monitoring by recording one to three short-term handheld ECGs per day provides effective, albeit less precise alternative methods.[79] So far, these rhythm monitoring methods have mainly been used in research settings.[80–82]

Practical considerations and summary

This group believes that ECG-diagnosed AF should be differentiated from device-detected AF in clinical care (*Figure 3*). The biological rationale is most likely a higher arrhythmia burden in patients with ECG-documented AF.[43] Electrocardiogram-documented AF remains a reason to initiate anticoagulation,[10] provide active rhythm management (see above), and treat cardiovascular comorbidities. Detection of device-detected AF by implanted devices should, in contrast, trigger

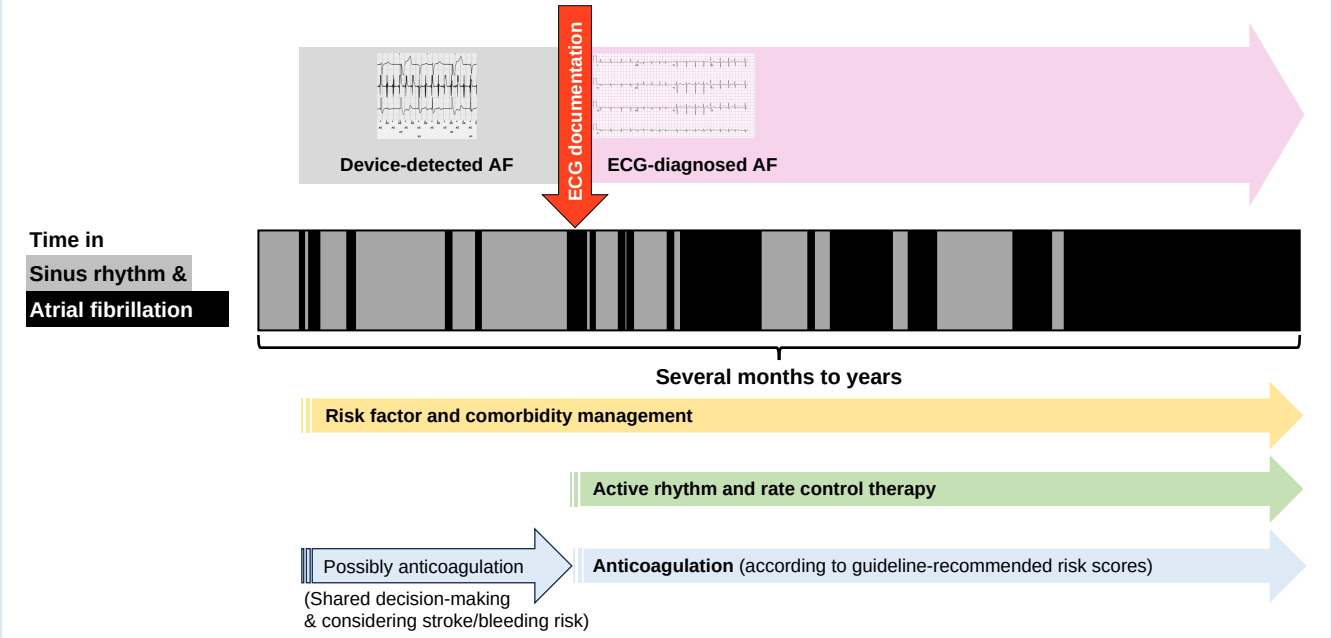

Figure 3 Device-detected compared with electrocardiogram-diagnosed atrial fibrillation in relation to atrial fibrillation progression (which can take several months to years) from very low to very high burden. Electrocardiogram documentation can be achieved using single-lead electrocardiograms or 6- to 12-lead electrocardiograms using accepted definitions of atrial fibrillation. Electrocardiogram documentation of atrial fibrillation is a simple, clinically operable method to identify patients with a high arrhythmia burden. AF, atrial fibrillation; ECG, electrocardiogram.

ECG monitoring to diagnose AF. Treatment of concomitant conditions that can lead to AF can be intensified upon detection of device-detected AF to prevent AF progression. The outcomes of NOAH-AFNET 6[1] and ARTESiA[4] with a small reduction of ischaemic stroke in the context of a low overall rate of stroke and with an expected increase in major but non-fatal bleedings provide solid information for a shared decision process on anticoagulation in selected patients with device-detected AF.

Knowledge gaps and hurdles

(1) The amount of AF that distinguishes low and high burden of AF, the interaction of arrhythmia burden with comorbidities, and the best methods to quantify AF burden require more research. To estimate this, research needs to include quantification of arrhythmia burden in patients with paroxysmal AF with an assessment of the extent of AF burden reduction achieved by active rhythm management and how this relates to prevention of AF-related outcomes.[83]
(2) Reducing AF burden is an emerging therapeutic goal in patients with AF based on this consensus document. Similar thoughts can be found in the recently published ACC/AHA/HRS AF guidelines.[20] The best methods to reduce AF burden in patients with different AF patterns and clinical situations need to be determined.
(3) Uncertainty also remains about the best management of patients with arrhythmias detected by wearables and handheld devices. These devices semi-continuously monitor rhythm, enable an estimation of arrhythmia burden, and are used by increasing numbers of individuals.[10,74,84]
(4) This group believes that quantifiable markers for AF-related disease processes are needed to enable this research. Further research is needed to explore the interaction between the number and severity of stroke risk factors, arrhythmia burden, and individual risk.
(5) Another important line of research should describe the range of arrhythmia progression and regression patterns found in patients and factors identifying patients who are unlikely to experience progression to ECG-documented AF.
(6) Based on the NOAH-AFNET 6 sub-study in patients with device-detected AF episodes ≥ 24 h,[8] it remains unclear whether detection of device-detected AF episodes ≥ 24-h duration is equivalent to progression to 'clinical' AF.
(7) The clinical relevance and utility of AF patterns and AF progression and regression detected by long-term rhythm monitoring need to be better understood to guide personalized treatments for AF.
(8) Finally, more precise methods are needed to identify patients with device-detected AF at risk of stroke.

Improved stroke prevention

The current clinical assessment of stroke risk using the CHA_2DS_2-VASc score[85] is limited by several factors, including the following:

(1) modest predictive ability of contemporary risk prediction scores with the potential for over-/under-treatment due to imprecise risk estimation[86] and variable stroke rates across different populations (leading to inaccurate assessment of risk/benefit)[87,88];
(2) the emergence of newer therapeutic interventions, such as early rhythm control therapy,[14] left atrial appendage removal or closure,[89] and others[65] that reduce stroke risk without having systemic antithrombotic effects; and
(3) the emergence of 'lower risk' AF populations not considered by traditional risk prediction schema, illustrated by patients with device-detected AF who show a relatively low stroke risk despite older age and multiple comorbidities.

These recent developments reinforce earlier calls[90] for improved and dynamic risk stratification schemes to re-evaluate the decision to use anticoagulants. Atrial fibrillation burden, concentrations of circulating biomolecules, and cardiovascular imaging parameters (e.g. atrial cardiomyopathy) have shown potential to improve and refine stroke risk prediction. At the same time, direct evidence is accumulating that AF therapy not only reduces stroke but also reduces heart failure events and cardiovascular death.[3,14]

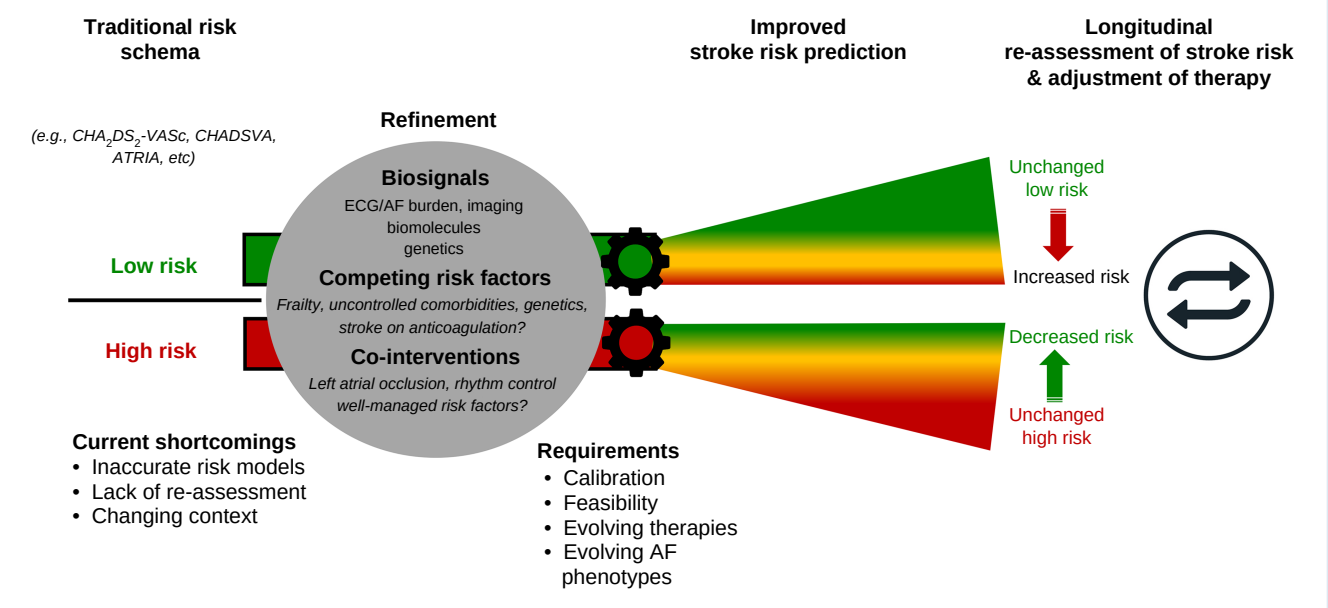

Figure 4 Refined risk assessment resulting in improved stroke risk prediction compared with traditional risk schemas. A longitudinal re-assessment of stroke risk may trigger adjustment of therapy (intensified therapies or de-escalation of therapy). AF, atrial fibrillation; ECG, electrocardiogram.

Clinical risk factors

Clinical stroke risk factors, summarized as the CHA_2DS_2-VASc score, are clinically used to start oral anticoagulation in patients with AF. Consideration of additional clinical features such as chronic kidney disease, tobacco use, ventricular hypertrophy,[91] hypertrophic cardiomyopathy, amyloid, and other inherited cardiac conditions may offer further discriminative ability.

Genetic risk

Initiated by the pioneering work in the population of Iceland,[92] a large body of data science now provides robust risk scores for AF and stroke based on genetic information.[93,94] These scores allow us to quantify AF and stroke risk with a five-fold range between the lowest-risk and highest-risk sub-populations.[93,94] Genetic risk alleles have been associated with recurrent AF on rhythm control therapy,[95,96] and AF risk scores can be used to predict the effectiveness of early rhythm control therapy.[97] Stroke risk can be refined by using genetic risk scores for stroke[98,99] and especially genetic changes related to both stroke and AF.[100] Recent data suggest that the genetic risk for AF overlaps with the genetic risk for heart failure, especially when rare variants are considered.

Atrial fibrillation burden

As discussed above, AF burden emerges as a promising modulator of stroke risk. Early rhythm management reduces cardiovascular events, including a numerical 30% reduction in ischaemic stroke, in anticoagulated patients.[14] This effect is of a comparable magnitude to surgical removal of the left atrial appendage during open heart surgery.[89]

Biomolecules

Circulating biomolecules play an important role in the diagnosis and management of patients with cardiovascular disease.[101] Several biomolecules have shown an independent added value for risk stratification in patients with AF.[86] The biomarker-based ABC-AF stroke and bleeding risk scores [Age, Biomarkers (N-terminal pro-B-type natriuretic peptide, troponin, haemoglobin, and GDF-15), Clinical history of stroke/TIA or bleeding in Atrial Fibrillation] improve prediction of stroke and bleeding.[86] Newer biomolecules that can be accurately quantified include fibroblast growth factor 23 and bone morphogenetic protein 10 (BMP10).[102] Elevated concentrations of these biomolecules are associated with prevalent[102] and recurrent AF[103,104] and with AF-related outcomes.[105]

Imaging

Atrial cardiomyopathy summarizes the histologic and anatomical disease processes that may lead to the development of AF, contribute to its recurrence and progression, and potentially enhance the risk of AF-related cardiovascular events. Left atrial size, a simple integral of atrial cardiomyopathy, has been variably associated with stroke and systemic embolism. Anticoagulation did not prevent strokes in patients with atrial cardiomyopathy, but without AF (ARCADIA),[70] adding to the evidence that AF is a required interacting factor for atrial cardiomyopathy to create a stroke risk. Atrial fibrosis, which can be visualized using late gadolinium enhancement cardiac magnetic resonance imaging, has been associated with an increased risk for major adverse cardiovascular and cerebrovascular events in patients with AF, primarily driven by increased risk for the occurrence of stroke or transient ischaemic attack.[106] More recently, echocardiographic parameters of left atrial function, including left atrial strain and left atrial appendage flow velocity, have been proposed as refined methods to quantify atrial cardiomyopathy and as risk modulators in patients with AF.

Longitudinal reassessment of risk and adjustment of therapy

Most patients with ECG-documented AF should be on oral anticoagulation to reduce their risk of stroke. Atrial fibrillation is a dynamic disease, progressing and regressing from self-terminating to sustained arrhythmia episodes.[107] Stroke risk increases with age or in the context of disease progression and new comorbidities. Stroke risk will decrease with early rhythm control,[14] especially when sinus rhythm is attained,[26] with better treatment of concomitant cardiovascular conditions, or with spontaneous regression of AF burden.

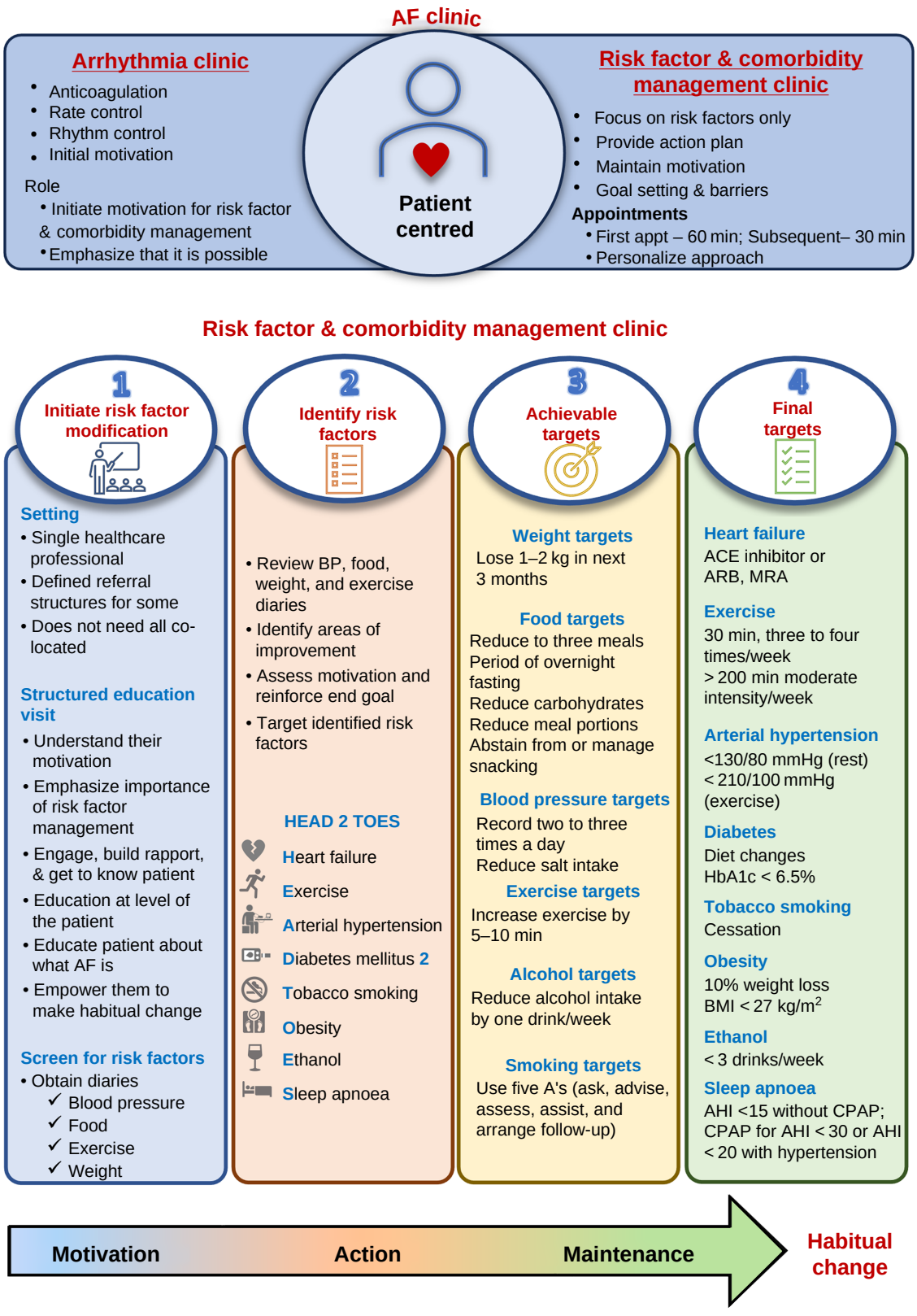

Figure 5 A risk factor and comorbidity management clinic according to the 'Adelaide' model: the risk factor and comorbidity management clinic is separated from the atrial fibrillation clinic and has a single healthcare professional who (i) initiates risk factor modification, (ii) identifies risk factors according to HEAD 2 TOES, (iii) sets achievable goals, and (iv) monitors progress towards habitual change. AF, atrial fibrillation; BMI, body mass index.

Table 2 Various groups of artificial intelligence

	Supervised machine learning Decision trees, support vector machines, random forest, boosted trees, etc.	**Unsupervised machine learning** Clustering, anomaly detection, dimensionality reduction, principal component analysis	**Supervised deep learning** Convolutional neural networks, recurrent neural networks, transformers, etc.	**Unsupervised deep learning** Autoencoders or generative adversarial networks
Feature	Input: quantified pre-defined individual features incl. annotation in training set • Transparent • Interpretable • Able to handle high dimensional and non-linear data sets • Feature-based training with annotated data required • Unknown features ignored	Input: quantified individual features • Transparent • Interpretable • Classification based on pre-defined features • No training	Input: pre-defined individual features, and/or raw signals or images, incl. annotation in training set • Large training/validation data set required • Interpretation requires post-processing • Transparency limited (black box)	Input: raw signals or images • Independent of choice of preselected features • Able to classify based on unknown features • Large training/validation data set required • Interpretation requires post-processing (e.g. saliency mapping) • Transparency limited (black box)
Output	Classification based on pre-defined features in pre-defined classes	Automatized classification in unknown number of not pre-defined classes • Provides information on underlying structure or patterns	Classification based on pre-defined and/or extracted features in pre-defined classes • Classification problems based on large number of variables	Classification based on raw signals or image analysis in which unidentified features might carry diagnostic or predictive information. Generation of synthetic signal or images.

There is a residual risk of ischaemic stroke despite anticoagulant therapy (1–2%/year in the pivotal randomized controlled trials), calling for augmented therapy.[65,108,109] Patients experiencing a stroke on anticoagulation can potentially benefit from a call to A-C-T-I-O-N to improve outcome.[110] Sub-optimal treatment of comorbidities and treatment with anticoagulation and low, untested, and non-approved doses[111] may contribute to stroke and cardioembolism.[109] The effects of LAAOS III[89] and EAST-AFNET 4[14] highlight the potential of treating atrial causes of stroke in patients with AF experiencing a stroke on anticoagulation. Whether novel FXIa inhibitors,[112,113] a distinct new class of drugs under investigation for thrombosis prevention, improve outcomes in patients with AF will be evaluated in ongoing registration trials. Phase 3 trial of asundexian in patients with AF has recently been stopped early due to lack of efficacy.[114] Trials with other compounds are ongoing.

Practical considerations and summary

Guideline-recommended risk prediction schemes are useful to guide the initial decision for oral anticoagulation. Genetic risk scores, imaging, and circulating biomolecules may be able to refine this initial assessment. Longitudinal assessment of dynamic risk modulators integrating AF burden, atrial myopathy, and circulating biomolecules of cardiovascular and inflammatory origin can improve risk prediction. Such dynamic risk assessment can result in intensified and combination therapies and in de-escalation of therapy (*Figure 4*).

Knowledge gaps and research opportunities

(1) Research is needed to evaluate novel quantitative risk predictors, including AF-burden, circulating biomolecules, imaging, and genetic markers and their effect on improving prediction of stroke risk, and prediction of the risk of other AF-related complications such as heart failure and cardiovascular death.
(2) Randomized clinical trials to prospectively evaluate biomarker-based risk scores for therapy selection and proteomic screening to better understand the pathophysiology of AF complications are ongoing.
(3) Evaluation of organ-specific atrial (e.g. BMP10) and cerebral health (e.g. neurofilament light chain polypeptide) biomolecules is ongoing with promising initial results. Biomolecules may also provide quantitative proxies for cardiac and atrial fibrosis.
(4) In addition to new randomized trials, individual participant data meta-analysis will generate adequate power to assess the risks and benefits of anticoagulation in patients at different risks.[115] This is currently addressed in a collaborative effort of the AF SCREEN and the AFFECT-EU consortia as well as in COMBINE-AF.[116]
(5) Stroke risk also appears low after AF ablation.[117–124] Randomized studies such as OCEAN[125] (NCT02168829) will determine whether the stroke risk after successful AF ablation is sufficiently reduced to withhold oral anticoagulation. REACT-AF (NCT05836987) will assess smartwatch-guided anticoagulation.

Risk factor and comorbidity management for secondary prevention of atrial fibrillation

A healthy lifestyle and effective treatment of concomitant cardiovascular conditions, often embedded in integrated care pathways, improve maintenance of sinus rhythm and quality of life,[126–130] in addition to the outcome-reducing effect in larger populations.[131,132] Managing individual risk factors in isolation, such as excessive alcohol consumption, can improve AF outcomes.[133] Similarly, behavioural weight loss[126,127,130] and bariatric surgery can prevent AF outcomes in severely

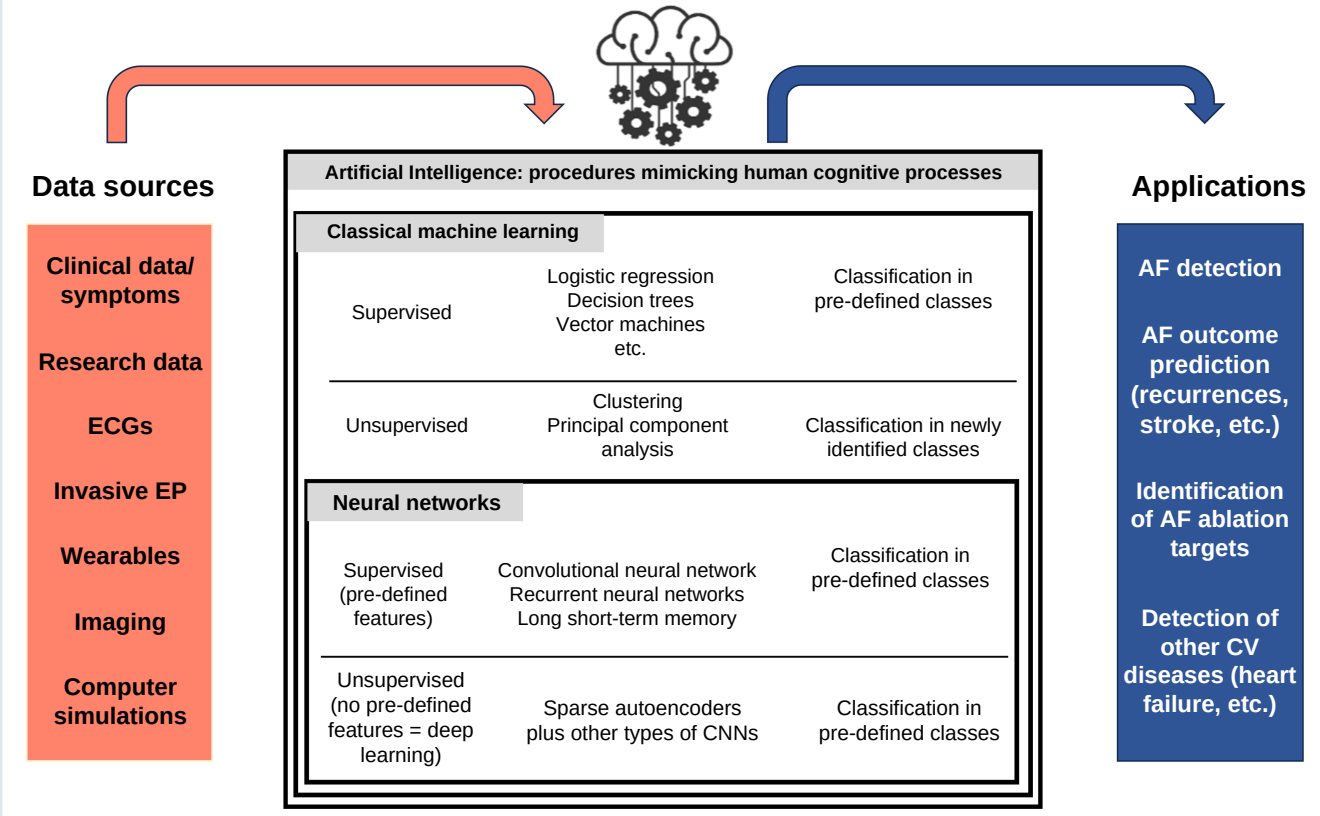

Figure 6 Various groups of artificial intelligence techniques using different data sources, their dominant features and outputs, and potential applications. AF, atrial fibrillation; CV, cardiovascular; CNN, convolutional neural network; ECG, electrocardiogram.

obese individuals.[134–138] Weight loss–inducing glucagon-like peptide (GLP)-1 receptor antagonists, e.g. orforglipron, semaglutide, and tirzepatide, can reduce cardiovascular events and may reduce AF in obese populations.[139–142] While regional patterns of care will vary, integrated risk factor and comorbidity management clinics and specialists can improve the prevention and treatment of concomitant conditions in patients with AF.[127,130] The concept of risk factor and comorbidity management for secondary prevention of AF can be exemplified by the 'Adelaide' model: In Adelaide, the risk factor and comorbidity management clinic are separated from the AF clinic,[143] while both services share a unified messaging emphasizing the importance of treatment of concomitant cardiovascular conditions. This risk factor and comorbidity management clinic have a single healthcare professional who uses academic detailing and structured education visits to build rapport, educate, engage and empower individuals to make informed decisions, set achievable goals, and monitor progress towards habitual behavioural change. Comorbidity treatment and risk factor modification can follow the 'HEAD 2 TOES' acronym (*Figure 5*),[144] enhanced by treatment of coronary artery disease and valvular disease.[145] While a single healthcare professional (not a 'village' of co-located healthcare professionals) primarily manages most aspects of risk factor and comorbidity management, appropriate referrals may be used as required and available. Remote consulting and digital health approaches incorporated in such referral structures may not replace but will support these inter-disciplinary referral structures for the management of comorbidities in patients treated in established AF clinics.[146,147] Importantly, genetic testing may be valuable for identifying underlying conditions in young patients without apparent identifiable factors, which may have not yet manifested as cardiomyopathies (see prior sections).[148] Pharmacological treatment of type-2 diabetes with SGLT2 inhibitors (Odds ratio 0.83, 95% CI 0.68–1.01)[149] or GLP-1 receptor agonists (Relative risk 0.86, 95% CI 0.76–0.97),[150] hypertension, vascular disease, and importantly of heart failure will have AF-reducing effects in addition to the outcome-reducing effects of these medications,[151,152] including treatment with SGLT2 inhibitors[153–157] and with finerenone.[158]

Practical considerations and summary

The presence of AF, probably including device-detected AF, should trigger treatment of concomitant cardiovascular conditions. To improve universal access and adoption of these treatments,[159] the participants of the 9th AFNET/EHRA consensus conference propose to implement integrative risk management clinics to improve this treatment domain in patients with AF.

Knowledge gaps and hurdles

(1) Lifestyle improvement interventions and pharmacological treatments need to be tested at scale.[160] A large randomized controlled study spanning different geographies and healthcare models focusing on hard endpoints such as mortality, stroke, and hospitalization and equally cost-effectiveness measures such as quality-adjusted life-year is needed.[161]

(2) Local institutional infrastructures and funding models have been identified as barriers to implementing risk factor and comorbidity management clinics in a recent survey.[159] The H2020 consortium EHRA-PATHS (EU grant agreement ID: 945260) aims to develop new systematic care pathways for the management of AF-related comorbidities across Europe.[162]

(3) Little is known about the direct antiarrhythmic properties of novel heart failure medications: Their antiarrhythmic mechanisms are not well understood and their effect on AF and AF-related outcomes requires robust quantification. Prospective trials are needed and ongoing.
(4) A comparative study of GLP-1 receptor therapy and surgical and and behavioural weight loss is needed to determine their relative antiarrhythmic effectiveness, safety, and cost-effectiveness.
(5) Furthermore, whether phenotyping of patients with AF may allow appropriate characterization of AF and identification of possible underlying causes that have specific treatment (e.g. hypertrophic cardiomyopathy—myosin inhibitors) requires further research.

Artificial intelligence in the detection and management of atrial fibrillation and stroke

Since the 6th AFNET/EHRA consensus conference, artificial intelligence (AI) and modern data science techniques have been a topic during each AFNET/EHRA consensus conference.[10,12,163] There has been progress in the research implementation of AI and the provision of explainable AI to improve stroke prevention, rhythm management, and comorbidity management.[164,165] Artificial intelligence consists of supervised and unsupervised methodologies. In supervised learning, the output or target is defined (e.g. recognition of a sinus rhythm or AF on the ECG). The learning process uses labelled data sets to solve classification and regression or prediction problems. In unsupervised learning, there is no prediction of any output or need for labelled data.[165] Data are sub-divided into classes that were not pre-specified and that are agnostic to the purpose of the investigation. An important domain of AI is machine learning, of which deep learning is an important sub-domain.[164] Deep learning is typically a feedforward artificial neural network, where each node is an activation function that can produce an output signal if the sum of the inputs exceeds a certain threshold level.[165] These techniques are often used for classification purposes based on unspecified features extracted from imaging data or ECGs. In *Table 2* and *Figure 6*, the various groups of AI techniques, their dominant features and outputs, and potential applications are summarized.

A growing clinical and consumer use of AI is the automated detection of AF episodes in ECG and sensor recordings (e.g. photoplethysmography and gyroscopes)[61,74,166–168]; AI models can also enhance AF prediction based on ECG during sinus rhythm,[169,170] chest X-ray,[171] or facial photoplethysmography signals using a digital camera.[172] Deep-learning models have been used for the prediction of recurrent AF on rhythm control therapy.[173,174] In addition, ECG analysis using AI has been applied to guide the identification of patients with low ejection fraction[175] and predict ischaemic stroke risk in AF patients.[176]

Explainable artificial intelligence

One of the rate-limiting factors for further implementation of AI in AF research and clinical practice is the black box nature of AI methods. The reliance on non-transparent AI algorithms raises concerns regarding understanding the systems' output and also about the responsibility and accountability for these outputs. To overcome this limitation, much effort has recently been invested in 'explainable AI' technology. Visualization techniques like attention maps, saliency maps, or heatmaps can highlight input variables and their effect direction within a structured data set, underscoring their importance and their influence on model decisions. Highlighting significant segments in ECGs or visualizing decision-making in structured data sets can provide insights that can be interpreted based on mechanistic understanding.[170,177–180] Additionally, the availability of generic frameworks enables the visualization of decisions from various deep neural networks, making them applicable to multiple data sources, including structured data sets.[181]

Knowledge gaps and research opportunities

(1) Artificial intelligence approaches have become essential tools for researchers to integrate data of a distinct nature such as genetics, cardiac tissue structure including atrial fat, biomolecules, information on comorbidities, and transcriptome data. This strategy requires sharing of multi-modal data coming from different centres, processing of data through the complex steps of regulatory, interoperability, annotation, pseudonymization, and then centralizing data in a data hub to generate and use algorithms.[182] This is the goal of the European H2020 consortium MAESTRIA (EU grant agreement ID: 965286), which was created in 2021 bringing together 18 academic and private partners including AFNET.
(2) For primary prevention strategy to prevent the development of AF and reduction of AF burden, AI can help to integrate information from multi-dimensional clinical parameters to create biomarkers that can inform on AF risk and risk of AF progression.[183]
(3) Whether the use of AI-generated risk markers can guide AF therapy[184,185] requires clinical evaluation, e.g. in the EU-funded MAESTRIA consortium in its prospective AFNET-10 cohort of patients with different types of AF.
(4) In addition, federated learning techniques offer opportunities for model development independent from the logistic challenges of data transfer, which warrants further investigations.

Summary

The conference attendees identified several changes in the management of patients with AF supported by good evidence:

(1) Active rhythm control therapy combined with rate control should be part of the default initial management of most patients with AF.
(2) Biomolecules, genetics, and imaging parameters may help to refine the risk of stroke and other AF-related complications and to identify patient groups with likely therapy failure.
(3) The stroke rate in patients with device-detected AF is low. Oral anticoagulation can reduce this low rate of stroke and induce major bleeding in patients with device-detected AF. More research is needed to identify patients with device-detected AF at high risk of stroke.
(4) The presence of AF should trigger treatment of concomitant cardiovascular conditions, as already implemented for patients with coronary artery disease. The evidence for such measures drawn from research in patients with AF data sets supports wide-spread implementation.
(5) Detection of AF and other chronic cardiovascular diseases is one of the first applications of unsupervised and supervised data science techniques. Iterative cooperation between clinicians and data scientists is needed to leverage the potential of data science and artificial explainable intelligence applications for patients with AF.

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Data availability

All data used for this report are publicly available, and their sources are cited. For further information, please contact info@kompetenznetz-vorhofflimmern.de.

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