

FRONTIERS IN CARDIOVASCULAR QUALITY AND OUTCOMES

Integrated Care in Atrial Fibrillation

A Road Map to the Future

ABSTRACT: Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice with an epidemiological coupling appreciated with advancing age, cardiometabolic risk factors, and structural heart disease. This has resulted in a significant public health burden over the years, evident through increasing rates of hospitalization and AF-related clinical encounters. The resultant gap in health care outcomes is largely twinned with suboptimal rates of anticoagulation prescription and adherence, deficits in symptom identification and management, and insufficient comorbid cardiovascular risk factor investigation and modification. In view of these shortfalls in care, the establishment of integrated chronic care models serves as a road map to best clinical practice. The expansion of integrated chronic care programs, which include multidisciplinary team care, nurse-led AF clinics, and use of telemedicine, are expected to improve AF-related outcomes in the coming years. This review will delve into current gaps in AF care and the role of integrated chronic care models in bridging fragmentations in its management.

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Atrial fibrillation (AF), the irregular and tremulous beat that heralds life fading¹ is the most commonly encountered arrhythmia in clinical practice and identified correlate of poor cardiovascular outcomes, with a strong relationship with ischemic stroke and heart failure.^{2,3} Its other associations include an increased predisposition for ischemic heart disease and development of cognitive impairment, disease processes thought to occur through systemic vascular inflammation, thromboembolic disease, and the development of endothelial dysfunction.^{4,5} Given these associations, it is unsurprising that comorbid AF confers a mortality risk, carrying a 1.5-fold increase in risk in men and 1.9-fold increase in risk in women.⁶

Of particular concern is the epidemiological coupling of AF and advancing age. Given the aging population, review of secular trends projects a near doubling of AF prevalence in the United States over the next 3 decades.⁷ Further, system demands of the disease have resulted in an increase in patient encounters, hospitalization rates, and associated health care expenditure.⁸ The incidence and impacts of AF have outpaced growth of health services, highlighting a rising clinical and public health dilemma.^{9,10}

TRIAL EVIDENCE: PEARLS AND PITFALLS

In recent years, significant progress has been achieved in the understanding of AF initiation and maintenance, as well as treatment of disease substrates and

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complications.¹¹ Due to well-characterized patient cohorts, minimization of confounders, and intimate capture of prespecified study end points, randomized controlled trials (RCTs) offer high internal validity.¹² In spite of these advantages, challenges remain in the application of RCT evidence to real-world clinical practice. This is in large part due to patient selection, with many populations underrepresented or not represented in RCTs. These include elderly patients, women, and racial minority groups, as well as special populations such as end-stage renal disease, frailty states, cognitive impairment, and cancer.¹³ Further, given the nature of trial design, validation of personalized management strategies in studied populations is largely unavailable.

In contrast to RCT, observational studies (OSs) lack investigator intervention and typically entail observation of a study population without external interference. OSs fall under the umbrella term of real-life studies due to their higher level of generalizability, in particular, to patient groups that would otherwise be poorly represented in RCTs.¹⁴ Although OSs afford for larger sample size and variation, there are a number of limitations that affect utility and uptake of study findings. Study populations involved in OSs are often not representative of the wider populace due to participants being recruited from single facilities and geographic regions. Moreover, patients with an increased health literacy and willingness to participate are more often recruited, adding further volunteer selection bias and reducing external validity.¹⁵

Both RCTs and OSs have paved the way for innovation in the understanding and management of AF, although both study designs have intrinsic limitations. Trial evidence of AF represents the tip of the iceberg for the overall burden of AF and multimorbid disease in the community (Figure 1).

GAPS IN AF-RELATED CARE: LOSS IN TRANSLATION

In AF study populations with available evidence, identified gaps in appropriate anticoagulation, symptom control, and risk factor management are readily demonstrated in OSs involving a treatment and control group. Control groups in observational cohorts have been shown to have lower rates of continuous positive airway pressure use,¹⁶ AF trigger assessment,^{17,18} and risk factor modification¹⁶ when compared with observed treatment groups. Additionally, there are higher rates of bleeding events and systemic thromboembolism found in control groups,^{19,20} in part, explained by lower rates of medication compliance and anticoagulation prescription.²⁰ Further, guideline-based therapies have been shown to promote higher quality-of-life scores and disease education,^{21,22} again with higher rates of

use in observed treatment groups (Table¹⁶⁻²⁷; Figure 2). In addition to the effects of active treatment relative to standard care, these findings suggest that more intensive follow-up and greater medical contact typically found in treatment groups allow for better delivery of guideline-based therapies and consequently improve patient outcomes.

Anticoagulation

Stroke prevention and risk assessment heralds a core component of AF management. AF is known to confer a 5-fold increase in risk of cardioembolic stroke when compared with age-matched patients in sinus rhythm and is causative in $\approx 18\%$ of strokes.²⁸ Comorbid AF in the presence of stroke is associated with higher rates of disability, longer hospital stay, and greater rates of stroke recurrence and need for institutionalization.²⁹ Further, stroke patients with AF are at high risk of death during both the acute phase of stroke and the proceeding year following the event.³⁰

Despite the availability of predictive tools and evidence illustrating the benefits of anticoagulation in stroke prevention, anticoagulant therapies remain underprescribed. Epidemiological studies in patients with AF have demonstrated that up to 34% of patients have not received appropriate anticoagulation without recorded contraindication, suggesting that one-third of patients who fulfill indication for anticoagulation therapy are not appropriately anticoagulated.³¹ Reasons for shortfalls in anticoagulant uptake include barriers to anticoagulation prescription and adherence, as well as gaps in evidence for its use in special populations.

Anticoagulation Prescription

There are several identified barriers to anticoagulation prescription, which encompass both physician- and patient-related factors and impact the clinical decision-making process. Physician-related barriers include perceived fear of precipitating bleeding events, therapeutic inertia, and herding, as well as errors in risk stratification; all factors leading to knowledge-to-action gaps.

Given the purpose and mechanism of action of anticoagulation, bleeding is an inherent potential complication of its use. Studies have shown that clinician reluctance to initiate anticoagulant therapy, in part, stems from fear of heightened bleeding risk. Serious bleeding events universally prompt caution in anticoagulation use³²; however, of concern, studies have also found that patient history of minor falls, treated peptic ulcer disease, and nose bleeds also lead to deviation in anticoagulation use from guideline-based therapy even in patients considered to have a high risk of stroke.³³ In the elderly, these fears are often exaggerated and can lead to underprescription of anticoagulants in a population with the greatest stroke risk.^{34,35}

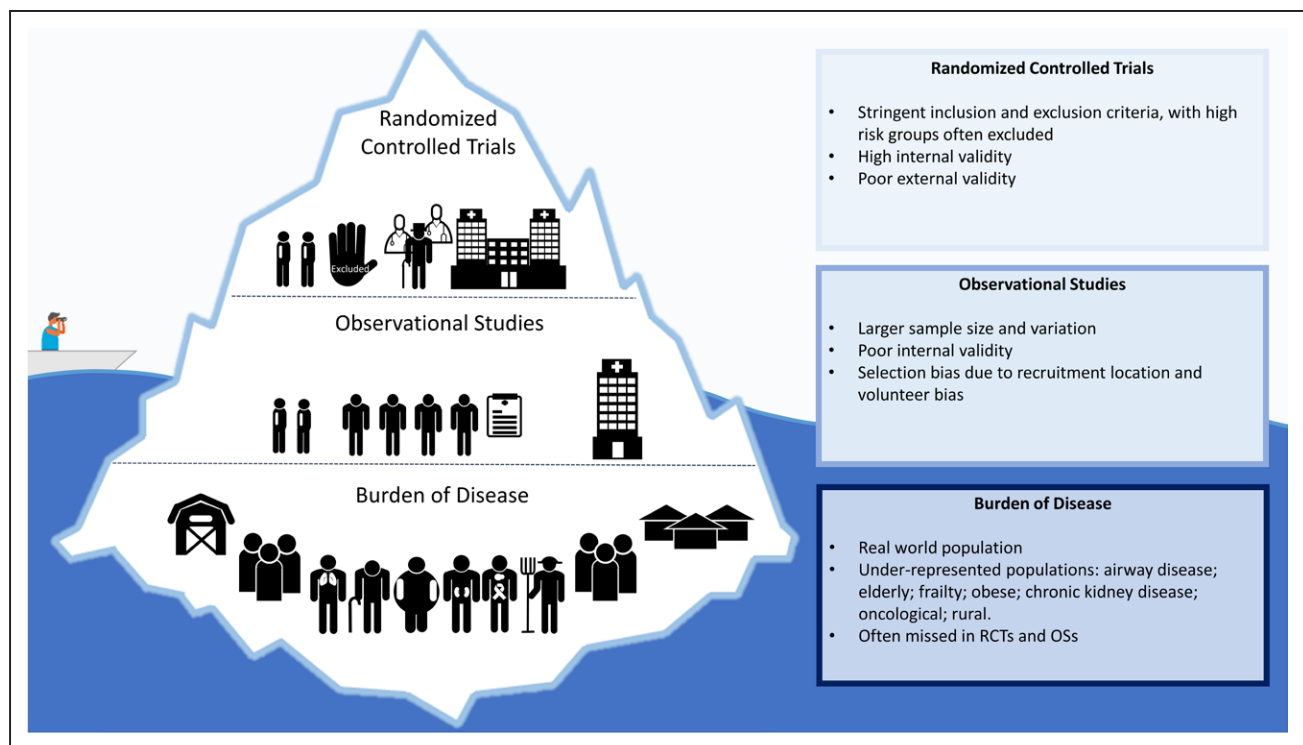


Figure 1. Trial evidence in atrial fibrillation (AF).

Pictorial representation of captured evidence with regard to AF. Intrinsic limitations in randomized controlled trials (RCTs) and observational studies (OSs) limit application of study findings to underrepresented populations.

Clinician aversion to risk and ambiguity have been consistently linked with therapeutic inertia and negative herding behavior, both factors associated with suboptimal anticoagulation prescription.^{36,37} Therapeutic inertia describes a lack of initiation or escalation of therapy when clinically indicated and is central to anticoagulation underprescription. Therapeutic inertia is prevalent, affecting up to 60% of physicians with regard to clinical decision-making in anticoagulation prescription.³⁶ Along a similar vein, herding is a phenomena where clinician decision-making is based on colleague or group recommendation rather than scientific evidence.³⁸ Negative herding behavior in anticoagulation prescription is similarly highly prevalent and found to affect up to 75% of clinicians.³⁶

Risk stratification is essential in the decision-making process, with the CHA₂DS₂-VASc score most commonly used in stroke prediction.³⁹ Despite its greater sensitivity and negative predictive value for prediction of incident stroke compared with its predecessor CHADS₂ score,⁴⁰ its uptake among physicians is variable, in part, due to greater scoring complexity and lack of information on the use of combination regimes in patients with comorbid vascular disease.²⁸ Examples of this ambiguity include a recent change in sex-related variation to the risk algorithm, with latest focused guideline updates placing female sex as a risk modifier rather than a risk factor, only additive in decision-making for anticoagulation when combined with another risk factor.⁴¹ Accordingly, differences in anticoagulation prescription patterns for

stroke prophylaxis between cardiologists and primary care physicians are apparent, with lower rates of anticoagulation prescription among non-cardiologists.⁴² Populations most affected include the elderly and those with paroxysmal AF.^{43,44}

In addition to physician factors, patient-related barriers to anticoagulation prescription exist and include limitations in knowledge regarding the disease process and treatment, as well as individual patient perceptions and attitudes.^{45,46}

Anticoagulation Adherence

Nonadherence to anticoagulation is prevalent and is a major determinant of poor outcomes in patients with AF, namely through higher rates of stroke and cardiovascular mortality.⁴⁷ Even in the era of direct oral anticoagulants, rates of adherence and persistence of therapy remain suboptimal, with <70% of patients demonstrating good adherence or persistence with anticoagulant therapy.⁴⁸ Suboptimal anticoagulation adherence is not only caused by gaps in therapy but also affected by lack of initiation, late initiation, and discontinuation of therapy among initiators.⁴⁹

Predictors of anticoagulation nonadherence are diverse and include active employment, higher educational level, poor cognitive function, alcohol use, co-existent antiplatelet use, poor reported physical health, and complexity and frequency of medication dosing regimens.⁵⁰⁻⁵²

Table. Summary of Outcome Measures in Control and Treatment Groups With Regard to AF Care

Aspect of management	Outcome measure	RCT and OS populations/control group	RCT and OS populations/treatment group	Treatment
Anticoagulation				
Bleeding	Rates of major bleeding	3.8% major bleeding per year (O)	2.1%–3.6% major bleeding per year (ARISTOTLE, ENGAGE, RE-LY, and ROCKET AF)	3 monthly follow-ups with OAC dispensed on each visit
Thromboembolism	Rates of stroke or systemic embolism	2.3% thromboembolism per year (G)	1.1%–2.2% thromboembolism per year (ARISTOTLE, ENGAGE, RE-LY, and ROCKET AF)	3 monthly follow-ups with OAC dispensed on each visit
Prescription of OAC	Percentage of patients who received OAC	Only 56.4% received OAC with 82.4% with CHA ₂ DS ₂ -VASc score ≥2 (G)	72.7%–83.4% continued OAC (ARISTOTLE, ENGAGE, RE-LY, and ROCKET AF)	Strict adherence to guideline- and protocol-based prescription
Symptoms				
Quality of life and symptoms	AFEQT score, 0–100	Mean score deterioration of 1.4 from baseline to 12 mo (Q)	Mean score improvement of 17.8 from baseline to 12 mo in antiarrhythmic group (C)	Symptom-based rate and rhythm control agent prescription
	AFSS	Mean AF symptom subscale score improvement, 23.1–13.3 (ARREST-AF)	Mean AF symptom subscale score improvement, 22–7.1 (ARREST-AF)	Active risk factor management in a dedicated AF clinic
AF knowledge and education	Improvement in JAKQ score over 12 mo	No significant change from 63.5% to 56.3% (<i>P</i> =0.82) with general education (JAKQ)	Increase from 75% to 87.5% with targeted education (JAKQ)	Targeted education based on gaps in knowledge
Risk factors				
Obstructive sleep apnea	CPAP compliance	32% CPAP compliance in control group (ARREST-AF)	77% CPAP compliance in active risk modification group (ARREST-AF)	Active risk factor management in a dedicated AF clinic
Thyroid disease	Screening for thyroid function	54% had thyroid function screening in standard care group (N)	91% had thyroid function screening in nurse-led integrated care group (N)	Nurse-led clinic supported by guideline-based software
Structural heart disease	Percentage of patients who underwent TTE	88% underwent TTE in standard care group (ICCP)	99% underwent TTE in integrated care group (ICCP)	Implementation of integrated chronic care program
Hypertension	Mean SBP	Mean SBP improvement of 20.6 mmHg over 12 mo in control group (ARREST-AF)	Mean SBP improvement of 34.1 mmHg over 12 mo in treatment group (ARREST-AF)	Active risk factor management in a dedicated AF clinic
Elevated body mass index	Mean weight loss	Weight loss of 1.5 kg over 12 mo in control group (ARREST-AF)	Weight loss of 13.2 kg over 12 mo in treatment group (ARREST-AF)	Active risk factor management in a dedicated AF clinic
Diabetes	Glycemic control	29% of patients had HbA1c <7% in control group (ARREST-AF)	100% of patients had HbA1c <7% in treatment group (ARREST-AF)	Active risk factor management in a dedicated AF clinic

AF indicates atrial fibrillation; AFEQT, Atrial Fibrillation Effect on Quality-of-Life; AFSS, Atrial Fibrillation Severity Score; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation²³; ARREST-AF, Aggressive Risk Factor Reduction Study in AF¹⁶; C, CABANA RCT: Effect of Catheter Ablation Versus Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation²⁴; CPAP, continuous positive airway pressure; ENGAGE, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation²⁵; G, GARFIELD-AF model for prediction of stroke and major bleeding in atrial fibrillation: a Danish nationwide validation study²⁰; HbA1c, glycosylated hemoglobin A1c; ICCP, improving guideline adherence in the treatment of atrial fibrillation by implementing an integrated chronic care program¹⁸; JAKQ, effect of reinforced, targeted in-person education using the Jessa Atrial fibrillation Knowledge Questionnaire in patients with atrial fibrillation: a randomized controlled trial²²; N, nurse-led care vs usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs routine clinical care in ambulatory patients with atrial fibrillation¹⁷; O, clinical characteristics, oral anticoagulation patterns, and outcomes of medicated patients with atrial fibrillation: findings from ORBIT-AF¹⁹; OAC, oral anticoagulant; OS, observational study; Q, defining clinically important difference in the atrial fibrillation effect on Quality-of-Life score²¹; RCT, randomized controlled trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy²⁶; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation²⁷; SBP, systolic blood pressure; and TTE, transthoracic echocardiography.

Active employment and greater education have been consistently associated with poor medication adherence across disease settings, as well as INR instability, possibly reflective of the nature of multiple competing interests and greater independent decision-making in this population.⁵³ Patients with poor health literacy, worse health indicators, and factors relating to low socioeconomic status also suffer from poor medication adherence, with greater rates of nonadherence among those eligible for low-income subsidies, again suggestive of these patients prioritizing available income on necessities of living,

rather than medications.⁴⁹ Further, drug regime complexity, frequency, and coexistent antiplatelet use worsen medication adherence, especially in elderly patients.⁵³

Special Populations

There are several special populations that are not well represented in high-quality clinical anticoagulation studies, yet form a significant proportion of patients with comorbid AF. These include patients with end-stage renal disease, cancer, cognitive impairment, and extreme elderly and frail populations.

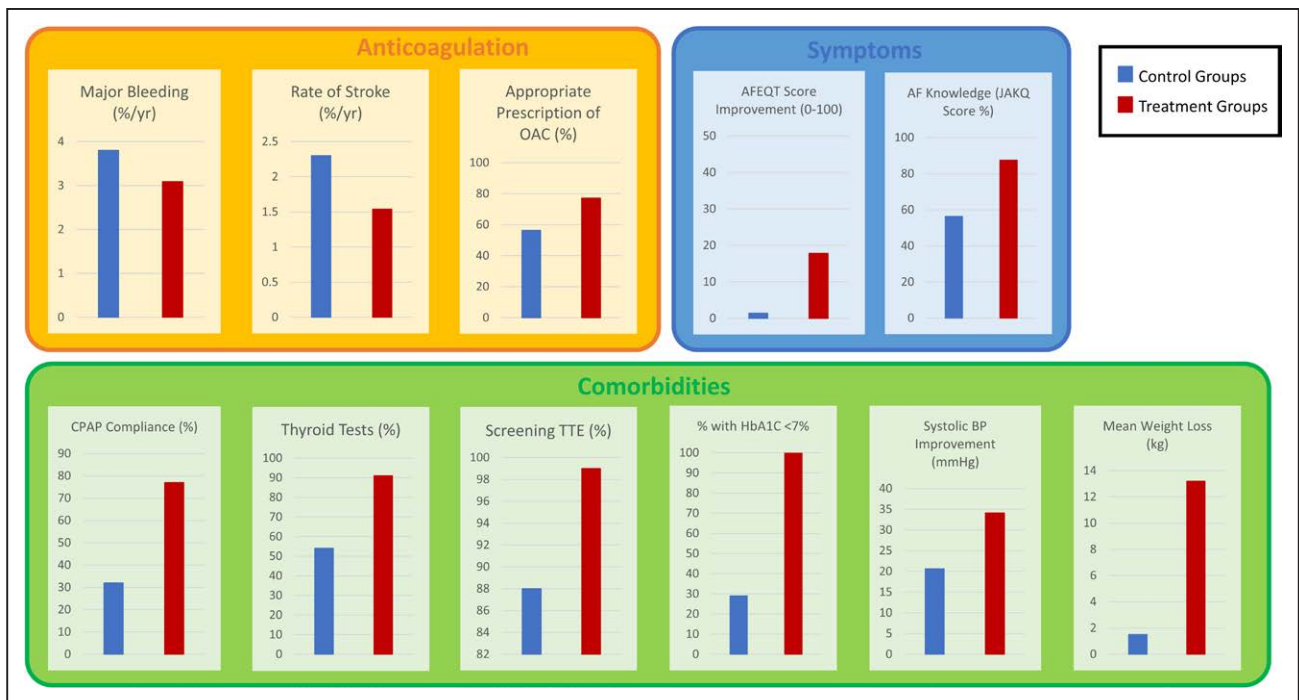


Figure 2. Gaps in care between control and treatment groups with regard to atrial fibrillation (AF) care.

Diagrammatic portrayal of differences in outcomes with regard to AF-related anticoagulation, symptomatology, and risk factor management in control and treatment groups across RCT and OS. Original sourced data from studies in the Table. AFEQT indicates Atrial Fibrillation Effect on Quality of Life; BP, blood pressure; CPAP, continuous positive airway pressure; HbA1c, glycosylated hemoglobin A1c; JAKQ, Jessa Atrial fibrillation Knowledge Questionnaire; OAC, oral anticoagulant; and TTE, transthoracic echocardiography.

Navigating anticoagulation decisions in these complex comorbid states is difficult and underpin an unfortunate irony, with significant parallel rises in stroke and bleeding risks. Reasons for unfavorable risk-benefit profiles in these populations are diverse and include alterations in drug pharmacodynamics and pharmacokinetics, major falls risk, lower medication adherence, and polypharmacy.^{53–56} Further high-quality studies in these populations are required to aid clinicians and patients in the clinical decision-making process.

Symptomatology

Patient symptomatology is a major determinant of quality of life and a significant predictor of AF-related hospitalization and adverse cardiovascular events.^{57,58} Common symptoms with AF include palpitations, chest pain, dyspnea, fatigue, and presyncope. Despite advances in the understanding and management of AF, greater than one-third of patients with the disease remain symptomatic 1 year after initial medical contact.⁵⁸

Challenges in management arise as AF-related symptoms are highly variable with heterogeneous manifestations, necessitating individualized therapeutic approaches to patient care.⁵⁹ Further, underrecognition of symptom burden and discordance between physician-estimated and patient-reported symptomatology is prevalent and can lead to suboptimal treatment in these patients.⁶⁰ Predictors of AF symptom persistence

include comorbid chronic heart failure, chronic obstructive pulmonary disease, hypothyroidism, and AF persistence.⁵⁸ Further, presence of concomitant heart failure has been shown to result in more severe and atypical symptomatology.⁶¹

Initial conventional thought advocated for rhythm control strategies only for select populations, such as those with symptomatic AF despite adequate ventricular rate control,⁶² as early landmark RCTs failed to demonstrate a mortality benefit from either rhythm or rate control strategies in the general AF population and in fact found greater rates of patient rehospitalization and adverse events in rhythm control groups.^{63,64} More recently, studies have shown rhythm control strategies to confer benefit with regard to cardiovascular outcomes in select populations such as heart failure. In an OS by Kelly et al,⁶⁵ use of a rhythm control approach for patients with diagnosed heart failure with preserved ejection fraction resulted in a reduction of all-cause death and rehospitalization. Further, the CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) study published by Marrouche and associates found the use of pulmonary vein isolation for management of paroxysmal or persistent AF to be effective in reducing cardiovascular hospitalization and mortality in select patients with heart failure with reduced ejection fraction compared with standard medical therapy (ie, pharmacological treatment with rate or rhythm control).⁶⁶

Finally, the recently published trial findings from the EAST-AFNET 4 (The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) represent a major change in treatment paradigms for initiation of an early and comprehensive rhythm control strategy for patients with recent-onset AF and comorbid cardiovascular disease.⁶⁷ The study, which was multicentered and of RCT design, evaluated the efficacy of rhythm control therapy, with antiarrhythmic medications or catheter ablation, delivered soon after AF diagnosis improves cardiovascular outcomes in patients with early AF when compared with conventional management. The conventional management arm followed current guideline recommendations, with patients initially managed with rate control therapies and rhythm control only initiated to improve AF-related symptomatology despite optimized ventricular rates. The study found a significant reduction in adverse cardiovascular outcomes, with a lower rate of composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome in patients managed with early rhythm control strategies. Remarkably, the clinical benefit of early rhythm control was consistent across patient subgroups, including asymptomatic patients, those in sinus rhythm at study randomization, as well as those without heart failure.

It is felt that use of catheter ablation and early initiation of rhythm control are the likely contributory factors accounting for the superiority of this approach, as atrial remodeling and AF chronicity provide positive feedback, and, therefore, later rhythm control strategies may be ineffective in curbing AF progression and its associated cardiovascular risk.

Risk Factors and Comorbid Disease

AF initiation, maintenance, and progression are fundamentally linked with cardiovascular risk factors and established cardiovascular disease.⁶⁸ Several physiological and disease states, including advanced age, obesity, diabetes, obstructive sleep apnea, hypertension, moderate-to-heavy alcohol consumption, smoking, heart failure, and valvular heart disease, activate signaling pathways that lead to changes in the atria. These changes include myocyte hypertrophy, fibroblast proliferation, and complex alterations of the extracellular matrix leading to tissue fibrosis.⁶⁹ The resultant electrophysiological substrate is characterized by shortening of atrial refractoriness and reentrant wavelengths, slowing of atrial conduction velocity and local conduction heterogeneities, which in turn promotes ectopic activity in the pulmonary veins and other sites.⁷⁰ These factors predispose to AF initiation and maintenance. Moreover, AF itself shortens atrial refractoriness and causes loss of atrial contractility, which further promotes this cycle of atrial remodeling—a positive feedback loop commonly described as AF begets AF.⁷¹

AF progression and persistence has established prognostic implications, with increased morbidity and all-cause mortality with persistent and permanent AF clinical phenotypes.^{72–74} In addition to hard clinical outcomes, AF progression is associated with symptomatic disease and impairment of health-related quality of life.⁷⁵ High comorbid disease in persistent and permanent clinical phenotypes also leads to polypharmacy and concurrent elevations in bleeding risk, factors further complicating management in these patients.

Optimization of AF treatment as largely shown through OS involves targeted education, investigation, and management in all three domains of AF-related care, namely anticoagulation, symptom control, and risk factor modification (Figure 3). Widespread implementation of these interventions remains challenging in current health care models and requires systemic changes in approach to AF management and resource allocation.

AF MANAGEMENT: FROM CURRENT MEDICAL MODELS TO AN INTEGRATED CARE APPROACH

The medical model has historically been defined as a systematic process of differentiation of a disease process through observation, description, and delineation in the context of a medical encounter. The focus of this model is understandably appealing to health care professionals in the quest to differentiate the disease state and initiate treatment plans to aid in recovery from illness.⁷⁶

The reactive and episodic nature of the medical model with heightened focus on the disease state allows for excellent acute medical care.⁷⁷ AF, however, is a chronic medical condition that requires management of not only acute complications but also modification of the disease process and long-term patient journey. Many health care systems that follow the medical model of care suffer from fragmentation of care of chronic disease processes, with lack of care coordination, duplication of services, and disproportionate resource allocation for tertiary prevention.⁷⁸ Australian health care expenditure analysis has revealed that approximately two-thirds of AF costs relate to disease complication and patient disability (Figure 4).⁷⁹

Given projected unfavorable epidemiological trends and increasing burden of chronic cardiovascular disease, long-term utility of the acute medical model for AF care is economically unsustainable. Further, its ability in addressing the causative shortfalls of AF-related disability, namely appropriate anticoagulation uptake, symptom control, and risk factor modification, is limited. In recognition of fragmentation of health care services for chronic diseases, integrated care models have been put forward as a solution.⁸⁰

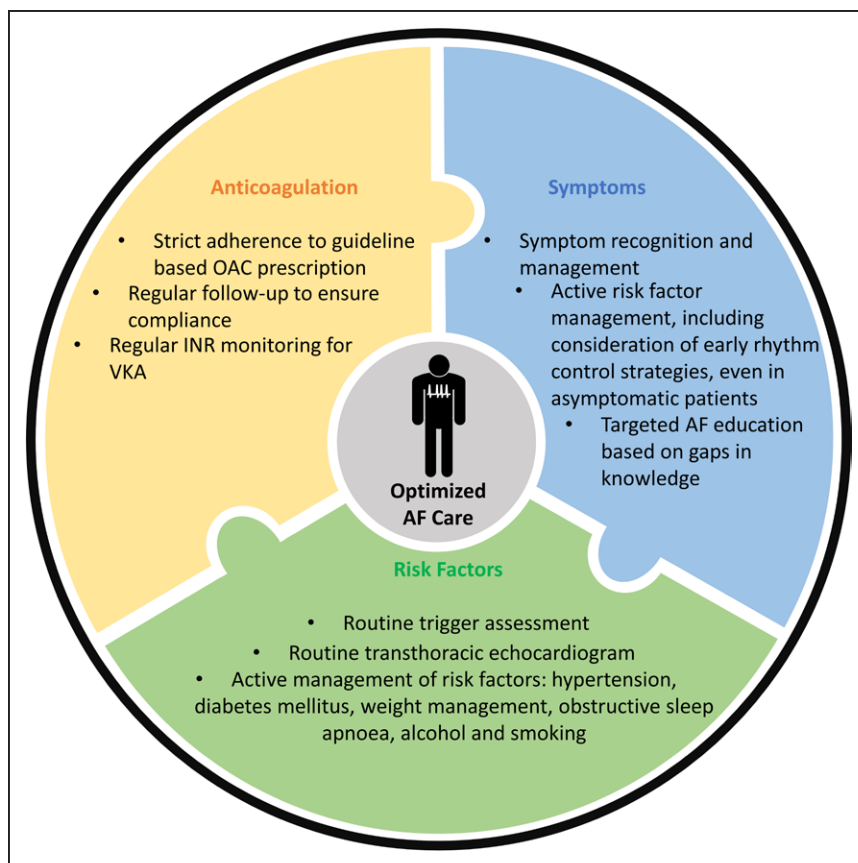


Figure 3. Optimized atrial fibrillation (AF) care.

Best clinical practice with regard to the three domains of AF-related care. INR indicates international normalized ratio; OAC, oral anticoagulant; and VKA, vitamin K antagonist.

Given its encompassing nature, diversity of definition, and utility across different stakeholders, integrated care can be considered conceptually ambiguous and difficult to understand.⁸¹ Practically, integrated care refers to organization and delivery of health care services in a coordinated, efficient, and effective approach with the aim of optimizing patient care. It typically consists of several components, including health care providers, policy makers, regulators, evaluators, managers, service carers, service users, and the community.⁸⁰

The practice of integrated care extends beyond a single medical provider and involves close collaboration between different health care services across primary, auxiliary, and tertiary care settings. This integration of medical services, commonly referred to as the medical neighborhood, places the patient journey at its heart with informed and active shared decision-making between the patient, family/carer, and health care providers (Figure 5).

Integrated chronic care models (ICCM) provide an avenue for effective coordination of the AF medical neighborhood with longitudinal, preventative, cost-effective, and evidence-based approaches to patient care. Key components of the ICCM include the health system, community, delivery system design, decision support, clinical information systems, and self-management support.⁸⁰

Health and Community Systems

Tertiary care is often the first point of medical contact for AF identification and management and is a large determinant of the total AF-related cost.⁸² Given its high utilization and therapeutic capture of AF patients, guideline-based initiation of care in the hospital setting provides a unique window of opportunity for sustained management of AF and its complications. Initiation of the American Heart Association Get With The Guidelines Atrial Fibrillation program has demonstrated significant improvements in appropriate anticoagulation prescription at discharge, increasing from 64.6% at program commencement to 87.6% at the end of the study period in AF patients without strict contraindication to anticoagulation therapy.⁸³

Structured, nurse-led, clinic-based AF care has shown great promise over the years, with initial randomized and OS showing significant improvements in cardiovascular mortality and hospitalizations secondary to improvements in adherence to guideline-based therapies relative to standard care.^{17,84,85} A recent multicenter randomized trial, RACE 4 (Rate Control Versus Electrical Cardioversion Trial 4—Nurse-Led Care Versus Usual-Care), showed a favorable effect of nurse-led care, although only in experienced centers.⁸⁶ Further trials (iCARE-AF [Integrated Care for Atrial Fibrillation Management: A Randomized Controlled Trial] study, ACTRN12616001109493) in this

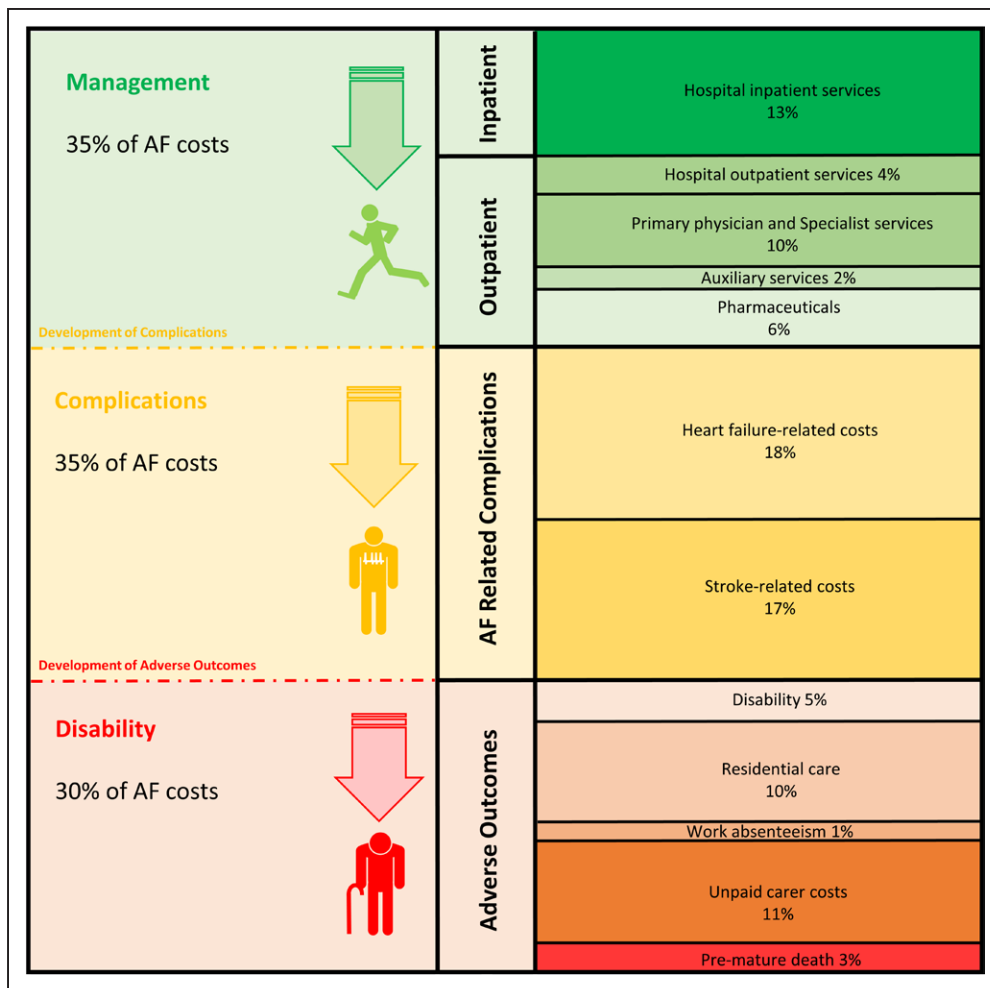


Figure 4. Atrial fibrillation (AF)-related expenditure.

Pictorial breakdown of AF-related expenditure in the Australian health care system. Percentages rounded to closest integer number. Data derived from PricewaterhouseCoopers⁷⁹.

area are currently underway and should hopefully shed further clarity to this research space.

Other hospital-based initiatives include utilization of dedicated emergency department AF treatment pathways aimed at providing early discharge with expedited cardiologist review and initiation of guideline-based anticoagulation. Feasibility studies have shown significant improvements in hospital length of stay and AF-related readmissions with the use of these strategies in comparison to routine care.^{87,88}

The role of community-based services in ICCM is to minimize AF-related hospitalization, implement risk factor modifications, and improve adherence to guideline-based therapies, while reducing expenditure and resource utilization of tertiary services.

Australian studies have shown that targeted risk factor management for secondary AF prevention using risk factor management clinics has resulted in significant improvements in AF burden, progression, and arrhythmia-free survival. The CARDIO-FIT study (Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With

Atrial Fibrillation), LEGACY (Long-Term Effect of Goal Directed Weight Management on Atrial Fibrillation Cohort: a 5 Year Follow-Up Study), and ARREST-AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation) evaluated the impact of physician-led outpatient exercise, weight loss, and risk factor management programs and found reductions in AF burden with corresponding gains in maintenance of sinus rhythm, despite a reduction in antiarrhythmic medication therapies in the interventional arms.^{16,89,90} Cost analysis of such a dedicated risk factor management clinic model found cost savings of \$12 094 over a 10-year period (incremental cost-effectiveness ratio of \$62 653 saved per quality-adjusted life-years gained).⁹¹ These studies have been instrumental in the thought shift from treatment of AF as a primary disease to understanding it as the end process of its antecedent risk factors. Limitations of these studies stem from their observational nature, use of a single center in trial design, and difficulty in discriminating the relative contribution of each risk factor in the outcome as many risk factors are collinear in nature.

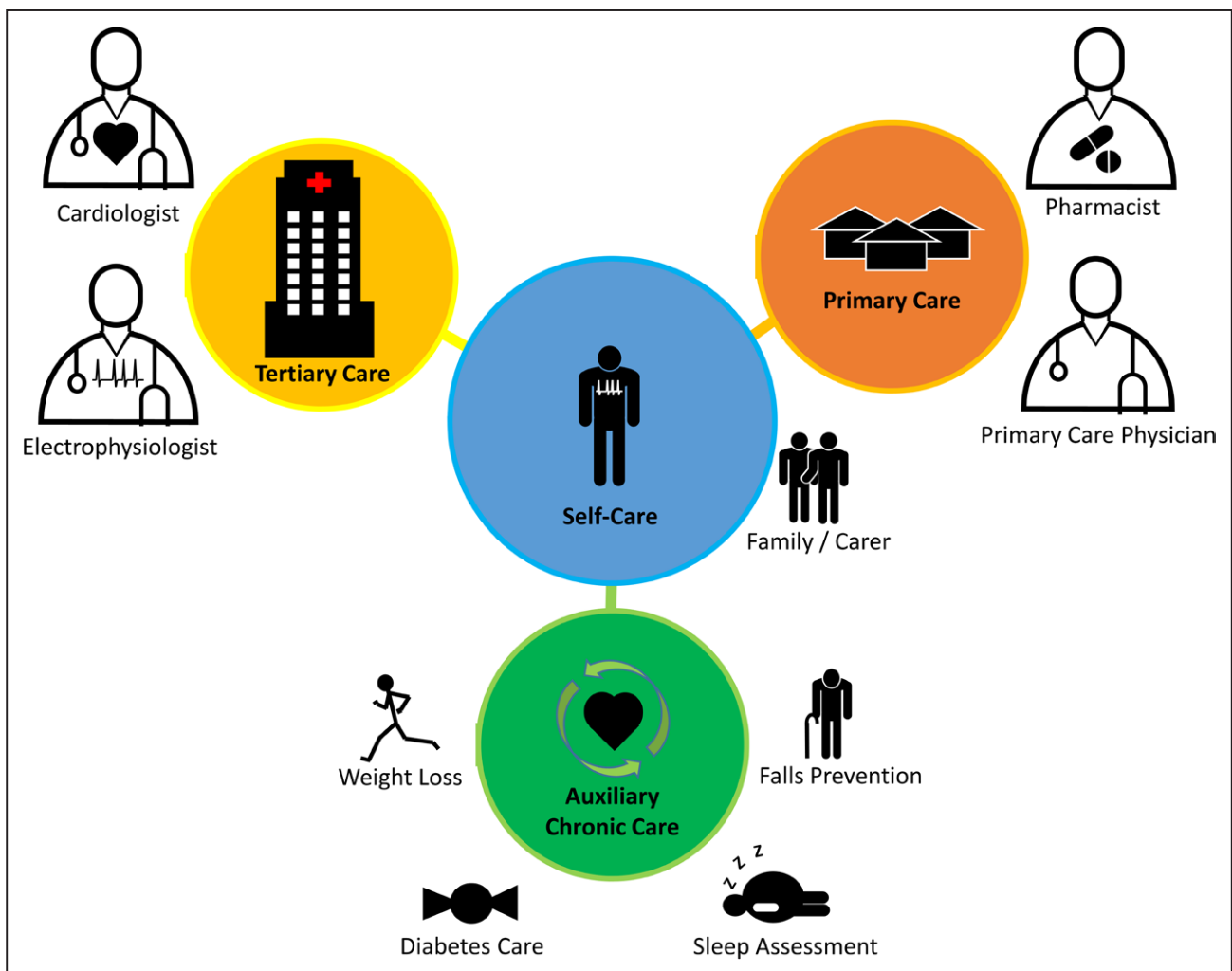


Figure 5. The atrial fibrillation (AF) medical neighborhood.

Hypothetical integrated medical neighborhood of an individual living with AF. Available support systems include primary, auxiliary, and tertiary levels of care with involvement of the primary care physician, pharmacist, cardiologist, electrophysiologist, family/carer, as well as auxiliary programs focused on risk factor modification.

Another Australian-based study evaluated the impact of risk factor modification with alcohol cessation in patients with diagnosed AF. The study, which was multicentered and of RCT design, evaluated adults who consumed ≥ 10 standard drinks per week and who had paroxysmal or persistent AF and randomized them to either alcohol abstinence or usual alcohol consumption. Methods of promotion of alcohol abstinence included oral and written advice, as well as monthly oral and electronic communication from investigators. Primary findings of the study were that alcohol abstinence was associated with reduction in arrhythmia recurrence, as well as a trend toward lower AF-related hospitalization in regular drinkers.⁹² Although dedicated pathways for alcohol dependence exist, there may be a role for integration of counseling and promotional services into an integrated care model even for patients with only moderate alcohol use. Further evaluation of efficacy and feasibility of such models is required.

There is a well-established epidemiological association between hypertension and AF,⁹³ with elevated

blood pressure mediating several structural and autonomic pathways that lead to initiation and progression of the arrhythmia.⁹⁴ Further, a recent data analysis from the SPRINT RCT (Systolic Blood Pressure Intervention Trial) found a reduction in AF risk with intensive blood pressure lowering.⁹⁵ This finding may in large part be explained by the favorable effects of blood pressure control on atrial remodeling, with previous human studies finding improvements in markers of left atrial size and function with use of antihypertensive treatment or intensive blood pressure lowering.^{96–99}

Similar to hypertension, smoking is a major prevalent modifiable risk factor and is causative of several adverse cardiovascular conditions, including AF.¹⁰⁰ It has been shown to have a dose-dependent effect with the arrhythmia¹⁰¹ and its continued use associated with AF recurrence following rhythm control therapy.¹⁰² Benefits of smoking cessation were shown in a recent study evaluating the impact of smoking cessation after newly diagnosed AF and its relationship with stroke risk and

mortality. The study, using national databases, found that compared with current smokers, ex-smokers had a 30% lower probability of stroke and a 16% reduction in likelihood of all-cause death, after accounting for confounding factors such as blood pressure, body mass index, and physical activity.¹⁰³ Given the established cardiovascular benefits for smoking cessation and adequate blood pressure control, targeted surveillance and management of these modifiable risk factors in patients with AF is recommended.¹⁰⁴

Despite evidence of benefit in specialized and tertiary AF clinics, until recently, little was known regarding the utility of ICCM in primary care—a setting often encumbered with more elderly and frail patients with multimorbid disease. The ALL-IN cluster randomized control trial evaluated the feasibility and impact of integrated care program utilization in the Dutch primary care setting. The intervention arm consisted of quarterly checkups by the practice nurse on AF symptoms and risk factors, assessment of anticoagulation regimes and adherence, and streamlined consultation to anticoagulation clinics or cardiologists. Following 2-year follow-up, the ICCM proved feasible and resulted in a 45% reduction in all-cause mortality when compared with usual care.¹⁰⁵ Hypothesized drivers of this outcome included early recognition of clinical deterioration or complication, as well as risk factor modification. These findings have significant implications for patients in rural communities and offer decentralization of care in the current coronavirus disease 2019 (COVID-19) climate, with patients being able to receive high-quality care closer to their homes.

Given the recent success of early and aggressive rhythm control measures in early AF (diagnosis of AF within 1 year), consideration should be given for incorporation of these strategies in this population. Further studies in this field are required for further risk stratification and information on choice of antiarrhythmic strategy.

Delivery System Design

It is recognized that the common multimorbid clinical state and variable complexity of disease in patients with AF is frequently associated with use of different health care services and providers. Increasing clinician participation can lead to increasing complexity of medication and treatment regimes, patient confusion, and duplication of services. In recognition of these pitfalls, the ICCM promotes a multidisciplinary care pathway through clinician coordination, shared assessment, and cross-education.

A British study revealed that adherence to guideline-based management through a multidisciplinary approach resulted in increased anticoagulation prescription with appropriate antiplatelet reduction in anticoagulation-eligible patients with AF.¹⁰⁶ The study involved 43

general practices across England, which utilized clinical support software, as well as shared decision-making via multidisciplinary video conferencing for complex patients, with discussion between the cardiologist, hematologist, general practitioner and clinical pharmacist. Integration of the programme into clinical practice was felt to be feasible and received positive feedback from both patients and health care providers. Given the increasing need for telemedicine services, utility of multidisciplinary video conferencing provides an avenue for early specialist input and streamlining of care for complex and multimorbid patients with AF.

Given the systemic effects and interactions of AF, it is unsurprising that a wide range of noncardiovascular disease states can precipitate and lead to progression of AF disease burden. There is a large body of evidence implicating lung disease and obstructive sleep apnea in AF disease progression and adverse outcomes in this population. Comorbid AF in patients with chronic obstructive pulmonary disease has been shown to be associated with more frequent infections, higher rates of respiratory failure, hepatic dysfunction, and need for intensive care, vasopressor treatment, and mechanical ventilation.¹⁰⁷ Further, an association with increased mortality has been found in those with both disease states.¹⁰⁸ Despite these associations, the benefits of management of COPD or AF in those with dual pathologies has yet to be established in prospective cohort studies.

Along a similar vein, obstructive sleep apnea has an established causal relationship with AF and has been associated with adverse atrial remodeling and AF disease progression, again leading to poor cardiovascular outcomes in this population.^{109,110} Appropriate management of the condition has been shown to result in reduced progression of AF chronicity, burden, and recurrence.¹¹¹ Given these disease associations, close multidisciplinary collaboration between the treating cardiologist, pulmonologist, and general practitioner should be maintained in the patient's journey.¹¹²

Design Support

The information age is graced with a rapid advancement in technology and medical information systems, with digital health technologies increasingly being used in aid of risk stratification and clinical support systems.

Clinical support systems and decision aids provide clarity to the clinical decision-making process by breaking down cognitively complex tasks for clinicians and patients with available evidence support in an easily palatable format. As anticoagulation prescription and adherence are intimately linked to clinician and patient conceptions, clinical support systems work best when decisions are shared, and the same evidence is available to both parties. Randomized trials have found the use of shared decision-making tools about anticoagulation

treatments in patients with AF to result in improvements in patient involvement and clinician satisfaction as well as reductions in decision conflict.^{113,114} These factors have been shown to improve patient willingness to initiate anticoagulant therapies.¹¹⁴

The use of Mobile Health technology as a tool in the management of AF has been identified as an emerging technological advancement in the field of design support. Recent landmark studies have evaluated the feasibility and efficacy of mobile AF applications on AF-related outcomes.^{115,116} These studies have found mobile AF applications, which incorporate inbuilt personal health records, clinical decision support tools, and education programs in keeping with integrated care principles, to improve patient quality of life, knowledge, anticoagulation satisfaction, and drug adherence.¹¹⁵ Further, these applications have also shown positive impacts on hard clinical end points, with demonstrable reductions in cardiovascular events and rehospitalization irrespective of AF type or patient comorbid state.¹¹⁶ The recently published longer term follow-up outcome study for this study population found maintained reductions in the composite outcome and hospitalizations, with associated good adherence and persistence with the mobile AF application program.¹¹⁷

Despite these promising findings, further evaluation of specific structures and interventions leading to success of these programs are required given previous equivocal or negative outcome studies with regard to use of mobile health technology and cardiovascular health.¹¹⁸ Further, incorporation of these technologies into integrated systems of care can add to technical complexity, however require study given the anticipated greater reliance and technological advancements with time.¹¹⁹

Clinical Information Systems

Clinical information systems refer to integration of health records and are important for facilitating clinician coordination, registration of data for patient risk stratification, and technologies that support remote patient monitoring.

Electronic health records are well suited in estimating AF incidence, prevalence, and risk given their longitudinal nature, intimate capture of outcome data, as well as their links to health providers. Sociodemographic, anthropometric, and clinical risk factor data are routinely collected in health care settings and can be used in algorithm-based risk stratification assessment for patients with AF.¹²⁰ This was confirmed in a recent study that used real-world multi-institutional electronic health data to derive a model for new-onset AF prediction and stratification of stroke risk in a population of patients without prevalent AF.¹²¹ The real-world implications for such automated risk prediction models are profound, as such systems may provide early identification of at-risk populations and allow for targeted early intervention

through public health endeavors and introduction of directed screening guidelines.

The role of user-owned wearable devices in the detection and management of AF is currently in their infancy but represents future avenues for patient-directed care and outpatient management paradigms. The Apple Heart Study represented the first large-scale OS to evaluate the use of opportunistic smartwatch-based notification software for detection of AF.¹²² Study user and methodological limitations led to a low detection rate and subsequent investigation for those receiving notification of irregular pulse. The authors acknowledge the study was not a screening study but rather provide foundation for future work into its clinical use. The HEARTLINE randomized trial (<https://www.clinicaltrials.gov>; unique identifier: NCT04276441) is currently underway to help answer this question in an at-risk population (participants aged ≥ 65 years).

Self-Management Support

Low health literacy has historically been linked to poor health outcomes¹²³ and is a significant determinant of self-management, anticoagulation adherence, and adverse effects.¹²⁴ Contemporary AF surveys have unmasked significant gaps in patient knowledge and understanding, with 1 in 4 patients with AF unable to explain their condition and greater than a third worried or fearful about their disease.¹²⁵ Accordingly, to foster success of any AF medical intervention or program, patient engagement, education, and empowerment are required critical factors.

Despite wide success of structured education-based interventions in many chronic disease states, there is a paucity of information on its impact in the AF population. A small pilot study performed by Lane et al¹²⁶ examined the impact of brief educational intervention on knowledge and perception of AF and anticoagulation treatment and found significant gains in understanding on key areas of anticoagulation. Larger studies are required to assess the clinical translation of educational intervention programmes on patient outcomes. The results of the HELP-AF study (Home-Based Education and Learning Program for Patients With Atrial Fibrillation; ACTRN12611000607976)—a prospective, multicenter, randomized controlled trial evaluating the impact of home-based education for patients with symptomatic AF on hospitalization and quality of life, are currently underway and should provide much needed answers.¹²⁷

Use of ICCMs represents a paradigm shift to the traditional medical encounter, with service and provider roles placed into a larger framework of care centered on achieving longitudinal, coordinated, and personalized gains for the patient (Figure 6). Its role in the care of AF—a chronic and complex disease state—has been

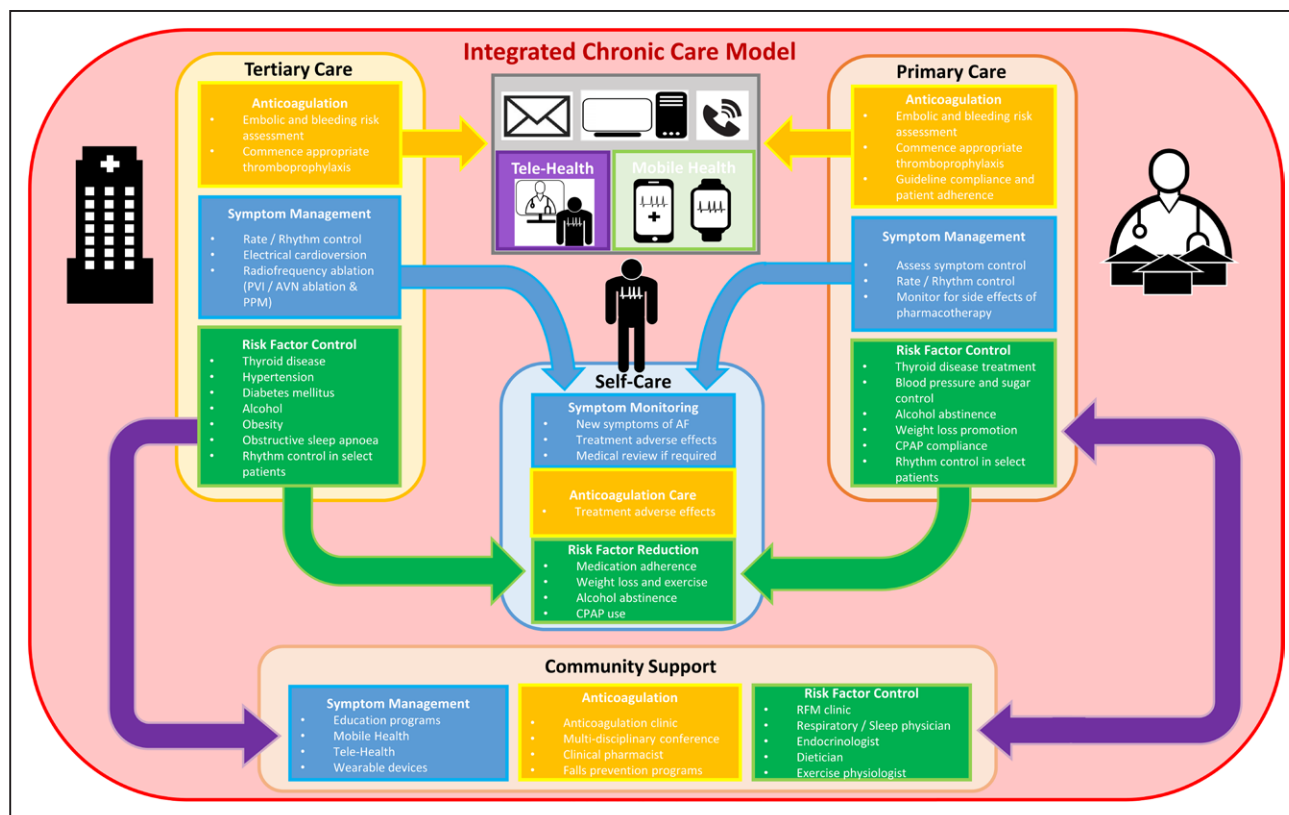


Figure 6. Atrial fibrillation (AF) integrated chronic care models.

Theoretical integrated care framework for management of an individual living with AF. The schema shows utilization of integrated care principles across different health care settings and providers, with special focus on anticoagulation, symptom management, and risk factor control. AVN indicates atrioventricular node; CPAP, continuous positive airway pressure; PPM, permanent pacemaker; PVI, pulmonary vein isolation; and RFM, risk factor modification.

well studied and shown promise in curtailing the looming epidemiological crisis of the disease.

FUTURE DIRECTIONS

Despite great advances in the understanding of AF as an evolving disease process and its management, further work is required. Information on optimal management of AF in several special populations with AF, including those with end-stage renal disease, cancer, cognitive impairment, and frailty, is lacking and requires further study. Additionally, given the recent positive evidence for rhythm control strategies in select AF populations, further evaluation of its mechanistic benefits and utility in real-world practice is needed. Although there has been an emerging body of evidence showing benefit of the components of integrated care models including multidisciplinary team care, nurse-led AF clinics, and the use of telemedicine, the challenge remains in the unification and real-world application of such systems.

CONCLUSIONS

The rising incidence of AF represents a looming public health disaster, with the true burden and complexity of

disease underestimated in clinical studies. In AF populations with available evidence, management has been shown to be suboptimal and fragmented, with identified gaps in anticoagulation, symptom control, and risk factor modification. The advent of integrated care models incorporating the community and health care systems, delivery and clinical information systems, and self-management support have shown promise in mitigating these pitfalls and represent a road map to best clinical practice for those afflicted by the disease and its complications.

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