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WHITE PAPER

Research Priorities for Atrial Fibrillation in Australia: A Statement From the Australian Cardiovascular Alliance Clinical Arrhythmia Theme

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Atrial fibrillation (AF) is highly prevalent in the Australian community, ranking amongst the highest globally. The consequences of AF are significant. Stroke, dementia and heart failure risk are increased substantially, hospitalisations are amongst the highest for all cardiovascular causes, and Australians living with AF suffer from substantial symptoms that impact quality of life. Australian research has made a significant impact at the global level in advancing the care of patients living with AF. However, new strategies are required to reduce the growing incidence of AF and its associated healthcare demand. The Australian Cardiovascular Alliance (ACvA) has led the development of an arrhythmia clinical theme with the objective of tackling major research priorities to achieve a reduction in AF burden across Australia. In this summary, we highlight these research priorities with particular focus on the strengths of Australian research and the strategies needed to move forward in reducing incident AF and improving outcomes for those who live with this chronic condition.

Keywords Atrial fibrillation • Mechanisms • Electrophysiology • Catheter ablation • Prevention • Genetics

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Background

The prevalence of atrial fibrillation (AF) amongst Australians is estimated to range from 1.4% to 5% [1–3] ranking 5th highest for AF globally [4]. Figure 1 shows the prevalence and disease burden of AF when compared to the USA, Europe and China [5]. These figures are likely an underestimate given the likelihood of AF going undetected in the absence of frequent monitoring. It is projected that over 600,000 individuals will be diagnosed with AF in Australia by 2034 [1].

Atrial fibrillation leads to a 2.4-fold increased risk of stroke, five-fold increased risk of heart failure, and two-fold increased risk of cardiovascular-related death [6]. Over just two decades, AF-related hospital admissions increased rapidly to become the most common cause of cardiovascular hospitalisation across Australia [7]. The economic burden of AF on the Australian healthcare system amounted to approximately AUD$874 million between 2008–2009, equating to an annual cost of $5,200 per affected individual [7,8]. These substantial financial implications underscore the need for prevention and effective management.

There is a substantial impact of AF on Indigenous Australians, who are more likely to have untreated AF and suffer AF-related stroke [9], resulting in increased mortality and more serious health consequences, particularly in younger Indigenous Australians [10]. Antecedents for AF amongst Indigenous Australians include rheumatic heart disease, elevated cardiovascular risk factors (hypertension and diabetes), and comorbidities such as heart failure and myocardial infarction, many of which occur in a higher prevalence and contribute to an increased risk of AF in Indigenous communities [9,11].

Setting the Goal

We propose an ambitious goal of reducing both age-adjusted AF incidence and AF-related hospital admissions across Australia over the next 10 years. This goal would result in significant health benefits coupled with a substantial reduction in healthcare costs due to AF. To better manage and ultimately reduce the burden of AF, we propose a three-pillar approach: (i) enhanced primary prevention, (ii) earlier detection of AF and (iii) better management of patients with established AF.

Development of Research Priorities

In August 2023, the Australian Cardiovascular Alliance (ACvA) convened national experts to form an AF Clinical Theme Workshop, facilitated by Professor Jamie Vandenberg and chaired by Professor Prashanthan Sanders and Professor Jonathan Kalman. The aim of this Workshop was to highlight strategic research priorities to address the growing burden of AF across Australia. The Workshop identified key topic areas, with a particular focus on research strengths within Australia, which are summarised in this review.

Bench to Bedside

Animal Models of AF

Animal models have been critical in the evaluation of mechanisms contributing to the onset and maintenance of AF [12,13], the development of an arrhythmogenic substrate with comorbidities [14–17], and molecular differences

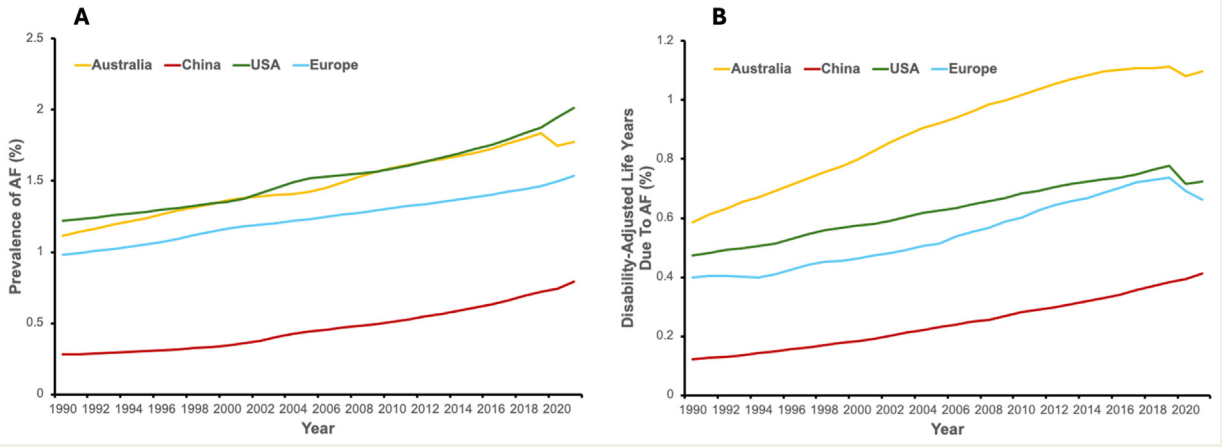

Figure 1 Comparison of A) the prevalence of atrial fibrillation (AF) and B) disability-adjusted life-years (DALY's) amongst Australians in comparison with populations in Europe, China and the United States. Data taken from the global burden of cardiovascular diseases study by Roth et al. [5].

between pathological and physiological atrial remodelling [18–20]. Animal models have also identified circulating biomarkers associated with AF [21] with potential to improve the prediction and diagnosis of AF in humans.

There are important knowledge gaps regarding the biological pathways that contribute to the atrial triggers and substrate, as well as mechanisms promoting atrial remodelling and thrombi leading to cardioembolic stroke. Revealing these pathways may enable the development of novel pharmacological therapies to treat AF and its consequences. Animal models will offer opportunity to assess the reversibility of the atrial substrate. Although atrial fibrosis had previously been considered irreversible [22], weight loss in an ovine model of obesity reduced atrial fibrosis and the propensity for AF [23]. Future work to define the reversibility of the atrial substrate in response to existing and novel therapies is a clear priority.

Animal models will be pivotal in understanding the mechanisms behind clinical observations such as differences in AF outcomes by sex [24], and the overlap between AF and other cardiac morbidities such as heart failure with preserved ejection fraction (HFpEF) [25]. Small and large animal models may reveal mechanistic pathways that enable targetted therapies for the treatment of AF in specific patient groups [26,27].

In Vitro Models for AF

Studies of human atrial tissue samples have been invaluable for understanding the underlying mechanisms of AF, although their availability is limited and typically confined to patients with significant comorbidities. Human-induced pluripotent stem cells can be utilised to develop a limitless source of human atrial cardiomyocytes for investigation (HiPSC-atrial CM) [28]. HiPSC-atrial CMs have been developed for high throughput electrophysiology, calcium handling and gene expression studies. A major potential advantage of HiPSC-atrial CM models is their suitability for high throughput drug screening, which could then be tested with *in vivo* animal models.

A recognised limitation of HiPSC-atrial CMs is the lack of complexity. Three dimensional engineered tissue models, incorporating a range of different cell types such as fibroblasts, endothelial cells, neurons and immune cells offer more realistic *in vitro* evaluation of complex microenvironments necessary for the study of arrhythmogenic processes such as fibrosis and inflammation. Other advantages of the engineered tissue approach include the potential to create larger tissues with adequate spatial scale to sustain re-entrant arrhythmias and the ability to recapitulate rotor activity. Looking forward, methods to incorporate pulmonary veins, or approximations of its structure and electrophysiology would be advantageous given the clearly defined role of these sources in the initiation of AF. Addressing these challenges will potentially permit improved matching of *in vitro* electrophysiological models to the AF seen in the clinic. There is also a need to consider the development of an *in vitro* model of atrial cardiomyopathy, incorporating stretch and mechanical load, to enable study of the underlying atrial disease that potentially contributes to AF development and associated consequences. Finally, the use of *in vitro* models to evaluate novel upstream therapies to treat the mechanisms of AF requires evaluation.

Research Themes for Primary and Secondary AF Prevention

Genetics

Single rare genetic variants that are sufficient to cause AF have been identified in families with AF and in early onset sporadic cases [29,30]. There is increasing knowledge about disease-causing rare variants. However, genetic testing yields a positive result in only a minority of cases. Further research is needed to find new AF disease genes, together with studies to elucidate the functional effects of variants and mechanisms responsible for atrial arrhythogenesis.

More frequently, AF occurs as a complex trait that involves varying contributions from age, comorbidities, lifestyle factors and genetic background. Hundreds of relevant common variants have been found using genome-wide association studies in large cohorts of AF patients and control subjects, with their cumulative effect demonstrated through derivation of polygenic risk scores (PRS) for AF (AF-PRS) [31].

To date, AF-PRS has so far provided only modest incremental predictive value over clinical risk scores, with the greatest potential value amongst younger individuals [32]. In a recent Australian study, higher AF-PRS was associated with a more advanced electrical substrate and greater AF recurrence after ablation procedures [33]. At present, genotyping is mainly undertaken in research settings and the role of AF-PRS for risk prediction and individual patient management should be assessed in prospective studies.

Pre-emptive genotyping may provide an opportunity for early detection of AF risk and early preventive strategies. Given the potential role of an underlying atrial cardiomyopathy in the development and progression of AF as well as associated events such as stroke and heart failure [34,35], there is a potential role for PRS to identify patients prior to AF onset. Ongoing refinement of AF-PRS and the derivation of new PRS for various parameters of atrial structure and function, may help to better identify individuals at risk of atrial cardiomyopathy and its complications. Background genetic variation can differ considerably with ethnicity. In this regard, it will be important to study AF genetic risk within the context of the ethnic diversity that exists across Australia, including Indigenous peoples [36].

Electrical Phenotyping

The pathophysiologic mechanisms that promote the development, maintenance and progression of AF can be broadly classified into ‘triggers’ and ‘substrate’. Triggers predominantly refer to electrical ectopic activity from the pulmonary

veins whilst the substrate for AF includes structural remodelling of the atrium characterised by fibrosis, fatty infiltration, and inflammation that can lead to conduction abnormalities promoting re-entry and the maintenance of AF. In humans, the atrial substrate can be assessed by electroanatomical mapping, in which regions of low voltage and fractionated electrograms may be quantified.

Electroanatomical mapping is an invasive procedure confined to the clinical electrophysiology labroratory. Non-invasive electrical biomarkers present an attractive proposition in the effort identify individuals at risk of AF and its progression, without the need for invasive procedures. An electrical biomarker would ideally provide additive information to that offered by existing clinical risk scores [37,38]. Several studies have demonstrated that features of the 12-lead electrocardiogram (ECG), including P-wave duration, amplitude and dispersion, provides potentially relevant information for the prediction of new-onset AF [39,40]. The utility of these parameters requires careful assessment in large cohorts of Australians.

The availability of machine learning has opened significant opportunities to explore associations between ECG features, and the risk of AF. Several studies have demonstrated that artificial intelligence (AI) models trained on ECGs can add to existing risk scores for the prediction of new-onset AF [41,42] and may hold important utility in the screening of AF [43]. The role of electrical biomarkers including significant input from machine learning, is likely to rapidly develop over the coming decade. Within Australia, there is a clear need to develop and validate models within a diverse sample of the Australian population. It is possible that models combining multiple raw data modalities including cardiac imaging may enhance risk prediction. Finally, a key question will be whether risk prediction can be followed by clinical actions, including early prevention, that reduce the development and progression of AF.

Atrial Imaging

Imaging of the left atrium (LA) provides valuable diagnostic and prognostic information [44]. Modalities including echocardiography, computed tomography (CT) and cardiac magnetic resonance imaging (CMR) enable quantification of LA size and function, as well as estimates of LA fibrosis potentially representing the underlying arrhythmogenic substrate [45,46]. Imaging may be used to assess LA remodelling in the presence of cardiovascular risk factors and comorbidities, as well as reverse remodelling in response to therapy.

Although there is a reasonable association between functional imaging parameters, such as LA strain, and measures of tissue structure such as LA fibrosis determined using CMR with late gadolinium enhancement (LGE) [47], a key question remains as to whether these parameters provide sufficient value to guide therapy. In a recent trial, LGE guided fibrosis ablation of persistent AF provided no significant benefit in AF recurrence over conventional catheter ablation alone [48]. The evaluation of novel imaging parameters, such as LA sphericity and mechanical dispersion should be considered, with particular attention to their clinical value in patients with AF. The ability of non-invasive imaging to contribute to quantification of an atrial cardiomyopathy is an obvious priority given the potential association between the extent of atrial disease and clinical outcomes. The refinement of existing techniques to quantify atrial fibrosis, coupled with the emergence of novel measures may improve the ability to non-invasively study the atrial substrate in response to therapy. Large-scale clinical trials are required to determine whether treatment of AF can be guided by non-invasive imaging.

Rhythm Control for AF

The past three decades have seen substantial developments in rhythm control of AF [49]. Catheter ablation has a class IA recommendation in clinical guidelines to reduce AF recurrence and symptoms amongst patients [50]. Recent developments has seen the accumulation of evidence in favour of early ablation amongst treatment-naïve patients [51], as well as the development of new energy sources such as pulsed field ablation (PFA) to achieve pulmonary vein isolation (PVI) [52]. In addition, Australian led research has been at the forefront of evaluating the additional benefit of ablation beyond the pulmonary veins in patients with persistent AF [53,54]. The absence of additional benefit with extensive ablation highlights the need for better understanding of the mechanisms of persistent AF [55].

Catheter ablation is favourable to anti-arrhythmic therapy, although there remains a high rate of recurrent AF suggestive of ongoing atrial disease despite PVI. This highlights several important research priorities; first, can long term maintenance of sinus rhythm be enhanced with aggressive reduction of the risk factors and targeting biological mechanisms that contribute to AF, either in addition or in comparison with catheter ablation. The important recent finding that delaying AF ablation by 1 year does not alter post-ablation outcomes [56], suggests there is a window of opportunity to implement such a strategy despite an increasing trend towards early ablation. Second, the selection of patients with AF that may be more amenable to catheter ablation will be an important priority to enable personalised therapy and reduce unnecessary procedures. Such a strategy may involve non-invasive phenotyping using a combination of electrical markers, genetics, imaging and multi-omic platforms. The long-term influence of catheter ablation on endpoints beyond AF recurrence, including patient-reported psychological outcomes, cogntition, and HFpEF should be further evaluated using existing strengths. Finally, the ongoing refinement of ablation technology, potentially including the development of novel catheter technology and ablation targets, will ensure Australian accessibility to world-class technology and expertise to improve outcomes.

Lifestyle Risk Factors and AF

There is a strong association between the presence of lifestyle-based, modifiable risk factors and the incidence, maintenance, and progression of AF [57]. The presence of these risk factors is associated with a more advanced arrhythmogenic substrate [58–61]. Australian-led randomised controlled trials of weight loss with aggressive risk factor reduction [62], exercise training [63] and alcohol abstinence [64] have demonstrated reduced AF recurrence and symptom burden amongst patients with symptomatic AF. The efficacy of weight loss and risk factor reduction is further supported in a longer-term observational studies in which >10% weight loss was associated with greater freedom from AF, reduced progression of AF, reduced AF symptom burden [65,66].

There are notable areas requiring further investigation of the effect of lifestyle intervention for the prevention and treatment of AF. The timing of intervention requires evaluation, particularly in considering whether pre-ablation intervention or referral to lifestyle intervention following catheter ablation can improve procedural and longer-term outcomes. In the era of new pharmacological strategies to manage risk factors such as obesity [67], the effect of these therapies on arrhythmia outcomes will be of particular interest. The extent to which lifestyle intervention can reverse the underlying atrial disease and consequent remodelling also requires further clarification. The high prevalence of AF in patients with HFpEF [25,68] also raises the possibility that lifestyle intervention may prove favourable in this specific cohort. The role of multidisciplinary teams in a structure of integrated care for the delivery of lifestyle intervention should be a clear priority. There is also demand for studies that define the effect of lifestyle intervention on outcomes beyond arrhythmia recurrence, including cognition, healthcare utilisation, stroke risk and longer term major cardiac events. Finally, the development of tailored, culturally-sensitive lifestyle interventions for Indigenous Australians living with AF should be prioritised.

Detecting and Managing AF in Indigenous Australians

Current management of AF in Indigenous people emphasises: (i) early detection and management, (ii) the importance of drug therapies especially oral anticoagulants, management of comorbidities like hypertension and diabetes, and lifestyle interventions such as exercise; and (iii) the need for improved health literacy and understanding about AF among the community.

Co-designed translational studies to enable and scale early detection and effective management of AF in Indigenous people is a key research priority. This will include:

1. Building Indigenous cardiovascular disease research capability through graduate educational programs and scholarships, early career pathways and culturally safe mentoring;
2. Co-creating knowledge with communities to embed best evidence into primary care including culturally safe health promotion, timely detection and evidence-based management of AF;
3. Co-creating pathways to effective, timely and culturally safe treatment for Indigenous patients within the wider healthcare system.
4. Prospective recruitment of Indigenous participants in AF research.

Research Translation

Primary Prevention of AF

To reduce the incidence of AF in Australia will demand a comprehensive and integrated approach. The development of enhanced risk scores for AF, potentially including polygenic risk scores, electrical or blood-based biomarkers, and novel indices from cardiac imaging, may enable targeted interventions for specific patients to reduce risk of incident AF. A focus on reducing the burden of modifiable risk factors such as hypertension, obesity, diabetes and physical inactivity amongst high risk individuals will contribute substantially to lowering incident AF [69]. Population-wide interventions, including public health campaigns promoting physical activity, hypertension treatment, healthy dietary habits, and smoking cessation, are also essential components of a preventive strategy.

The emergence of AI will likely enhance the capacity to identify individuals from the community who may then be referred to patient education, intensive risk factor reduction or upsteam therapy to slow or prevent AF onset. As new tools become available, large-scale primary prevention trials are required to quantify the efficacy of these approaches. This will require collective input from researchers and clinicians with a broad range of expertise, including primary care, incorpoprated into a national approach to provide effective translation to all Australians including those living in rural, remote and Indigenous communities.

Early Detection

Timely identification of AF is paramount to reduce the progression of AF and lower the development of complications, including stroke. Screening programs targeting high-risk populations and individuals with predisposing conditions may facilitate early intervention prior to further progression of the arrhythmogenic susbtrate. Advanced monitoring technologies and screening programs are pivotal components of early detection strategies although to date have yielded low benefit [70].

Population-based screening initiatives, particularly in high-risk groups, facilitate the identification of individuals with undiagnosed AF [71]. Although this has shown mixed results for stroke prevention [71,72], early identification of AF in

high-risk groups may provide opportunity for risk reduction and early therapy to reduce progression of AF, lower healthcare demands, and improve patient-reported outcomes. Although a range of technologies exist for the monitoring of heart rate and rhythm [43,73,74], a careful large-scale assessment of AF detection is warranted to establish the optimal methodology with consideration of sensitivity, specificity and cost-effectiveness. Furthermore, the extent of AF detected on screening may be an important parameter that requires incorporation into clinical decision-making.

Secondary Prevention

Australian-led research has significantly enhanced the care of patients with AF, including pivotal trials of catheter ablation in patients with persistent AF [53,54] and heart failure [75], as well as the establishment of risk factor modification as a class IA recommendation based on randomised trials of weight loss, alcohol abstinence and exercise intervention.

There are notable opportunities to further enhance the care of Australians living with AF. Given the rise in AF-related hospital admissions, strategies to reduce hospitalisation and readmissions require specific evaluation. Potential strategies include AF education programs, rapid access clinics outside of the emergency department, and programs incorporated into primary care. The timing of catheter ablation has generated significant discussion, with recent Australian evidence suggesting delayed intervention may not adversely effect outcomes [56]. Clinical trials are required to establish whether a delayed approach with aggressive risk factor intervention may be superior to early ablation. The development of novel therapies to manage AF risk factors including obesity, hypertension and type 2 diabetes, as well as reversing fibrosis and targeting the underlying atrial cardiomyopathy, raises new opportunities regarding AF secondary prevention that will require testing in clinical trials. In addition, the effect of specific risk factor reduction such as through continuous pulmonary airway pressure therapy for patients with obstructive sleep apnoea will fill an important knowledge gap. Finally, there are important sex-specific differences in the pathophysiology of AF [24] that may respond differently to treatment. We strongly advocate for research that ensures equity of both men and women in their cohort, as well as review of treatment efficacy for women living with AF [76,77].

Collaborative efforts between the patient, academia, industry, and healthcare providers foster a translational research continuum, aiming to swiftly transition scientific discoveries into tangible clinical applications. A multifaceted approach that combines cutting-edge technologies, rigorous clinical trials, and a deepening understanding of the pathophysiology of AF will make a substantial contribution to patient outcomes.

Patient Education and Empowerment

Empowering individuals with AF through comprehensive education is pivotal for enhancing self-management, treatment adherence, reduction in hospitalisation and overall quality of life [78,79]. Patient education initiatives should encompass a thorough understanding of AF, its symptoms, potential complications, and the importance of adherence to prescribed medications and lifestyle modification [80]. A patient-centred approach, involving shared decision-making, ensures that individuals actively participate in their care plans [81]. Raising awareness about the significance of routine monitoring, including regular heart rate checks and self-assessment of symptoms, empowers patients to play an active role in their healthcare journey. Support groups and online communities can serve as valuable platforms for patients to share experiences, seek advice, and gain emotional support. Integration of digital health tools, such as mobile applications and wearable devices, can facilitate real-time monitoring and engagement.

Health System Integration

Effective management of AF necessitates seamless integration within healthcare systems to ensure comprehensive and coordinated care. Integration begins with the establishment of standardised protocols for AF diagnosis, treatment, and follow-up across diverse healthcare settings. Electronic health records (EHRs) play a key role in facilitating communication and information exchange between primary care providers, cardiologists, and other healthcare professionals involved in AF care. Interdisciplinary collaboration is essential, emphasising the formation of specialised AF care teams that leverage the expertise of cardiologists, electrophysiologists, nurses, and pharmacists [82]. Integration extends beyond hospital settings to primary care, emphasising the importance of ongoing patient education, risk factor management, and consistent monitoring in community-based settings. Telemedicine initiatives and remote monitoring technologies further enhance healthcare systems integration by providing real-time data and facilitating timely interventions, as well as access to care for those in remote or rural settings. Additionally, fostering partnerships between healthcare providers, policymakers, and payers is critical to address systemic barriers and promote the implementation of evidence-based practices. Embracing a comprehensive, integrated approach, healthcare systems can optimise the delivery of care for individuals with AF, enhancing both clinical outcomes and the overall efficiency of the healthcare system.

Capacity Building

Addressing the burden of AF across Australia would benefit from an increase in national capacity at several steps of the research pipeline. The ability to conduct large-scale clinical trials across multiple states within Australia would provide a significant foundation to address many of the priorities outlined in this summary. A coordinated national registry and biobank would provide the basis for prospective studies, ideally with consideration of enabling capacity to embed clinical trials [83]. A coordinated, national data linkage

platform with a specific focus on AF will improve research outcomes that influence patient care, provide the basis for assessment of national implementation and enable quantification of health and economic impact [84]. This will also be an important step towards ensuring high-quality data relating to trends in the incidence, prevalence and consequences of AF, which will be required to evaluate national strategies to reduce these outcomes. To further future-proof the capacity of AF research across Australia, a focus on developing and retaining the brightest early and mid-career researchers should be prioritised through diversification of career pathways and ensuring funding models that promote retention [85].

Public Awareness and Advocacy

Public awareness and advocacy play pivotal roles in addressing the multifaceted challenges posed by AF. Raising awareness about AF within the broader community is essential for early detection, prompt treatment, and prevention of complications [86]. Educational campaigns should focus on disseminating information about AF symptoms, risk factors, and the importance of seeking medical attention for timely diagnosis and intervention. Emphasizing the link between AF and serious complications, such as stroke, can underscore the significance of proactive management. We aim to engage in advocacy efforts involving collaborating with patient advocacy groups, healthcare organisations, and policymakers to drive policy changes that support increased access to AF screenings, improved patient care, and enhanced research funding.

Summary

Atrial fibrillation imposes a significant disease burden on Australians. These research priorities, aimed at the enhancement of primary prevention, early detection and secondary prevention draw on existing strengths across Australia and alongside international partners to deliver a roadmap of research to reduce the incidence of AF and its associated healthcare burden (Figure 2). To achieve our goals will require a multidisciplinary approach across the breadth of Australia. A key research priority will be to ensure these research priorities provide benefit for all Australians

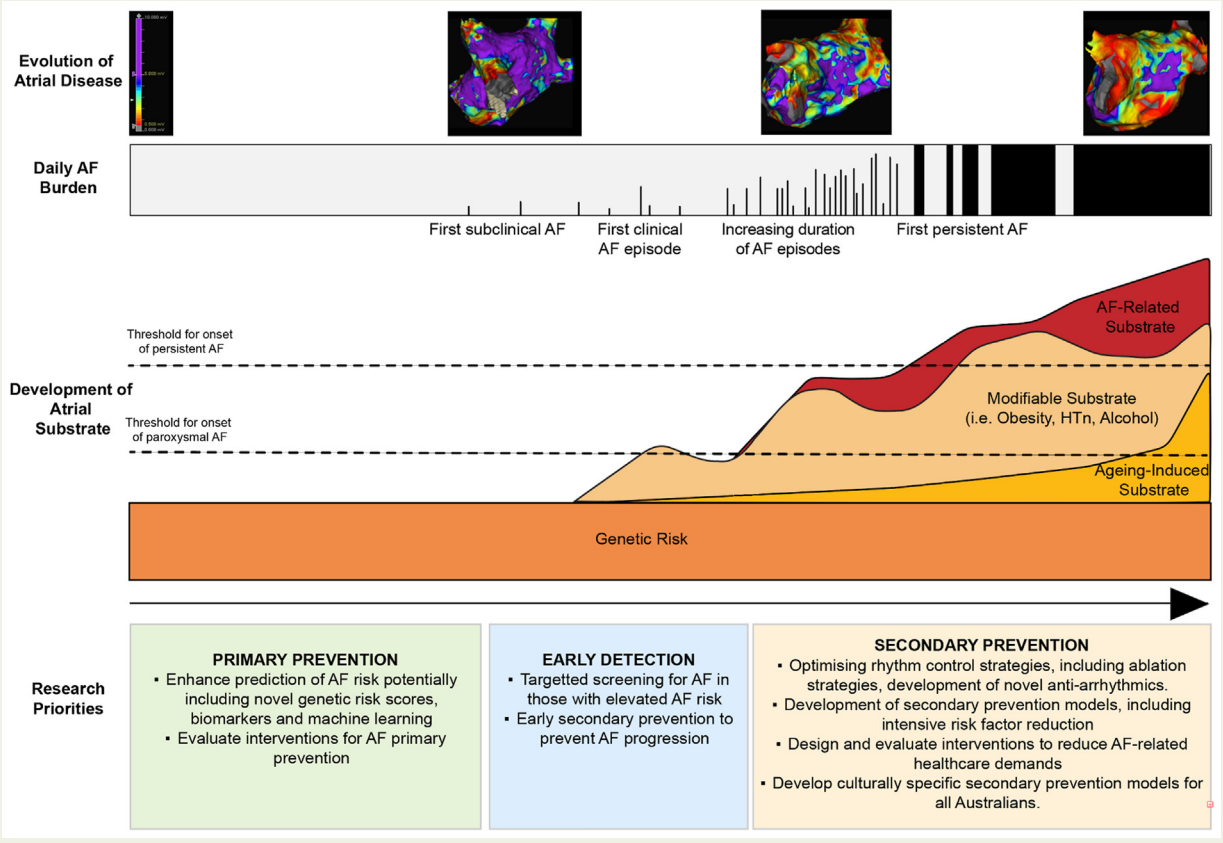

Figure 2 Atrial fibrillation (AF) is a progressive disease involving an evolving atrial substrate in the presence of ageing, modifiable risk factors and underlying genetic risk. To reduce the burden of AF, research priorities have been proposed across all stages of AF from primary prevention through to early detection and enhanced secondary prevention. Abbreviation: HTn, hypertension.

including those within our remote, rural and Indigenous communities.

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Conflicts of Interest

JK reports that The Royal Melbourne Hospital has received on his behalf research and fellowship support from Medtronic, Biosense Webster, Abbott Medical, Boston Scientific, and Zoll Medical. PS reports that The University of Adelaide has received on his behalf, lecture and/or consulting fees from Medtronic, Abbott Medical and Boston Scientific, and research funding from Medtronic, Abbott Medical, Boston Scientific, and Microport CRM.

Appendices

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2024.08.008

References

[1] Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, Stewart S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. Med J Aust. 2015;202:32–5.
[2] Sturm JW, Davis SM, O'Sullivan JG, Vedadhaghi ME, Donnan GA. The Avoid Stroke as Soon as Possible (ASAP) general practice stroke audit. Med J Aust. 2002;176:312–6.
[3] Diouf I, Magliano DJ, Carrington MJ, Stewart S, Shaw JE. Prevalence, incidence, risk factors and treatment of atrial fibrillation in Australia: The Australian Diabetes, Obesity and Lifestyle (AusDiab) longitudinal, population cohort study. Int J Cardiol. 2016;205:127–32.
[4] Li H, Song X, Liang Y, Bai X, Liu-Huo WS, Tang C, et al. Global, regional, and national burden of disease study of atrial fibrillation/flutter, 1990–2019: Results from a global burden of disease study, 2019. BMC Public Health. 2022;22:2015.
[5] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76:2982–3021.
[6] Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016;354:i4482.
[7] Gallagher C, Hendriks JM, Giles L, Karnon J, Pham C, Elliott AD, et al. Increasing trends in hospitalisations due to atrial fibrillation in Australia from 1993 to 2013. Heart. 2019;105:1358–63.
[8] PricewaterhouseCoopers. The Economic Costs of Atrial Fibrillation in Australia [Internet]. Pricewaterhouse Coopers (Australia) for the National Stroke Foundation. Available at: https://www.hps.com.au/wp-content/uploads/2016/10/Economic-costs-of-atrial-fibrillation-in-Australia.pdf. [accessed 8.8.24].
[9] Nedkoff L, Kelty EA, Hung J, Thompson SC, Katzenellenbogen JM. Differences in stroke risk and cardiovascular mortality for Aboriginal and other Australian patients with atrial fibrillation. Med J Aust. 2020;212:215–21.
[10] Katzenellenbogen JM, Teng TH, Lopez D, Hung J, Knuiman MW, Sanfilippo FM, et al. Initial hospitalisation for atrial fibrillation in Aboriginal and non-Aboriginal populations in Western Australia. Heart. 2015;101:712–9.
[11] Clarke N, Gallagher C, Pitman BM, Tu SJ, Huang S, Hanna-Rivero N, et al. Atrial fibrillation in remote Indigenous and non-Indigenous individuals hospitalised in central Australia. Heart Lung Circ. 2021;30:1174–83.
[12] Heijman J, Voigt N, Nattel S, Dobrev D. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. Circ Res. 2014;114:1483–99.
[13] Lau DH, Linz D, Schotten U, Mahajan R, Sanders P, Kalman JM. Pathophysiology of paroxysmal and persistent atrial fibrillation: rotors, foci and fibrosis. Heart Lung Circ. 2017;26:887–93.
[14] Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999;100:87–95.
[15] Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Worthington M, Rajendram A, et al. Short-term hypertension is associated with the development of atrial fibrillation substrate: a study in an ovine hypertensive model. Heart Rhythm. 2010;7:396–404.
[16] Mahajan R, Lau DH, Brooks AG, Shipp NJ, Manavis J, Wood JP, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. J Am Coll Cardiol. 2015;66:1–11.
[17] Iwasaki Y-K, Kato T, Xiong F, Shi Y-F, Naud P, Maguy A, et al. Atrial fibrillation promotion with long-term repetitive obstructive sleep apnea in a rat model. J Am Coll Cardiol. 2014;64:2013–23.
[18] Sapra G, Tham YK, Cemerlang N, Matsumoto A, Kiriazis H, Bernardo BC, et al. The small-molecule BGP-15 protects against heart failure and atrial fibrillation in mice. Nat Commun. 2014;5:5705.
[19] Chen YC, Voskoboinik A, Gerche A, Marwick TH, McMullen JR. Prevention of pathological atrial remodeling and atrial fibrillation: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021;77:2846–64.
[20] Chen YC, Wijekoon S, Matsumoto A, Luo J, Kiriazis H, Masterman E, et al. Distinct functional and molecular profiles between physiological and pathological atrial enlargement offer potential new therapeutic opportunities for atrial fibrillation. Clin Sci (Lond). 2024;138:941–62.
[21] Tham YK, Jayawardana KS, Alshehry ZH, Giles C, Huynh K, Smith AAT, et al. Novel lipid species for detecting and predicting atrial fibrillation in patients with Type 2 Diabetes. Diabetes. 2021;70:255–61.
[22] Shinagawa K, Shi Y-F, Tardif J-C, Leung T-K, Nattel S. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. Circulation. 2002;105:2672–8.
[23] Mahajan R, Lau DH, Brooks AG, Shipp NJ, Wood JPM, Manavis J, et al. Atrial fibrillation and obesity: Reverse remodeling of atrial substrate with weight reduction. JACC Clin Electrophysiol. 2021;7:630–41.
[24] Wong GR, Nalliah CJ, Lee G, Voskoboinik A, Chieng D, Prabhu S, et al. Sex-related differences in atrial remodeling in patients with atrial fibrillation: Relationship to ablation outcomes. Circ Arrhythm Electrophysiol. 2022;15:e009925.
[25] Ariyaratnam JP, Elliott AD, Mishima RS, Kadhim K, McNamee O, Kuklik P, et al. Identification of subclinical heart failure with preserved ejection fraction in patients with symptomatic atrial fibrillation. JACC Heart Fail. 2023;11:1626–38.
[26] Tong D, Schiattarella GG, Jiang N, Daou D, Luo Y, Link MS, et al. Impaired AMP-activated protein kinase signaling in heart failure with preserved ejection fraction–associated atrial fibrillation. Circulation. 2022;146:73–6.
[27] Sharp TE 3rd, Scarborough AL, Li Z, Polhemus DJ, Hidalgo HA, Schumacher JD, et al. Novel Göttingen miniswine model of heart failure with preserved ejection fraction integrating multiple comorbidities. JACC Basic Transl Sci. 2021;6:154–70.
[28] Thorpe J, Perry MD, Contreras O, Hurley E, Parker G, Harvey RP, et al. Development of a robust induced pluripotent stem cell atrial cardiomyocyte differentiation protocol to model atrial arrhythmia. Stem Cell Res Ther. 2023;14:183.
[29] Fatkin D, Santiago CF, Huttner IG, Lubitz SA, Ellinor PT. Genetics of atrial fibrillation: State of the Art in 2017. Heart Lung Circ. 2017;26:894–901.
[30] Kany S, Jurgens SJ, Rämö JT, Christophersen IE, Rienstra M, Chung MK, et al. Genetic testing in early-onset atrial fibrillation. Eur Heart J. 2024. Jul 19. https://doi.org/10.1093/eurheartj/ehae298.
[31] Roselli C, Rienstra M, Ellinor PT. Genetics of atrial fibrillation in 2020: GWAS, genome sequencing, polygenic risk, and beyond. Circ Res. 2020;127:21–33.
[32] Khurshid S, Mars N, Haggerty CM, Huang Q, Weng LC, Hartzel DN, et al. Predictive accuracy of a clinical and genetic risk model for atrial fibrillation. Circ Genom Precis Med. 2021;14:e003355.
[33] Al-Kaisey A, Wong GR, Young P, Chieng D, Hawson J, Anderson R, et al. Polygenic risk scores are associated with atrial electrophysiologic

substrate abnormalities and outcomes after atrial fibrillation catheter ablation. Heart Rhythm. 2023;20:1188–94.
[34] Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace. 2016;18:1455–90.
[35] Kessler Iglesias C, Pouliopoulos J, Thomas L, Hayward CS, Jabbour A, Fatkin D. Atrial cardiomyopathy: Current and future imaging methods for assessment of atrial structure and function. Front Cardiovasc Med. 2023;10:1099625.
[36] Reis ALM, Rapadas M, Hammond JM, Gamaarachchi H, Stevanovski I, Ayuputeri Kumaheri M, et al. The landscape of genomic structural variation in Indigenous Australians. Nature. 2023;624:602–10.
[37] Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc. 2013;2:e000102.
[38] Segan L, Canovas R, Nanayakkara S, Chieng D, Prabhu S, Voskoboinik A, et al. New-onset atrial fibrillation prediction: the HARMS2-AF risk score. Eur Heart J. 2023;44:3443–52.
[39] Conte G, Luca A, Yazdani S, Caputo ML, Regoli F, Moccetti T, et al. Usefulness of P-wave duration and morphologic variability to identify patients prone to paroxysmal atrial fibrillation. Am J Cardiol. 2017;119:275–9.
[40] Nishimura T, Senoo K, Makino M, Munakata J, Tomura N, Shimoo S, et al. Prediction model for the new onset of atrial fibrillation combining features of 24-hour Holter electrocardiogram with 12-lead electrocardiogram. Int J Cardiol Heart Vasc. 2023;47:101245.
[41] Raghunath S, Pfeifer JM, Ulloa-Cerna AE, Nemani A, Carbonati T, Jing L, et al. Deep neural networks can predict new-onset atrial fibrillation from the 12-lead ecg and help identify those at risk of atrial fibrillation-related stroke. Circulation. 2021;143:1287–98.
[42] Khurshid S, Friedman S, Reeder C, Di Achille P, Diamant N, Singh P, et al. ECG-based deep learning and clinical risk factors to predict atrial fibrillation. Circulation. 2022;145:122–33.
[43] Noseworthy PA, Attia ZI, Behnken EM, Giblon RE, Bews KA, Liu S, et al. Artificial intelligence-guided screening for atrial fibrillation using electrocardiogram during sinus rhythm: a prospective non-randomised interventional trial. Lancet. 2022;400:1206–12.
[44] Thomas L, Abhayaratna WP. Left atrial reverse remodeling: mechanisms, evaluation, and clinical significance. JACC Cardiovasc Imaging. 2017;10:65–77.
[45] Ferkh A, Clark A, Thomas L. Left atrial phasic function: physiology, clinical assessment and prognostic value. Heart. 2023;109:1661–9.
[46] Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009;119:1758–67.
[47] Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circ Cardiovasc Imaging. 2010;3:231–9.
[48] Marrouche NF, Wazni O, McGann C, Greene T, Dean JM, Dagher L, et al. Effect of MRI-guided fibrosis ablation vs conventional catheter ablation on atrial arrhythmia recurrence in patients with persistent atrial fibrillation: The DECAAF II randomized clinical trial. JAMA. 2022;327:2296–305.
[49] Parameswaran R, Al-Kaisey AM, Kalman JM. Catheter ablation for atrial fibrillation: current indications and evolving technologies. Nat Rev Cardiol. 2021;18:210–25.
[50] Kistler PM, Sanders P, Amarena JV, Bain CR, Chia KM, Choo WK, et al. 2023 Cardiac Society of Australia and New Zealand Expert position statement on catheter and surgical ablation for atrial fibrillation. Heart Lung Circ. 2024;33:828–81.
[51] Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. N Engl J Med. 2021;384:305–15.
[52] Verma A, Haines DE, Boersma LV, Sood N, Natale A, Marchlinski FE, et al. Pulsed field ablation for the treatment of atrial fibrillation: PULSED AF Pivotal Trial. Circulation. 2023;147:1422–32.
[53] Kistler PM, Chieng D, Sugumar H, Ling L-H, Segan L, Azzopardi S, et al. Effect of Catheter Ablation Using pulmonary vein isolation with vs without posterior left atrial wall isolation on atrial arrhythmia recurrence in patients with persistent atrial fibrillation: The CAPLA Randomized Clinical Trial. JAMA. 2023;329:127–35.
[54] Verma A, Jiang C-y, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372:1812–22.
[55] Meng S, Al-Kaisey AM, Parameswaran R, Sunderland N, Budgett DM, Kistler PM, et al. Pulmonary veins function as echo chambers in persistent atrial fibrillation: Circuitous re-entry generates outgoing wavefronts. JACC Clin Electrophysiol. 2024;10:1313–25.
[56] Kalman JM, Al-Kaisey AM, Parameswaran R, Hawson J, Anderson RD, Lim M, et al. Impact of early vs. delayed atrial fibrillation catheter ablation on atrial arrhythmia recurrences. Eur Heart J. 2023;44:2447–54.
[57] Elliott AD, Middeldorp ME, Van Gelder IC, Albert CM, Sanders P. Epidemiology and modifiable risk factors for atrial fibrillation. Nat Rev Cardiol. 2023;20:404–17.
[58] Mahajan R, Nelson A, Pathak RK, Middeldorp ME, Wong CX, Twomey DJ, et al. Electroanatomical remodeling of the atria in obesity: Impact of adjacent epicardial fat. JACC Clin Electrophysiol. 2018;4:1529–40.
[59] Voskoboinik A, Wong G, Lee G, Nalliah C, Hawson J, Prabhu S, et al. Moderate alcohol consumption is associated with atrial electrical and structural changes: Insights from high-density left atrial electroanatomic mapping. Heart Rhythm. 2019;16:251–9.
[60] Nalliah CJ, Wong GR, Lee G, Voskoboinik A, Kee K, Goldin J, et al. Sleep apnoea has a dose-dependent effect on atrial remodelling in paroxysmal but not persistent atrial fibrillation: a high-density mapping study. Europace. 2021;23:691–700.
[61] Ariyaratnam JP, Elliott AD, Mishima RS, Kadhim K, Emami M, Fitzgerald JL, et al. Structural, Functional, and Electrical Remodeling of the Atria With Reduced Cardiorespiratory Fitness: Implications for AF. JACC Clin Electrophysiol. 2024;10:1608–19.
[62] Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013;310:2050–60.
[63] Elliott AD, Verdicchio CV, Mahajan R, Middeldorp ME, Gallagher C, Mishima RS, et al. An Exercise and Physical Activity Program in Patients With Atrial Fibrillation: The ACTIVE-AF Randomized Controlled Trial. JACC Clin Electrophysiol. 2023;9:455–65.
[64] Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, et al. Alcohol abstinence in drinkers with atrial fibrillation. N Engl J Med. 2020;382:20–8.
[65] Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-Term Effect of Goal Directed Weight Management in an Atrial Fibrillation Cohort: A Long-term Follow-Up StudY (LEGACY Study). J Am Coll Cardiol. 2015;65:2159–69.
[66] Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, et al. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. Europace. 2018;20:1929–35.
[67] Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389:2221–32.
[68] Sugumar H, Nanayakkara S, Vizi D, Wright L, Chieng D, Leet A, et al. A prospective STudy using invAsive haemodynamic measurements foLLowing catheter ablation for AF and early HFpEF: STALL AF-HFpEF. Eur J Heart Fail. 2021;23:785–96.
[69] Elliott AD, Benjamin EJ, Middeldorp ME. Prevention of atrial fibrillation: a call to action. Eur Heart J. 2023;44:4994–6.
[70] Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. Thromb Haemost. 2013;110:213–22.
[71] Svendsen JH, Diederichsen SZ, Hojberg S, Krieger DW, Graff C, Kronborg C, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): A randomised controlled trial. Lancet. 2021;398:1507–16.
[72] Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): A multicentre, parallel group, unmasked, randomised controlled trial. Lancet. 2021;398:1498–506.
[73] Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. N Engl J Med. 2019;381:1909–17.
[74] Linz D, Gawalko M, Betz K, Hendriks JM, Lip GYH, Vinter N, et al. Atrial fibrillation: epidemiology, screening and digital health. Lancet Reg Health Eur. 2024;37:100786.

[75] Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, et al. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study. J Am Coll Cardiol. 2017;70:1949–61.
[76] Verdicchio CV, Mahajan R, Middeldorp ME, Gallagher C, Mishima RS, Lau DH, et al. Influence of sex on efficacy of exercise training for patients with symptomatic atrial fibrillation: Insights from the ACTIVE-AF randomised controlled trial. Eur J Prevent Cardiol. 2023. zwad242.
[77] Noubiap JJ, Pathak RK, Thomas G, Elliott AD, Sanders P, Middeldorp ME. Sex differences in outcomes of an intensive risk factor modification program in patients with atrial fibrillation. Circ Arrhythm Electrophysiol. 2024;17:e012534.
[78] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.
[79] Potpara TS, Pison L, Larsen TB, Estner H, Madrid A, Blomstrom-Lundqvist C, et al. How are patients with atrial fibrillation approached and informed about their risk profile and available therapies in Europe? Results of the European Heart Rhythm Association Survey. Europace. 2015;17:468–72.
[80] Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: A long-term follow-up study (LEGACY). J Am Coll Cardiol. 2015;65:2159–69.
[81] Seaburg L, Hess EP, Coylewright M, Ting HH, McLeod CJ, Montori VM. Shared decision making in atrial fibrillation: where we are and where we should be going. Circulation. 2014;129:704–10.
[82] Hendriks JM, de Wit R, Crijns HJ, Vrijhoef HJ, Prins MH, Pisters R, et al. 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 fibrillation. Eur Heart J. 2012;33:2692–9.
[83] Ahern S, Gabbe BJ, Green S, Hodgson CL, Wood EM, Zalcberg Oam JR, et al. Realising the potential: Leveraging clinical quality registries for real world clinical research. Med J Aust. 2022;216:273–7.
[84] Paige E, Doyle K, Jorm L, Banks E, Hsu M-P, Nedkoff L, et al. A versatile big data health system for Australia: Driving improvements in cardiovascular health. Heart Lung Circ. 2021;30:1467–76.
[85] Climie RE, Wu JHY, Calkin AC, Chapman N, Inglis SC, Mirabito Colafella KM, et al. Lack of Strategic funding and long-term job security threaten to have profound effects on cardiovascular researcher retention in Australia. Heart Lung Circ. 2020;29:1588–95.
[86] Calvert M, Brundage M, Jacobsen PB, Schunemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: Implications for clinical trials and practice. Health Qual Life Outcomes. 2013;11:184.