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Atrial fibrillation: the current epidemic

Carlos A Morillo[1,2], Amitava Banerjee[3], Pablo Perel[4,5], David Wood[5,6], Xavier Jouven[7,8]

[1]*Department of Cardiac Sciences, Division of Cardiology, Libin Cardiovascular Institute, University of Calgary, Calgary, AB, Canada*
[2]*Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, ON, Canada*
[3]*Farr Institute of Health Informatics Research, University College of London, London, UK*
[4]*Centre for Global NCDs, London School of Hygiene & Tropical Medicine, London, UK*
[5]*World Heart Federation, Geneva, Switzerland*
[6]*International Centre for Circulatory Health, Imperial College London, London, UK*
[7]*Department of Cardiology, European Georges-Pompidou Hospital, Paris, France*
[8]*Paris Cardiovascular Research Center, Paris Descartes University, Inserm U970 (PARCC), Paris, France*

Abstract

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in clinical practice. The consequences of AF have been clearly established in multiple large observational cohort studies and include increased stroke and systemic embolism rates if no oral anticoagulation is prescribed, with increased morbidity and mortality. With the worldwide aging of the population characterized by a large influx of "baby boomers" with or without risk factors for developing AF, an epidemic is forecasted within the next 10 to 20 years. Although not all studies support this evidence, it is clear that AF is on the rise and a significant amount of health resources are invested in detecting and managing AF. This review focuses on the worldwide burden of AF and reviews global health strategies focused on improving detection, prevention and risk stratification of AF, recently recommended by the World Heart Federation.

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1 Introduction

As the population ages globally, atrial fibrillation (AF) is predicted to affect 6–12 million people in the USA by 2050 and 17.9 million in Europe by 2060.[1–3] AF utilizes significant health resources globally,[4] and constitutes a public health challenge with high comorbidity,[5] and increased mortality risk.[6] The reasons for the increase in the prevalence of AF remain elusive[7,8] and are related to multiple factors including; enhanced detection, increased incidence, and greater survival after onset of AF.[9–11] The purpose of this review is to assess the evidence related with the increased overall prevalence of AF and to propose a global strategy focused on enhanced detection and multidisciplinary management of AF envisioned by the World Heart Federation.[1,2,7–12]

Correspondence to: Carlos A Morillo, MD, Department of Cardiac Sciences, Division of Cardiology, Libin Cardiovascular Institute, University of Calgary, Population Health Research Institute, McMaster University, Foothills Medical Centre, Room C823, 1403 29th Street NW, Calgary, AB T2N 2T9, Canada.
E-mails: carlos.morillo@ucalgary.ca, morillc@mcmaster.ca
Telephone: +1-403-944-2670 **Fax:** +1-403-944-2906
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2 AF global burden

AF is the most frequently encountered arrhythmia in clinically practice.[3] Between 1990 and 2013, although the global prevalence rate of AF decreased slightly, the overall number of AF cases increased (Table 1).[13] AF is associated with an increase in morbidity, as measured by disability-adjusted life years (DALYs). Estimates of prevalence of AF, and DALYs associated with AF, are likely to underestimate true burden due to the high prevalence of asymptomatic AF.[3] AF also leads to increased health care resource utilization and may have a significant impact on global health budgets.[14–17] Several long-term cohorts have clearly established that several clinical outcomes are increased in patients with AF.[18] Among other clinical outcomes, AF is associated with increased risk of stroke and is found in one third of all ischemic strokes.[19]

AF burden has regional variations, with high-income countries experiencing a higher prevalence, incidence, DALYs and mortality associated with AF than low-middle

income countries (LMIC).[3] However, estimates of the extent of this difference should be interpreted with caution, as the lower rates of AF documented in developing countries may be related to under reporting, limited access to health care services and geographical disparity in published data.[3,20]

Table 1. Global burden of AF in 1990 and 2013, data from Global Burden of Disease Study 2013.[13]

Global Prevalence	*Cases (All ages)		Rate per 100,000 (Age-standardized)	
Year	Mean	95% UI	Mean	95% UI
1990	6841147	(6602764, 7114686)	213.7	(205.9, 222.6)
2013	11178627	(10655102, 11683727)	191.3	(182.1, 200.1)
Global DALYs	***Cases (All ages)**		**Rate per 100,000 (Age-standardized)**	
Year	Mean	95% UI	Mean	95% UI
1990	854714	(693332, 1049075)	26.7	(21.7, 32.7)
2013	1888690	(1590032, 2224863)	32.5	(27.5, 38.2)

*Cases rounded to the nearest whole number. DALYs: disability-adjusted life years; UI: uncertainty interval.

Estimating the global burden of AF is challenging and few studies have systematically reviewed population-based AF studies (Figure 1). Chugh, *et al.*,[3] reviewed all population based AF studies between 1980 to 2010, from 21 global burden of disease regions. These investigators estimated global/regional prevalence, incidence, and morbidity and mortality related to AF. The estimated number of individuals with AF globally in 2010, was 33.5 million (20.9 million men and 12.6 million women) with significant regional variations and heterogeneity (Table 1). Mortality associated with AF was increased by 2-fold in both genders from 1990 to 2010 (Figures 2–4).[3]

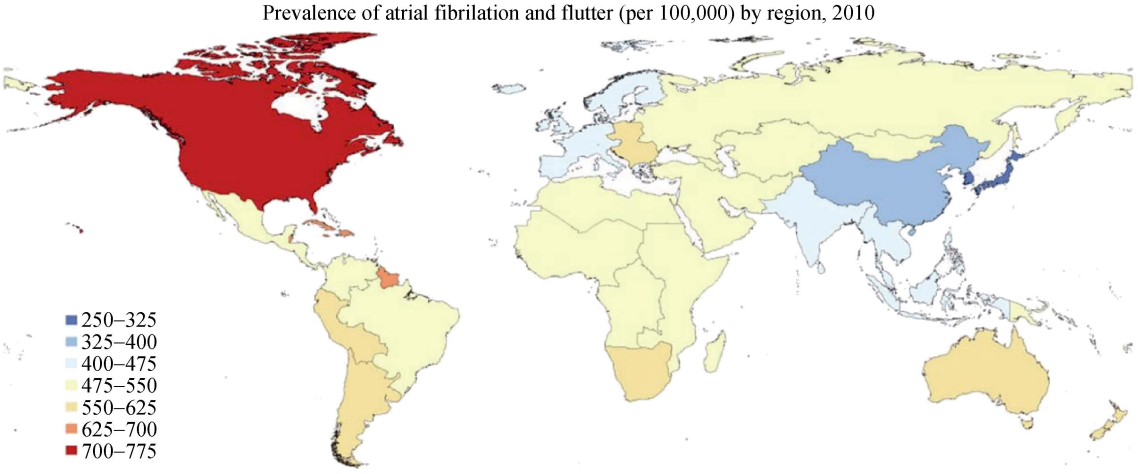


Figure 1. Global age-adjusted prevalence rates of AF (per 100,000 persons). Reproduced with permission from Chugh, *et al.*[3] AF: atrial fibrillation.

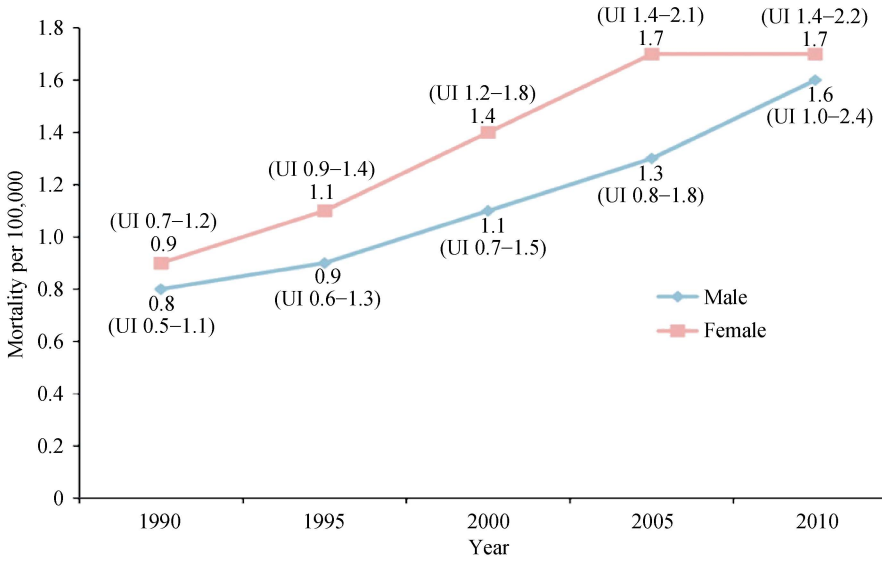
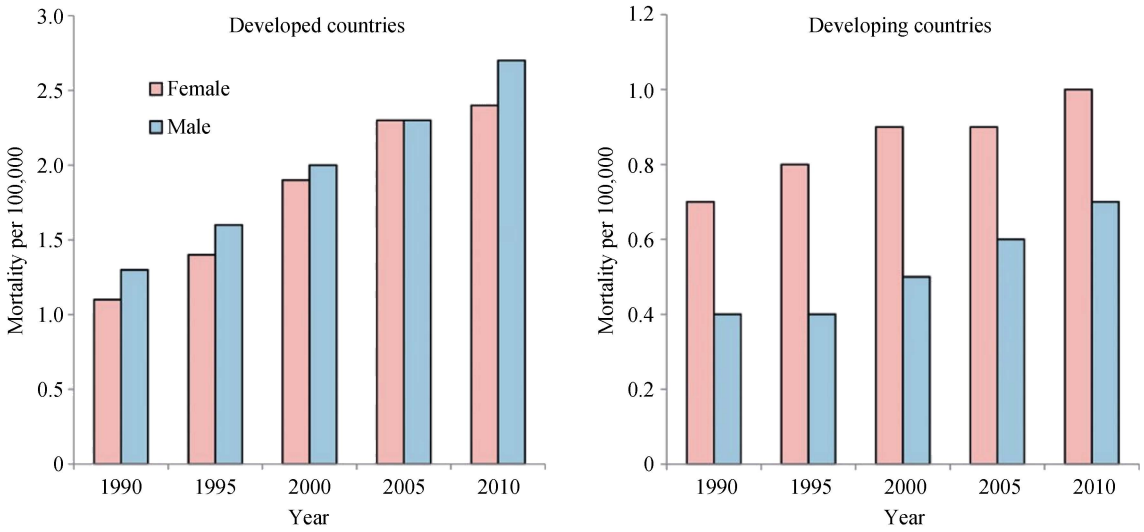


Figure 2. Mortality associated with AF: 1990–2010 (per 100,000 persons). Reproduced with permission from Chugh, *et al.*[3] AF: atrial fibrillation; UI: uncertainty interval.



F**igure 3. Mortality associated with AF by gender and region (developed *vs*. developing).** Reproduced with permission from Chugh, *et al*.[3] AF: atrial fibrillation.

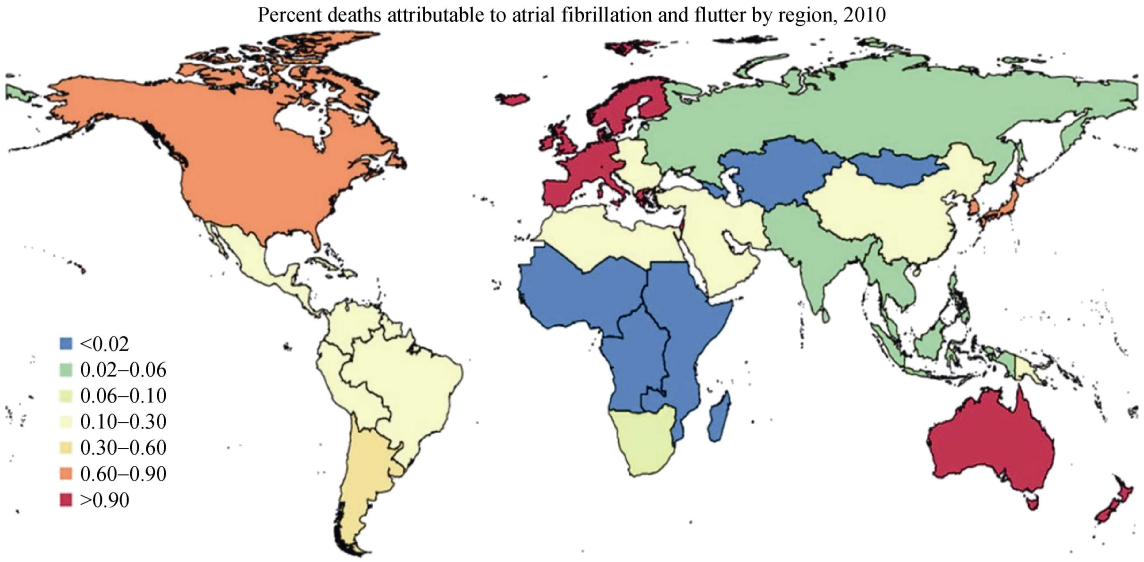


Figure 4. Global mortality associated with AF in 2010. Colors represent percentages. Reproduced with permission from Chugh, *et al*.[3] AF: atrial fibrillation.

Furthermore, in all countries regardless of development, a substantial proportion of AF cases are subclinical,[21] limiting the ability to appropriately identify and detect AF without advanced medical technology. Recent data from the ASSERT II trial suggests that the prevalence of subclinical AF > 5 min in subjects over 65 years with either a $CHA_2DS_2VASc \geq 2$, sleep apnoea or body mass index (BMI) > 30 kg/m^2 with no evidence of clinical AF is around 30%, indicating that subclinical AF may be detected in almost 1/3 of the population that otherwise has a low-intermediate risk of developing symptomatic AF and subsequent AF associated comorbidities.[22]

The occurrence of death and stroke in patients presenting to a hospital emergency department vary widely across geographical regions. The RELY-AF Registry recently reported the 1-year mortality and stroke rates in patients from 47 countries.[23] Marked and unexplained differences in mortality and stroke rates were observed. Over 15,000 individuals were enrolled and 1758 (11%) died within 1 year. Fewer deaths occurred among patients presenting to the emergency department with primary AF compared with those with secondary AF, 6% *vs*. 16% ($P < 0.0001$). Twice as many patients had died by 1 year in South America (17%) and Africa (20%) compared with North America, Western

Europe, and Australia (10%, $P < 0.0001$). Heart failure was the most common cause of death (30%); stroke caused deaths (8%), and 4% patients had had a stroke by 1 year; 3% of those with primary AF and 5% with secondary AF ($P < 0.0001$). The highest number of strokes occurred in patients in Africa (8%), China (7%), and Southeast Asia (7%) and the lowest occurred in India (< 1%). Only 3% of the patients in North America, Western Europe, and Australia had a stroke.

Patients with AF in LMIC tend to be a decade younger, are more likely to experience heart failure, and are less likely to be managed according to recommended AF guidelines (i.e., patients with AF in LMIC have significantly lower use of oral anticoagulants (OACs), and lower time in therapeutic range which may be related with limited access to health care systems.[24] Differences in AF burden among LMIC and high-income countries should also be interpreted in light of the risk factor profile of this condition. European ancestry has been identified as a risk factor for AF (compared to African or Asian ancestry),[25,26] the risk of AF mainly increases with age,[27] and is higher among those with CVD such as myocardial infarction and CVD risk factors that include hypertension, diabetes mellitus, obesity, smoking, and alcohol use.[25,28–34] Other non-conventional risk factor such as sleep apnoea have also been identified as potential markers of increased AF prevalence.[35] As these risk factors continue to increase in LMIC, likely will the burden of morbidity and mortality from AF. This burden may be further compounded by the shortage of health care resources in many LMIC, as successful management of AF requires consistent and long-term interaction between the patient and health care system and clear public health policies addressed to controlling modifiable risk factors such as hypertension, obesity, etc.

3 Primary prevention

Primary prevention of AF, i.e., reducing the risk of first onset by targeting modifiable risk factors (Figure 1), is the ultimate goal. However, this approach is challenging due to significant knowledge gaps related with understanding the multiple mechanisms of AF. Some models such as CHARGE-AF have been developed to predict the risk of AF, and identify patients who may benefit from preventative interventions, based on age, race, height, weight, blood pressure, smoking, use of antihypertensive medication, diabetes, and history of myocardial infarction and heart failure.[36] However, this model has only been validated for populations in the United States and Western Europe.[36] There is some evidence of causality between BMI and AF

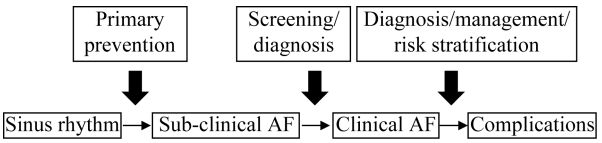


Figure 5. AF stages and proposed interventions. Modified from the WHF AF roadmap. AF: atrial fibrillation. WHF: world hemophilia federation.

and some intervention studies seem to indicate that outcomes after AF ablation may be better when modifiable risk factors are aggressively approached.[37] Although the benefits of interventions to manage risk factors such as weight, blood pressure, smoking and diabetes for health outcomes generally are well-established and relevant to populations globally, primary prevention trials for AF have yet to establish a role for interventions for specific risk factors (Figure 5). There is an urgent need for research that can inform primary prevention efforts for AF in more geographically and racially diverse populations, while also evaluating the effectiveness of preventative strategies aimed at reducing the risk of AF globally.[38]

4 Screening

Identifying individuals at risk of developing AF is important, however, there is stronger evidence that early detection and treatment of modifiable risk factors can reduce morbidity and mortality due to AF. Current guidelines advocate that "all patients who present with symptoms of AF—breathlessness, palpitations, syncope, chest discomfort or stroke—should have their pulse checked for irregularities as well as 12-lead ECG".[39] Prolonged ECG monitoring may be especially useful in patients with heart failure and post-stroke, in order to enhance detection and reduce health resource utilization and costs, depending on local resource and expertise. The role of routine screening of individuals at risk for asymptomatic AF, remains debatable and probably untenable as a population intervention. Nonetheless, a recent randomized trial comparing routine practice versus targeted population-based screening and opportunistic screening, opportunistic palpation (pulse-taking) of patients aged 65 and over, with or without known AF risk factors (with follow-up ECG for those with an irregular pulse) was found to be the cheapest and most effective method of screening for AF [opportunistic screening was found to detect similar numbers of new cases compared with systematic screening (1.64% *vs.* 1.62%, and requires fewer resources)].[40] One limitation of opportunistic pulse palpation is the high number of false positives that can result in unnecessary ECGs. A recent meta-analysis has suggested that newer

technologies such as modified blood pressure monitors (BPMs) and single-lead ECGs may be more accurate in detecting AF,[41] and at-home BPMs have been estimated to reduce strokes and save costs by the UK National Institute of Clinical Evaluation.[42] However, these technologies are not widely available and therefore their use for population-wide screening initiatives is limited.

5 Diagnosis

Although an irregular pulse may point to AF, an ECG is still required to confirm the diagnosis. A negative ECG does not exclude the diagnosis of AF by pulse-taking since AF may be paroxysmal. In patients with suspected AF, diagnosis should be confirmed using a single-lead rhythm strip or 12-lead ECG documenting ≥ 30 s of AF.[43,44] A 12-lead ECG can detect other abnormalities such as left ventricular hypertrophy, ischemia, and other clinical features. At first diagnosis, AF can be classified as one of four types: paroxysmal (self-terminating, usually within 48 h), persistent (lasts longer than 7 days), long-standing persistent (has lasted one year or more) or permanent (when presence of arrhythmia is accepted and no rhythm control, i.e., stabilizing sinus rhythm, is attempted). Although paroxysmal AF is associated with somewhat lesser risk of stroke and systemic embolism than non-paroxysmal AF,[45] all types of AF are associated with sufficiently increased risk, especially for stroke,[46] making detection of even paroxysmal AF critical and warranting oral anticoagulation therapy in the majority of those aged 65 years or more. Further prolonged monitoring techniques may be indicated but are not cost-effective and of limited value from a population based perspective.[47–50] Inexpensive smart phone-based rhythm monitoring equipment has potential applications in LMIC, but systems for deployment and validation require further assessment.

Presence of CVD and other risk factors affects the risk of stroke and prognosis in patients with AF, and should be systematically assessed. An in-depth discussion of the multiple risk scores for identification of patients at higher risk of stroke is out of the scope of this review. It is important to highlight that many of these scores are underutilized by primary care physicians and therefore significant proportions of patients globally remain under diagnosed and undertreated with oral anticoagulation therapies and poor control of modifiable risk factors.

6 Management policy recommendations

The role of OACs for the prevention of stroke and systemic embolism in patients with AF is clearly established and today several options are available. The main challenges are related with the perceived threat of bleeding in contrast to the prevention of a disabling stroke. Populations that derive the greatest benefit from OACs are the elderly that are also at higher risk of bleeding; nonetheless multiple databases demonstrate the evidence that OACs and most likely direct oral anticoagulants are the preferred strategy. Anticoagulation for medium- and high-risk non-valvular AF is identified as a recommended policy option by the World Health Organization (WHO) in the WHO Global Action Plan for the Prevention and Control of NCDs 2013–2020.[51] Nevertheless, warfarin remains the most widely available anticoagulant and is the only anticoagulant on the World Health Organization's Essential Medicines list.[52] Aspirin, which is widely used as an antithrombotic therapy for AF is neither effective nor safe and has very limited indications and is rarely indicated by most guidelines.[53] The combination of aspirin plus clopidogrel is more effective than aspirin alone but less effective than warfarin, and has no advantage over warfarin in terms of major bleeding.[54] However, this combination may be an alternative particularly in LMIC and for patients that live in remote rural areas where proper OAC follow-up may be unrealistic.[55]

The decision to initiate OAC therapy to reduce risk of stroke must be weighed against the risk of major bleeding complications associated with anticoagulant therapy, the most treacherous of which is intra-cerebral hemorrhage.[56] The highest the risk of stroke estimated by most risk scores; the higher the risk of bleeding. From the population perspective implementation of all these scores is impractical particularly if detection of subjects at risk in LMIC and rural areas globally is primarily implemented by non-physicians. A simplistic approach called CHADS 65 implemented by the Canadian Cardiovascular Society may be more approachable from the global perspective.[57]

Monitoring of AF patients by primary health care providers also presents the opportunity to monitor and treat co-morbid cardiovascular conditions,[58,59] in particular hypertension, heart failure, diabetes and valvular abnormalities. Valvular AF is not the focus of this review, but nonetheless management of AF should include consideration of the management of rheumatic heart disease and valvular heart disease, which are common in LMIC and associated with development of AF in a significant proportion.[60]

7 The "ideal" patient care pathway for AF patients

The ideal patient care pathway will vary among geogra-

phies and is primarily based on health resource availability. Key global recommendations for detection, diagnosis and management of AF, or the "ideal patient pathway" for AF patients, are summarized in Figure 2. Stepwise approach includes: (1) screening of individuals with known AF risk factors and opportunistic screening of patients 65 years or older; (2) 12-lead ECG to confirm suspected AF; (3) assessment of stroke risk; and (4) initiation of anticoagulant therapy, combined with lifestyle modification advice if appropriate (e.g., weight reduction, smoking cessation). Further management strategies are clearly established and are not the focus of these recommendations.

8 Strategies for global AF care improvement

Several lines of evidence derived from administrative databases and registries clearly indicate both under diagnosis and under utilization of appropriate guideline recommended therapy of both modifiable risk factors and oral anticoagulation. Opportunistic pulse palpation of individuals over 65 years of age, with confirmatory ECG,[40] despite being documented in only one randomized clinical trial is sensible and easily implemented from the population perspective.

The GARFIELD registry, a study of 19 countries in 2009–2011, revealed that 38.0% of patients with high risk of stroke had not received anticoagulant therapy, whereas 42.5% of those at low risk (score 0) did.[61] The PINNACLE Study in the United States found that less than half of high-risk patients were receiving OACs therapy.[62] In the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) general registry of nine European countries, while use of OACs was higher (approximately 81% of high stroke risk patients), persistence of therapy was still not optimal (84% of those prescribed with vitamin K antagonist remained on therapy 1 year later), and despite guidelines, anti-platelet therapy (commonly aspirin) was used in 15% of low risk patients, and in 31% of high-risk patients.[63]

Treatment and management gaps exist worldwide and older populations are the ones at highest risk but remain largely untreated due to the perceived risk of bleeding; these gaps vary in degree across countries, but are more prominent in LMIC.[64] Data from LMIC are limited and suggest very low rates of oral anticoagulation therapy among AF patients.[38,59] A few studies reported that estimated rates of anticoagulant use range from only 2.7%–50% in China,[59,65–67] 26%–44% in Pakistan,[68] 16% in Malaysia,[69] 46.7%–57.8% in Brazil,[70] 36.8% in Mexico,[71] 72.7% in Argentina,[72] 33% in South Africa,[73] 34.2% in Cameroon,[74] from 11.5% (rural) to 26.5% (urban) in Zimbabwe,[75] 62% in Senegal,[76] 30.1%–67.3% in Turkey,[77] 13%–53.9% in Serbia,[78] 27% in Kosovo,[79] and 7.1% in Moldova.[80] The Gulf SAFE registry revealed similarly low rates of anticoagulation use (49% of patients) in six Gulf countries (Bahrain, Kuwait, Oman, Qatar, United Arab Emirates and Yemen).[80]

Most evidence on AF knowledge-practice gaps LMIC focuses on gaps in management of stroke risk among AF patients with OACs. However, there is evidence of gaps across the continuum of care for AF globally, which are likely to apply in LMIC. For example, research in Canada suggested that non-cardiologist physicians lack sufficient knowledge, skills and confidence to diagnose AF, with diagnosis of paroxysmal or asymptomatic AF being particularly challenging, and that continuous professional education and development is necessary to strengthen the capacity of physicians to navigate AF screening and diagnosis guidelines.[81]

9 Improving accessibility and availability of screening for rural populations

The World Heart Federation recommends that screening for AF is best conducted via opportunistic palpation (pulse-taking) of patients aged 65 and over, with or without known AF risk factors, with follow up ECG for those with an irregular pulse. Following this recommendation may be challenging, particularly in remote settings in LMICs, and the opportunity to utilize non-physician health professionals who are trained to implement novel technologies that allow for cardiac rhythm assessment by non-specialist health care workers may be feasible.[82] Further studies are needed to implement this strategy.

10 Summary and conclusions

AF affects millions of people worldwide and, left untreated, increases the risk and severity of stroke, heart failure and death. The global aging of the population will determine an endemic that will result in significant burden on health care systems and physicians taking care of these populations. There exist significant gaps globally that put LMICs at higher risk of negative outcomes that merit a global approach that promotes conscious identification and management of modifiable risk factors as well as proper risk stratification and treatment. Further education of both non-specialists and non physician workers may improve screening, detection and appropriate management of AF that may in turn improve global outcomes. The World Heart Federation is committed to promote this approach in an attempt to halt the progression of the inevitable endemic.

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Guest Editors: Manuel Martínez-Sellés & Antoni Bayés de Luna