

Global Burden of Atrial Fibrillation in Developed and Developing Nations

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ABSTRACT

Atrial fibrillation is the most common heart rhythm disorder in the world, with major public health impact especially due to increased risk of stroke and hospitalizations. The recently published results on epidemiology of atrial fibrillation from the Global Burden of Diseases, Injuries, and Risk Factors Study confirm the existence of a significant and progressive worldwide increase in the burden of atrial fibrillation. However, there appears to be regional variation in both the burden of atrial fibrillation and availability of epidemiological data regarding this condition. In this review, the authors identify issues that are unique to the developed versus developing regions and outline a road map for possible approaches to surveillance, management, and prevention of atrial fibrillation at the global level.

Atrial fibrillation (AF) is a common cardiovascular disorder that contributes significantly to risk of symptoms, hospitalization, and stroke [1]. The recently published findings on the worldwide epidemiology of AF from the GBD 2010 (Global Burden of Diseases, Injuries, and Risk Factors) study provide clear evidence of a long-suspected phenomenon—a burgeoning population of patients with AF on a global level [2]. This study estimated that in 2010, there were 33.5 million patients with AF in the world, constituting approximately 0.5% of the total world population. Individuals of European descent in high-income countries appear to have a higher likelihood of developing AF, resulting in a higher overall burden of AF in high-income nations. However, there appear to be significant differences in the developed versus developing world related to mortality associated with AF that could have a significant impact on management of AF in these regions [2]. There are additional considerations in the developing world that relate to distinct distribution of etiologies, comorbid conditions, and approaches to management that are likely to require unique sets of approaches for these regions [3,4]. The purpose of this review is to compare AF epidemiology, burden, and associated mortality in the developed versus developing nations, with a special focus on the recently published results of the GBD 2010 study. We have attempted to identify issues that are unique to these separate regions of the world with the overall goal of outlining a road map for possible approaches to management and prevention of this condition in what is clearly a sizeable and growing population of patients with AF at a global level.

RISING GLOBAL PREVALENCE, INCIDENCE, AND BURDEN OF AF

AF is the most common heart rhythm disorder worldwide. Between 1990 and 2010, there was a modest increase in

prevalence and a major increase in incidence of AF [2]. In 2010, the prevalence rates per 100,000 population were 596.2 (95% uncertainty intervals [UI]: 558.4 to 636.7) in men (5% increase since 1990) and 373.1 (95% UI: 347.9 to 402.2) in women (4% increase since 1990). AF incidence per 100,000 population was 77.5 (95% UI: 65.2 to 95.4) in men (28% increase from 1990) and 59.5 (95% UI: 49.9 to 74.9) in women (35% increase from 1990). For both men and women, prevalence (Fig. 1) and incidence (Fig. 2) of AF were disproportionately higher in developed nations compared with developing nations.

In GBD 2010, the burden associated with AF was measured as disability-adjusted life-years (DALYs). DALYs combine information regarding premature death (years of life lost [YLL]) and disability caused by the condition (years lived with disability [YLD]) [5]. Effects or sequelae of AF resulting in disability were defined as “daily medication and at least minimal interference with daily activities.” On the basis of previously determined disability weights for sequelae of several disease conditions [6], AF sequelae were assigned a disability weight of 0.031. One DALY corresponds to 1 lost year of health and is calculated as YLL + YLD. In 2010, the estimated age-standardized global burden, expressed as DALYs, resulting from AF (per 100,000 population) was 64.5 (95% UI: 46.8 to 84.2) in men and 45.9 (95% UI: 35.7 to 58.5) in women, representing increases of 18.8% (95% UI: 15.8 to 19.3) and 18.9% (95% UI: 15.8 to 23.5) for men and women, respectively. Coinciding with the higher incidence and prevalence of AF in the developed world, age-standardized DALY rates were higher in developed compared with developing nations (Fig. 3). An important consideration while interpreting these new data is the significant lack of community-based data on AF and other cardiovascular diseases in the developing world and especially in Sub-Saharan Africa. In fact, this same study reported that the vast majority of published studies (all

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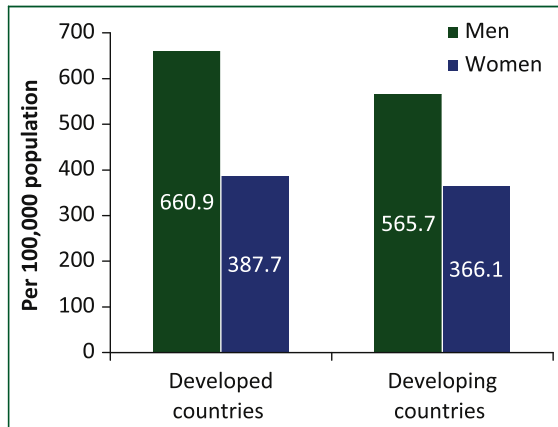


FIGURE 1. Age-adjusted prevalence rates of atrial fibrillation for men and women in developed versus developing countries (2010).

languages) were performed in either Western Europe (35.9%) or North America (35.6%) [2]. As a result, any current estimate of the AF global burden is likely to be affected by this limitation.

MORTALITY ASSOCIATED WITH AF

Although overall burden of AF was higher in the developed nations (inclusive of AF mortality and disability due to nonfatal AF), the recent GBD 2010 findings related to mortality associated with AF in the developed versus developing nations warrant specific attention, especially regarding the difference between sexes [2]. Estimation of the mortality associated with AF was performed based on modeling the causes of death after using input from all available cause of death data. The age-adjusted mortality rate for AF (per 100,000 population) increased between 1990 and 2010 to 1.6 (95% UI: 1.0 to 2.4) for men and 1.7 (95% UI: 1.4 to 2.2) for women. This represented a 2-fold (95% UI: 2.0 to 2.2) and 1.9-fold (95% UI: 1.8 to 2.0)

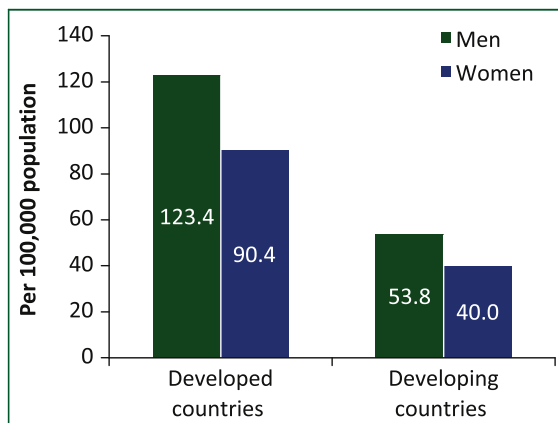


FIGURE 2. Age-adjusted incidence rates of atrial fibrillation for men and women in developed versus developing countries (2010).

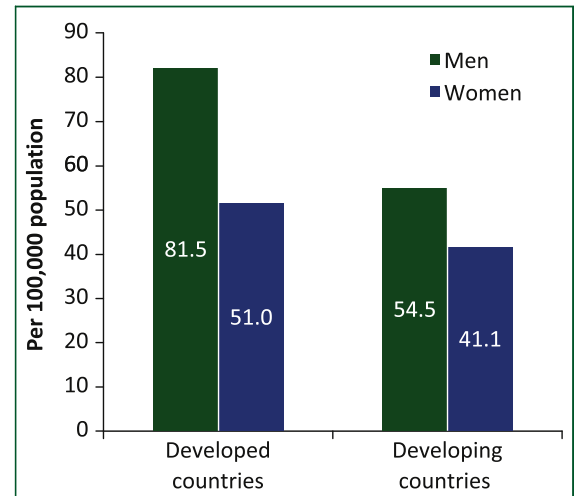


FIGURE 3. Age-adjusted disability-adjusted life year rates of atrial fibrillation for men and women in developed versus developing countries (2010).

increase for men and women, respectively. Thus, although AF prevalence rate was substantially lower in women than in men in both developed and developing countries, global mortality rate associated with AF was slightly higher in women; this paradoxical difference appeared to result from a disproportionately higher mortality rate among women (1.0) than men (0.7) with AF in the developing than in developed (2.4 vs. 2.7, respectively) nations (Fig. 4). In the absence of systematic studies that could explain the higher mortality among women in developing nations, there are a few potential explanations. This finding could be explained in part by the types of AF-associated conditions that are significantly more prevalent among women in the developing world compared with the developed world. One important example could be AF related to valve disease. The vast majority of patients with AF in developed nations have nonvalvular AF. In the developing world, a significant proportion is likely to have valvular AF, most likely related to rheumatic heart disease [7]. Because rheumatic heart disease may be more common among women [8], with a significant proportion manifesting during pregnancy [9], this factor needs to be explored as a potential explanation for the higher mortality rates observed among women with AF in developing nations. Another factor could be the lower social status and poorer access to medical care of women than men in many developing countries. Finally, misclassification bias in death records will need to be evaluated, with the reported underlying cause being attributed more commonly to AF for women than for men.

SEX DIFFERENCES IN AF AT A GLOBAL LEVEL

Sex differences in the death rate due to AF vary across regions of the world, even within the developed and developing categories. The highest disparity is seen in East Asia, where age-adjusted mortality due to AF in 2010 was

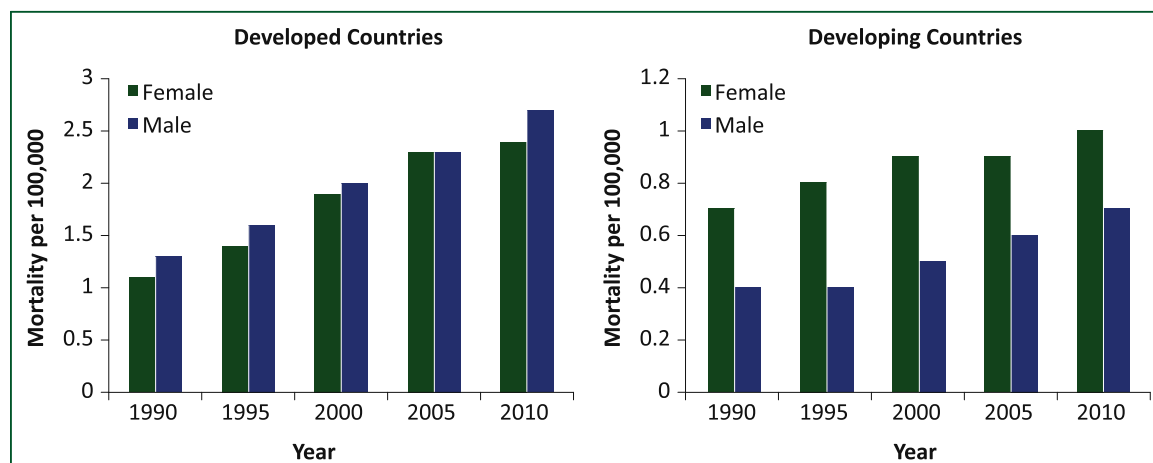


FIGURE 4. Mortality associated with AF stratified by sex and type of region (developed vs. developing). Mortality associated with atrial fibrillation (AF) was higher in males and females in developed regions. However, the disproportionately higher mortality in females in developing regions was responsible for the overall higher AF-related mortality among females compared with males. ©American Heart Association (Reprinted from: Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 study. *Circulation* 2014;129:837-47 [2]).

more than twice as high in women (1.32 deaths per 100,000; 95% uncertainty interval [UI]: 0.49 to 2.92) compared with men (0.58; 95% UI: 0.17 to 1.6). This female predominance in AF-related deaths also occurred in Central, Western, and Eastern Sub-Saharan Africa and South Asia. In contrast, some regions had markedly higher

death rates in men than in women. For example, the high-income countries of the Asia Pacific region had age-adjusted mortality rates due to AF of 2.44 deaths per 100,000 (95% UI: 1.27 to 4.50) among men but only 1.45 (95% UI: 0.86 to 2.40) among women. These sex differences between men and women are not seen in high-income North America,

TABLE 1. Regional distribution of atrial fibrillation-associated mortality rates in males and females

Location	Sex	Deaths			Sex	Deaths			Ratio of Male to Female Death Rates
		per 100,000	Upper	Lower		per 100,000	Upper	Lower	
East Asia	Female	1.32	2.92	0.49	Male	0.58	1.60	0.17	2.26
Central Sub-Saharan Africa	Female	0.64	1.37	0.26	Male	0.31	1.02	0.09	2.05
Western Sub-Saharan Africa	Female	0.72	1.65	0.28	Male	0.37	1.04	0.12	1.94
Eastern Sub-Saharan Africa	Female	0.57	1.16	0.24	Male	0.34	0.96	0.11	1.67
South Asia	Female	0.75	1.86	0.23	Male	0.54	1.95	0.09	1.39
Andean Latin America	Female	0.75	1.02	0.53	Male	0.64	0.97	0.39	1.18
Western Europe	Female	3.69	4.57	2.97	Male	3.42	4.83	2.21	1.08
Southeast Asia	Female	0.30	0.41	0.22	Male	0.28	0.43	0.19	1.04
High-income North America	Female	2.57	4.71	1.38	Male	2.84	5.69	1.49	0.90
Australasia	Female	2.96	5.48	1.59	Male	3.39	5.93	1.81	0.87
Eastern Europe	Female	0.38	0.65	0.19	Male	0.44	0.73	0.23	0.86
Central Latin America	Female	0.79	1.07	0.59	Male	0.91	1.36	0.62	0.86
Latin America and Caribbean	Female	1.20	1.61	0.93	Male	1.40	2.24	0.96	0.86
Southern Latin America	Female	1.54	2.23	1.07	Male	2.00	2.92	1.35	0.77
Southern Sub-Saharan Africa	Female	1.63	2.52	1.07	Male	2.12	4.04	1.08	0.77
Oceania	Female	2.96	6.08	1.24	Male	3.88	7.49	1.37	0.76
North Africa and Middle East	Female	1.28	1.69	0.96	Male	1.71	2.84	1.03	0.75
Central Europe	Female	1.16	1.42	0.95	Male	1.63	2.24	1.06	0.71
High-income Asia Pacific	Female	1.45	2.40	0.86	Male	2.44	4.50	1.27	0.60
Central Asia	Female	0.11	0.15	0.08	Male	0.29	0.42	0.20	0.37

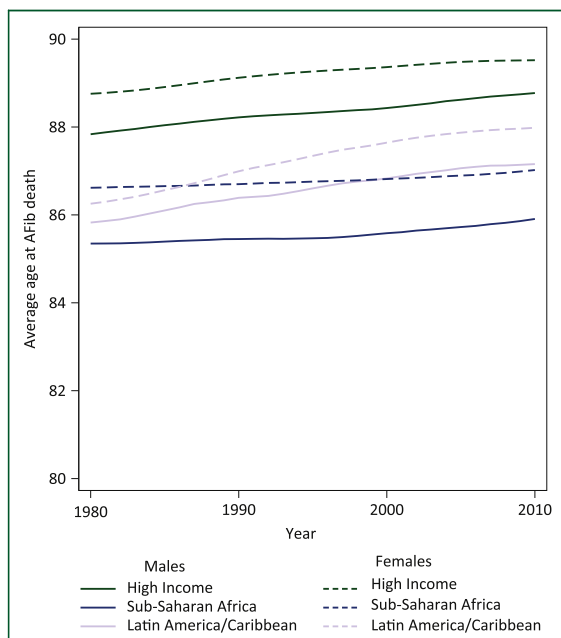


FIGURE 5. Average age at time of death associated with atrial fibrillation in high- versus low-income regions. AFib, atrial fibrillation.

Western Europe, Southeast Asia, and Australasia (Table 1). The cause of these sex disparities is unclear and deserves further investigation to determine whether it reflects differences in risk factors, health system performance, or even biases in the attribution of deaths in vital registration. Sex disparities in age at time of death are also observed globally. The age at death associated with AF in 2010 was older in women than in men across all regions of the world. The differences were greatest in the low- and middle-income regions of Eastern Europe/Central Asia, East Asia/Pacific, and Sub-Saharan Africa. However, the age of death associated with AF increased across all regions between 1990 and 2010 (Fig. 5).

FACTORS CONTRIBUTING TO RISE IN GLOBAL AF BURDEN

Although AF is a complex and multifactorial condition, there are several risk factors that have been identified, most of which can be readily assessed for individual patients in primary care settings. In a recent report, a simple 5-year predictive model that included the variables age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes, and history of myocardial infarction and heart failure had acceptable discrimination (C-statistic: 0.765; 95% CI: 0.748 to 0.781) [10]. Are there trends in AF risk factors at a global level that could explain the rising burden of AF? It may be instructive to evaluate key AF risk factors in the context of the understanding of current global health

trends, especially as reported by the recently completed GBD 2010 project.

Aging trends of the world population

Population aging is a well-studied phenomenon and a powerful determinant of the total global burden of diseases of aging such as AF [11]. The number of people aged 60 and older doubled between 1980 and 2012 [12]. By 2050, 2 billion people (22% of the total) are projected to be 60 years and older, with the most rapid changes occurring in countries like Brazil and China. The percentage of the population 65 years and older increased from 6.2% in 1990 to 6.9% in 2000 to 7.7% in 2010 and is expected to reach 16.1% by 2050 [13]. It took 69 years for the percentage to double from 7% to 14% in the United States (1944 to 2013), but this doubling of the over 65 age group is expected to occur in only 26 years in China (2000 to 2026). The burden of AF at age 65 years (226 DALYs/100,000) is nearly 7 times that at age 45 years (33 DALYs/100,000) and only one-quarter that at ages 80 and older (936 DALYs/100,000). Population aging will be associated with rapidly increasing numbers of persons living with chronic conditions such as AF, ischemic heart disease, and stroke and increasing healthcare costs.

Hypertension and cardiovascular disease

Hypertension is a powerful independent risk factor for cardiovascular disease and the leading risk factor for disease burden worldwide [3]. Like AF, it is also very common, affecting nearly 1 in 3 adults worldwide. More than a billion people had hypertension in 2008, with an estimated 978 million individuals who had uncontrolled high blood pressure (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) [14]. Given these numbers, it would not be uncommon to find the coexistence of hypertension and AF. However, there are hemodynamic and pathophysiological bases for an association of hypertension and AF. Chronic exposure of the cardiovascular system to hypertension leads to left ventricular pressure overload, resulting in increased left atrial pressure, left atrial enlargement, and left atrial hypertrophy [15]. Besides hypertension, other cardiovascular diseases in which left atrial pressure or volume overload occurs (as in mitral stenosis or regurgitation, left ventricular diastolic heart failure, and severe systolic heart failure with cardiac chamber enlargement) also predispose to AF. In addition, chronic hypertension and heart failure lead to activation of the renin-angiotensin-aldosterone (RAA) axis, with resultant myocardial and atrial fibrosis predisposing to AF. Not surprisingly, recent studies have shown that therapeutic antagonism or blockade of the RAA axis can be effective for both primary and secondary prevention of AF in patients with hypertension [15]. More recently, a molecular genetic basis of AF has been suggested [16]. Several genetic association studies have shown that genetic variants or polymorphisms linked to AF are also associated with genes related to ionic channels, calcium handling proteins,

fibrosis, conduction, and inflammatory processes important in the pathogenesis of common AF as well as several cardiovascular diseases [16,17].

Obesity and the metabolic syndrome

Obesity and the metabolic syndrome have been linked to increased risk of AF. In the prospective Framingham Heart study, obesity was associated with a 4% to 5% increased risk of AF over a mean follow-up of 14 years, independently of hypertension, diabetes, and myocardial infarction [18]. The same study reported that this relationship may be mediated by an increase in left atrial diameter, a risk factor that can be at least partially attenuated by weight loss [19]. However, it is likely that AF in obesity is determined by multiple factors that include overlap with the metabolic syndrome [20], as well as obstructive sleep apnea [21,22]. The Women's Health study reported a linear relationship between body mass index (BMI) and AF, with a 5% increase in risk of AF for a 1-unit increase in BMI [23].

Diabetes

Several studies have reported a modestly increased incidence or prevalence of AF among patients with type 2 diabetes [24] and an increased incidence of stroke among patients with diabetes with AF [25]. However, other studies have failed to find a significant association. If future studies confirm diabetes as a risk factor for AF, the obesity-related risk in occurrence of type 2 diabetes must be considered as a contributor to the rising occurrence of AF.

FACTORS RELATED TO RACE AND ETHNICITY THAT INCREASE RISK OF AF

White European descent

There are strong indications that individuals of white European descent have a higher risk of AF compared with individuals of other races, a finding that at least partially explains the significantly higher prevalence of AF in developed nations. In a cross-sectional study of 1.89 million adults aged 20 years or older enrolled in a large health maintenance organization in California, AF was identified in 1% [26]. In this large, ethnically diverse population, AF was more common in white (2.2%) than in black (1.5%; $p < 0.001$) patients. Similar results were recently reported from a comparison between white and black older adults [27], also confirmed using genetic testing for ancestry informative markers [28]; however, there is a lack of data for other races. Consistent with these findings, European Union estimates indicated that 8.8 million adults older than 55 years had AF in 2010 (95% CI: 6.5 to 12.3 million), comprising >25% of the worldwide AF population [29]. These numbers are projected to double by 2060 to 17.9 million (95% CI: 13.6 to 23.7 million), as long as age- and sex-specific prevalence remains stable [29].

Body height and AF

In the few analyses that have been conducted, a consistent relationship has been identified between body height and risk of AF, which may partly explain the higher AF prevalence in high-income countries. Among 684 male and 568 female incident cases of AF in the Cardiovascular Health study, greater height was significantly associated with risk of AF, with hazard ratios per 10 cm of 1.26 and 1.32 for men and women, respectively [30]. In fact, the incremental risk of AF from male sex was completely attenuated by the inclusion of height. In this detailed study, echocardiographic left atrial size, commonly believed to be the mediator of this relationship, did not explain the association between greater height and AF, with the intriguing possibility that genetic mechanisms may play a role [30]. Two of the genetic loci associated with AF, paired-like homeodomain 2 [31] and zinc finger homeobox 3 [32], are also associated with growth pathways. The lower rates of AF in some regions of the developing world, especially South Asia, could in part be explained by the established differences in height from individuals of white European descent in the developed world [33]. In addition, both height and left atrial size are smaller in women compared with men and may explain in part the significantly higher prevalence of AF in men [34].

IMPLICATIONS

Investment in regional AF surveillance

High-quality epidemiological studies at the local, national, and regional levels will be essential if we are to estimate the regional and global burden of AF with accuracy. At present, systematic population-based surveillance of AF is scarce, especially in low- and middle-income countries. Where surveys have been conducted, there is marked heterogeneity in diagnostic methods, clinical settings, and the presence or absence of symptoms [35]. In light of recent findings in population growth and aging, and the associated epidemiological transition with increasing burden of chronic noncommunicable diseases that predispose to AF, a strong case can be made for increased investment in AF surveillance. The 2 approaches that have been proposed to increase the rate of detection of incident cases to enable early intervention, especially for the prevention of stroke and other sequelae of AF, are 1) systematic and 2) opportunistic screening for AF [36]. In a review of evidence from the United Kingdom, Moran et al. [36] recently showed that although both approaches compared favorably on AF diagnosis rate, from the health service provider perspective, the cost of systematic screening was significantly more than that of opportunistic screening. There are specific challenges involved in AF surveillance because the condition can often be asymptomatic as well as sporadic (or paroxysmal). This will require the development of innovative approaches likely involving current mobile and wireless technologies.

Prevention

Interventions to prevent or delay AF and other cardiovascular conditions offer the best hope for moderating the future burden of these diseases. Evidence is lacking to recommend specific interventions for the prevention of AF beyond those generally recommended for hypertension control and prevention of ischemic heart disease and stroke. However, clinical and epidemiological evidence suggests that diagnosis, close supervision, and management of patients with obstructive sleep apnea, likely feasible only in high-income countries, may be of value in preventing AF. Further, avoidance of heavy alcohol intake (i.e., greater than 2 drinks daily in men or 1 drink daily in women) may also be prudent.

Approach to stroke prophylaxis

In the developing world, there is a distinct lack of studies that have assessed prevalence of stroke prophylaxis. Given the economic challenges of establishing an infrastructure of warfarin clinics that would monitor the international normalized ratio, the majority of patients in low-resource settings likely receive aspirin as antithrombotic therapy. The low use of oral anticoagulants (in the range of 0.5% to 3%) [7,37] in low-income countries is in stark contrast to the significantly higher use in high-income countries (in the range of 70%) [38]. However, even in high-income countries, prevalence of oral anticoagulation is lower than expected, with fewer than two-thirds of high-risk patients on oral anticoagulation [39], likely due to concerns regarding bleeding risk in an aging population and the challenges of achieving adequate and safe adherence. Along with significant variability in regional burden of AF, attitudes toward and practice of stroke prophylaxis are likely to be heterogeneous. The major efforts conducted in high-income countries to establish guidelines for stroke prophylaxis and bleeding risk have not even been initiated in low-income countries. Systematic surveillance of stroke prophylaxis patterns and assessment of potential beneficial and harmful effects attributable to oral anticoagulation versus aspirin therapy in developing nations will provide the region-specific basis for the establishment of guidelines that would educate health-care providers as well as the population.

Management of symptoms and hospitalizations due to AF

The large randomized trials of AF management conducted primarily in high-income nations provide strong evidence for the equivalence of rate versus rhythm control in the older patient with at least moderate risk of stroke, as long as anticoagulation guidelines are followed. However, there exist large numbers of patients at all ages who require amelioration of symptoms due to AF by use of rhythm control. Antiarrhythmic drugs have long been the main therapeutic approach with pacemaker implantation—atrioventricular junction ablation and the surgical maze procedure used for a selected subgroup of patients. Almost 2 decades ago,

therapeutic catheter-based radiofrequency ablation was introduced into the AF treatment armamentarium and is currently finding increasing use but is restricted largely to high-income countries [40]. Although comparative evaluation of these different treatment modalities is ongoing [41], the growing burden of AF will also require assessment at a population level. Is it possible that the one-time expense of an electrophysiological procedure is more cost effective than long-term rate control and anticoagulation in low-resource settings, with limited chronic care infrastructure in some cases? The answer to this question is likely to be complex given both the regional heterogeneity in AF burden as well as disparities in allocation of resources in developed versus developing countries. It is therefore imperative that regional AF surveillance be combined with comparative effectiveness evaluation of different AF management approaches.

SUMMARY

New findings from the GBD 2010 study indicated that the last 2 decades have witnessed a significant rise in the worldwide prevalence, incidence, and overall burden of AF. Although the burden of AF is greater in high-income countries (possibly due to increased predilection for AF among white Europeans), mortality associated with AF in women is higher in low-income countries. This latter finding is currently unexplained and warrants urgent attention. Besides the older age of the global population, other factors such as the rising tide of hypertension, obesity, and diabetes could contribute to the overall increased global burden of AF. Given the significant variation in AF burden in both developing and developed nations, there is a critical need for investment in regional AF surveillance that will serve as a starting point for region-based prevention of AF, stroke prophylaxis, and systematic approaches to manage symptoms and hospitalizations due to AF.

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