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Atrial fibrillation in low- and middle-income countries: a narrative review

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Preventing premature non-communicable disease mortality necessitates a thorough review of one of the most important risk factors for stroke, which is atrial fibrillation (AF). The latter and AF-related stroke are still considered to be problems of high-income countries and are frequently overlooked in low- and middle-income countries (LMICs). In this narrative review, we provide an overview of studies that evaluated at least one of the following determinants of AF burden in LMICs: current epidemiology and trends, stroke prevention, health outcomes, and economic burden. Studies focusing on samples close to the general population (including community- and primary care-based samples) indicate sex-specific prevalence rates up to 7.4% in LMICs. Although AF prevalence is still higher in high-income countries than LMICs, the gap in AF burden between these two groups has been reducing in the past three decades. Oral anticoagulant (OAC) therapy for stroke prevention is underused in LMICs, and there are little data on OAC therapy in relation to stroke risk scores, such as CHA_2DS_2-VASc. Available data also points to higher morbidity and mortality for patient with AF in LMICs than their counterparts in high-income countries. Data on the consequent economic burden in LMICs is scarce, but it is reasonable to consider it will follow the same trend as that observed for health outcomes. Raising the visibility of AF as a public health problem in LMICs is necessary as a first step to providing adequate care for patients with this condition.

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Introduction

In October 2015, the World Health Organization (WHO) launched the WHO 25 × 25 initiative with the specific goal of achieving a 25% decrease in premature mortality due to non-communicable diseases (NCDs) by 2025. The initiative involved government institutions, scientific and professional societies, academic institutions, and health policy bodies across the world. In the context of NCD mortality, stroke is particularly relevant, representing the second largest cause of death globally[1]; thus, adequate stroke prevention is a key factor to reducing premature NCD mortality.[2]

Preventing premature NCD mortality due to stroke necessitates a thorough review of one of the most important risk factors for stroke: atrial fibrillation (AF). Dai *et al.*[3] estimated that in 2017 there were 37.6 million prevalent AF cases and 3.1 million incident cases of AF globally. Moreover, AF contributed to ~290 000 deaths globally, with an age-standardized mortality rate of 4.0/100 000 people.

The healthcare burden of AF and AF-related stroke are still mostly (and erroneously) considered as problems of wealthy countries, and frequently overlooked in low- and middle-income countries (LMICs). In fact, according to the Global Burden of Disease (GBD) 2017 data,[3,4] the five countries or territories with the highest age-standardized AF or flutter prevalence (New Zealand, USA, Sweden, Australia, and Austria) and incidence (USA, New Zealand, Sweden Greenland, and Australia) rates are high-income countries. However, although AF prevalence rates are lower in LMICs, 61% of global disability-adjusted life years (DALYs) are located in these countries.[4]

Although gaps in the current literature still exist, there is a substantial amount of data registering the impact of AF in LMICs. Even more importantly, it also highlights the increasing importance of AF epidemiology in this country group in the near future.

In this review article, we discuss the epidemiology, use of medication for stroke prevention, outcomes, and economic consequences of AF in LMICs. Our aim was to provide an overview of the impact of this disease on LMIC populations.

Methodology

In this narrative review, the LMIC group was defined according to the current World Bank criteria[5] (Supplementary material online, *Appendix S1*). This classification categorizes countries according to the gross national income per capita as low-income [≤ US dollars (USD) 1035], lower-middle income (USD 1036–4045), upper-middle income (USD 4046–12 535), and high-income (≥USD 12 536) groups. Low- and middle-income countries refer to the union of low, low-middle, and upper-middle income groups. We included articles published since 2000 that evaluated at least one of the following determinants of AF burden in LMICs: current epidemiology and trends, stroke prevention, health outcomes, and economic burden. We also included articles that evaluated high-income countries but which retrieved LMICs data. It must be acknowledged, however, that the World Bank income groups may still yield high intragroup heterogeneity. However, other classifications (as the International Monetary Fund classification of countries based on their level of development, the United Nations Development Programme Human Development Index, or the Global Burden of Disease Study Socio-Development Index) are very similar. All classifications use GNI or other socioeconomic indicators highly correlated with GNI as their main criteria. Because of the high intragroup heterogeneity, in most cases, we present original article results according to the geographical location of the sample.

Current epidemiology and trends

The reported prevalence of AF in LMICs is heterogeneous. Studies focusing on samples close to the general population (including community- and primary care-based samples) indicate sex-specific prevalence rates up to 7.4% (*Figure 1* and Supplementary material online, *Table S1*)[9–36] and most show prevalence rates between 0.5% and 3.0%. This wide variation may be at least partly explained by differences in study design and populations, mainly age of participants and AF subtype and duration. As expected, prevalence rates are even higher when specific groups are studied, such as those with heart failure,[6] stroke,[7] or rheumatic heart disease.[8]

The relatively low prevalence of AF in the general population in LMICs compared with high-income countries should not be interpreted as a sign of a stable low burden of AF in LMICs.[37] As shown in *Figure 2*, epidemiological trends in the past 30 years have demonstrated a reducing gap between high-income countries and LMICs for AF-related burden. Data in this figure were extracted from the GBD results tool (http://ghdx.healthdata.org/gbd-results-tool). Detailed information about the GBD methodology for these estimates can be found elsewhere.[38] *Figure 1* shows age-standardized rates for multiple GBD metrics (prevalence, incidence, deaths, years of life lost, years lived with disability, and disability-adjusted life years) from 1990 to 2017. Rates for each group from 1990 to 2017 are presented in proportion to 1990 levels (presented as 100%, in the horizontal dotted line).

These plots, together with recently published GBD AF data,[3] highlight two main patterns. First, for metrics mainly focused on morbidity [prevalence, incidence, and years lived with disability (YLD)]; global rates are falling mainly due to a decreasing trend in high-income countries. Comparing 1990 and 2017 rates, the steepest decreases in these metrics were observed in Portugal, Italy, Spain, Andorra, and France, all of which are high-income countries.

On the other hand, metrics that are influenced by higher and/or premature mortality [deaths and years of life lost (YLL)] or represent total disease burden (DALY) have a different pattern. Although global rates are relatively stable, there are important increases in these rates for the LMIC group. A detailed look at the information by country reveals that, except for Bahrain (a high-income country) and Burkina Faso (a low-income country), the 10 countries

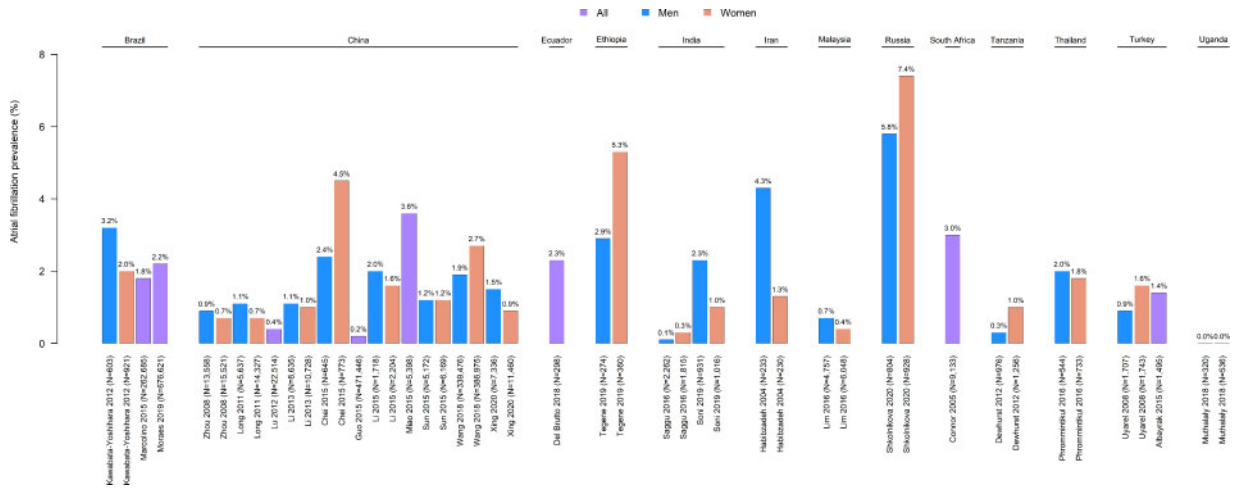

Figure 1 Atrial fibrillation prevalence rates in low- and middle-income countries, according to sex.

with the steepest increases in death, YLL, and DALY rates are in the lower or upper middle-income group.

Atrial fibrillation burden is multifactorial, and, therefore, it is not possible to identify one single reason to explain these trends. It is related to epidemiological transition, a phenomenon partly driven by income level. Analyzing the current trends, we can see three stages of AF burden evolution worldwide. First, a stage of low prevalence and consequent low mortality, influenced by the existence of competing premature death. Low-income countries may still be facing this scenario, mostly due to the premature mortality caused by infection, injury, and ischaemic heart disease.[39-42] Additionally, limited health care access and consequent underdiagnosing in economically deprived areas should be considered in the interpretation of this low burden.[43] In the second stage, as the causes of premature mortality are progressively avoided, there is a rise in AF prevalence and mortality. Finally, a third stage is a decline in AF burden, mainly due to improving treatment and control of risk factors. Bearing in mind this evolution, it is reasonable to consider that (i) the rise in AF mortality-related and total burden currently found for middle-income countries will be seen in low-income countries in the future and (ii) the fall in AF morbidity-related burden currently seen in high-income countries is yet to be seen in middle- and low- income countries. Taken together, these trends suggest that, in the next decades, LMICs will be responsible for an escalating proportion of global AF burden. Reducing AF burden in the coming decades will probably be more challenging, and it will be crucial to consider the specifics of healthcare systems in LMICs to achieve this goal.

Anticoagulants for stroke prevention

An overview of the available literature on the use of anticoagulants for stroke prevention in LMICs needs to be contextualized. Most studies presenting data about the use of anticoagulants as a seminal pathway to the treatment of AF are from the USA and Europe.[44,45] Even when other countries from Asia, Latin America, or Africa are included,[46] they are not usually LMICs as there are few studies describing the treatment of AF in LMICs compared with the number of studies focusing high-income countries. In large and multicenter studies, individuals from LMICs are part of the sample, but frequently the results are not presented by continent or region, which impairs access to specific information from these countries.[47]

Some initiatives in LMICs to conduct registries of AF have appeared in recent years, such as The Mexican Registry of Atrial Fibrillation (Registro Mexicano de Fibrilación Auricular—ReMeFa),[48] the Atrial Fibrillation and Embolic Risk Registry (CARMEN-AF),[49] both in Mexico, and the Brazilian Cardiovascular Registry of Atrial Fibrillation (the RECALL Study) in Brazil.[50] However, some of them have not published data until now.[48,50]

Another challenge in LMICs data interpretation is the heterogeneity in the presentation of results, including incomplete reporting. Only recent studies present results according to $CHADS_2$ or CHA_2DS_2-VASc scores.[51-56] Moreover, an expressive number of recent studies do not present results according to these scores yet.[57-60] Additionally studies in LMICs rarely involve population- or community-based samples.[12,13,61] One study used data from National Health Care Systems,[62] which may be resemble more the general population, although the proximity depends on how national systems of care are organized. Most samples are from hospitals,[55,57,59,63-65] outpatient departments,[66,67] or anticoagulation clinics,[68,69] which often reflect more selective samples. Designs also vary widely, including cross-sectional or registry studies,[52,54,57] cohort studies,[58,70] and systematic reviews,[71] limiting comparability.

Figure 3 and Supplementary material online, *Table S2* describe LMIC studies about oral anticoagulant (OAC) use for stroke prevention in patients with AF.[12,31,51-59,61-67,70,72-77] We excluded multicentric studies including both LMICs and high-income countries, from which it was not possible to retrieve the LMIC results separately. Of the studies in Supplementary material online, *Table S2*, 20 have information about a single country; 2 have information describing several LMIC countries but presenting

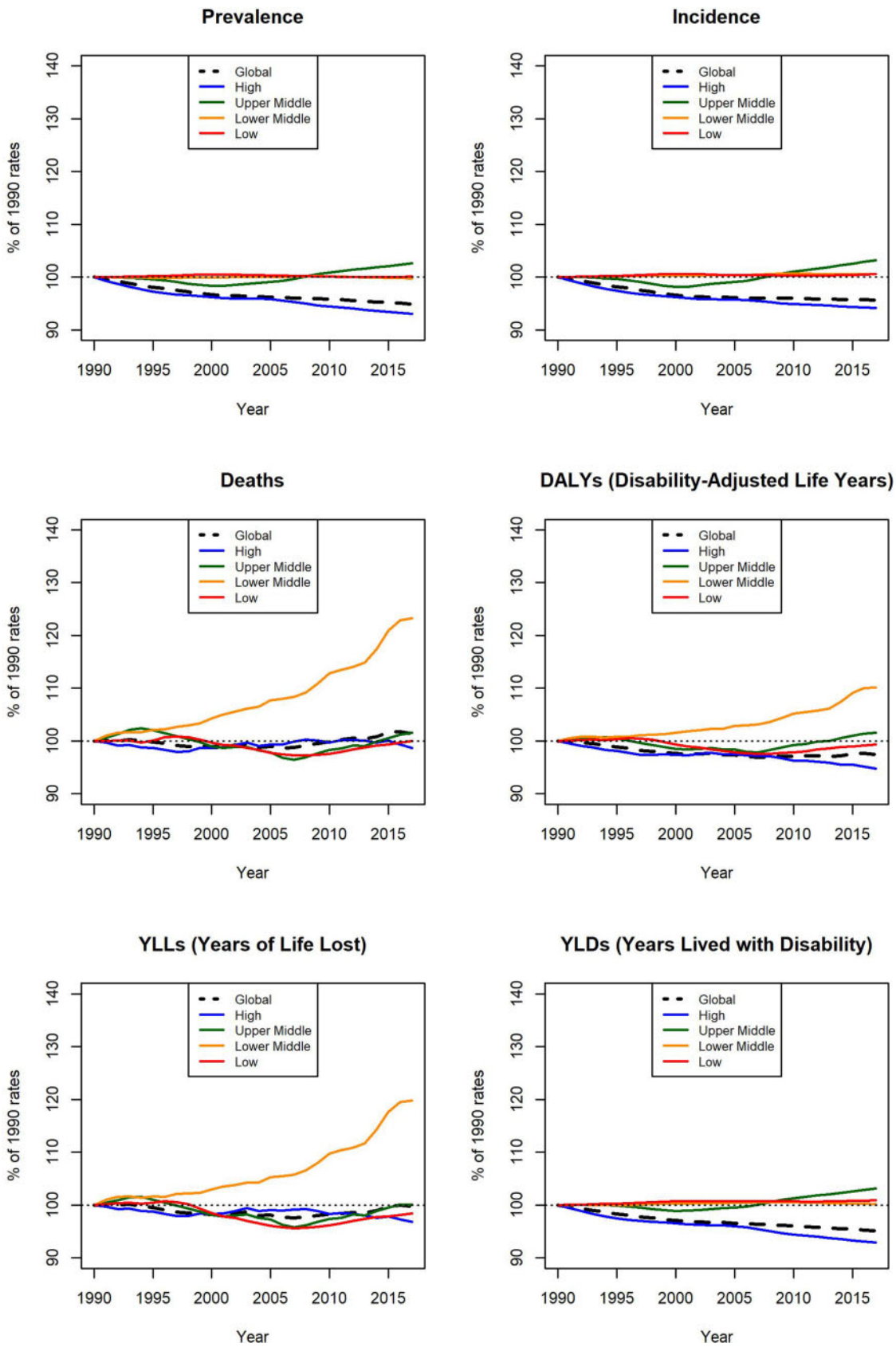

Figure 2 Epidemiological trends for atrial fibrillation, from 1990 to 2017, according to the World Bank income groups.

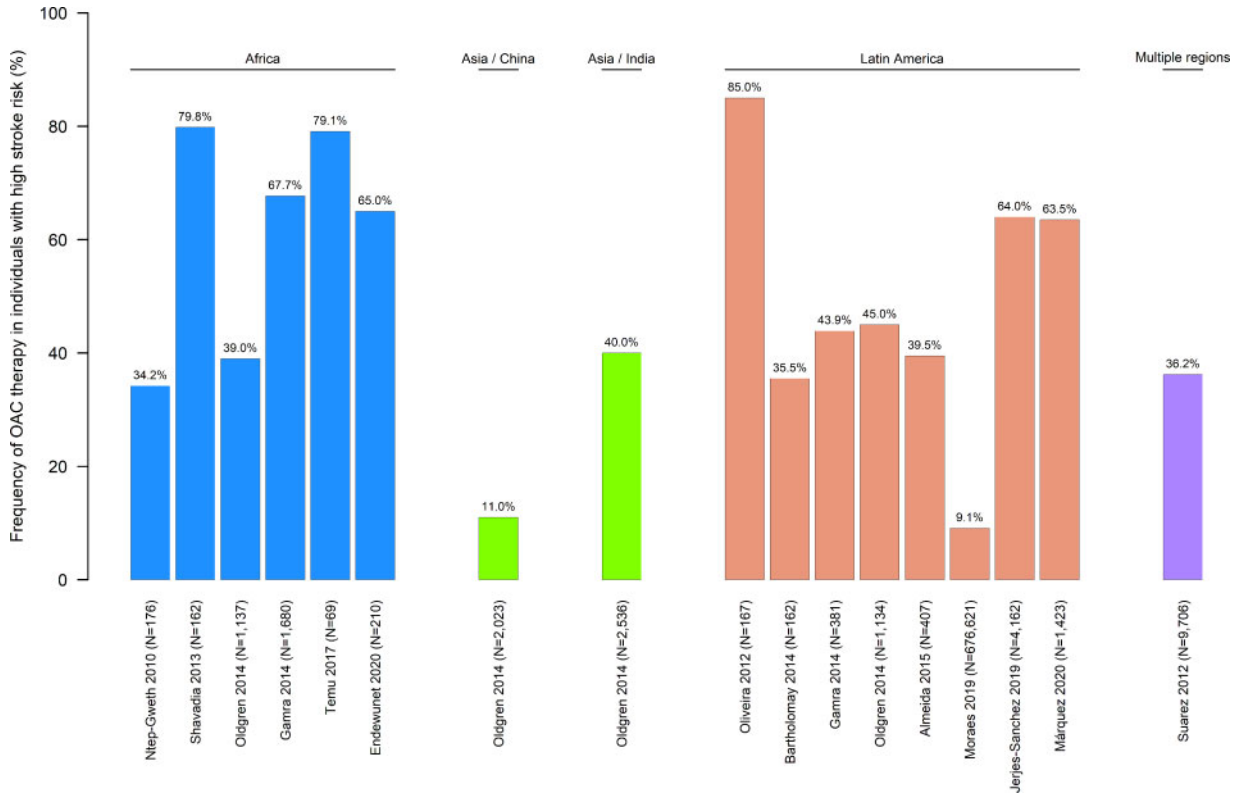

Figure 3 Oral anticoagulant therapy for high stroke risk patients with atrial fibrillation in low- and middle-income countries.

consolidated results[54,70] and 2 have information about more than one country, with results stratified by location.[62,72] The Realize AF Survey[51] presented two arms, one with African countries and Lebanon and the other with Latin American countries. In that study, results are presented for each of these groups. The RE-LY International Registry[57] results were divided into South American and African countries, India, and China. Due to its intrinsic nature, in studies based in anticoagulation clinics all patients receive OAC therapy.[68,69,78-80] Therefore, we opted to remove these articles from our review.

The new ESC 2020 AF guidelines for OAC therapy highlight the importance of considering stroke prevention in higher risk men with CHA_2DS_2-VASc scores ≥ 1 or women with CHA_2DS_2-VASc scores ≥ 2. For men with CHA_2DS_2-VASc score $= 1$ and women with CHA_2DS_2-VASc scores $= 2$, OAC therapy should be considered, while for those with higher scores, OAC therapy is recommended. NOACs are generally recommended as the first line therapy, but vitamin K antagonists (VKAs) can be used as an alternative, ensuring a high time within the therapeutic range (TTR) is achieved (at least two-thirds). It is important to address modifiable bleeding risk factors in all patients with AF. However, high bleeding risk scores should be used to identify patients who need strict follow-up and frequent re-evaluations rather than as a reason to withhold OAC therapy.[81]

Only 13 studies present data describing anticoagulation according to participants' $CHADS_2$ or CHA_2DS_2-VASc scores.[51-54,57-59,63,66,72,78-80] In these studies, underuse of OAC is relatively common, with a high proportion of patients with CHA_2DS_2 or CHA_2DS_2-VASc scores ≥ 2 using only antiplatelets (APT) or nothing. The non-prescription of OAC in these studies cannot be explained by a high risk of bleeding, since HAS-BLED was calculated in only four of these studies.[52,58,59,80]

Gamra *et al.*[51] compared OAC therapy prescription by geographic region. They assessed compliance with the 2006 American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) guidelines (which were relevant to patients enrolled between 2009 and 2010). They concluded that appropriate antithrombotic treatment was prescribed in 66.7% of the patients with $CHADS_2$ score ≥ 2 in Middle East/Africa, 55.3% in Europe, 43.9% in Latin America, and 31.7% in Asia.

In a study by Oldgren *et al.*,[57] the prescription of OAC therapy in India, China, South American (Argentina, Brazil, Chile, Colombia, Ecuador, and Venezuela), and African countries (Cameroon, Kenya, Mozambique, Nigeria, Senegal, South Africa, Sudan, Tanzania, Uganda, and Zambia) was compared with the global rates. This proportion was 45% of individuals with CHA_2DS_2-VASc scores ≥ 2 receiving OAC therapy in South American countries, 40% in India, 39% in African countries, and 11% in China compared with the global proportion of 44%. High-income regions, such as North America and Western Europe, presented proportions at 66% and 63%, respectively. Eastern Europe presented 39%, closer to the global findings.

The Prospective Urban Rural Epidemiology (PURE) study, a prospective population-based cohort in 27 geographical regions of the world, presented information about antithrombotic therapy use in their sample. Overall, 70% of participants with AF had a $CHADS_2$ score ≥ 1, with a similar

distribution in high-income countries (74%) and LMICs (70%). Overall, use of stroke prevention medication was low. There were also differences between these country groups, with warfarin more commonly used in high-income countries and antiplatelet use more common in LMICs.[82]

A recent systematic review of African AF studies states that AF is frequently under-reported in the published literature. Prevalence studies in Africa are scarce, and data about AF management is even scarcer. As most studies are performed in different populations, using different designs and different strategies to collect data, the results are very heterogeneous.[71]

It is important to highlight that use of OAC is the first step to preventing ischaemic stroke in patients with AF. However, in patients using VKAs, another important step is to maintain patients at a high time within TTR for effective stroke prevention. Most studies describing OAC do not include information about time in TTR. Another important point is that the new ESC guidelines refine the use of OAC according to sex, with different cut-off points in treatment recommendations between men and women.[81] No study included in this review presented results according to sex.

This is another consideration in the care of LMIC patients with AF. Due to the challenges associated with maintaining a high TTR, the non-vitamin K antagonist oral anticoagulants (NOACs) would be more effective than VKAs in clinical practice. However, the main barrier to the use of NOACs is the price of the drugs, which is too high, especially for widespread use in LMICs. The price of NOACs may be an even greater barrier in LMICs compared with high-income countries, deepening the social inequalities in treatment of AF. Although there is a decrease in laboratory costs, as prothrombin time determination is not necessary, public health policies in several LMICs must be implemented to make the change from VKAs to NOACs. Patents expiration and the consequent drop in prices may help adopting these policies in the future.

Although we focused on OAC undertreatment in LMICs, it is important to acknowledge this problem is not limited to this setting. A recent systematic review,[83] with data from several studies, including some high-income countries, showed that treatment of AF with OAC does not follow published treatment guidelines and a significant proportion of patients are exposed to high risk of ischaemic stroke with high costs to health systems.

Health outcomes

In *Table 1*, we summarize the main findings from published studies set in LMICs in the last decade that evaluated fatal (all-cause, cardiovascular, non-cardiovascular causes of death) and non-fatal outcomes (stroke, major bleeding and dementia) related to AF in clinical and non-clinical settings.[15,54,84–88] Systemic embolism is an additional AF-related outcome. However, it is relatively rare, and usually described with stroke as a combined endpoint. Among the outcomes most frequently evaluated in these studies, mortality rate has high impact in LMICs, particularly when data are compared with rates reported in high-income countries.[85,86]

Fatal outcomes

Recently, two major AF registries involving LMICs have clearly documented the difference in the case-fatality rates, which are highest in low-income areas.[85,86] In the RE-LY Atrial Fibrillation Registry and Cohort Study Investigators, 1-year mortality was evaluated in 47 countries. This registry, comprising more than 15 000 participants, compared data from low-middle income regions (South America, Eastern Europe, Middle East, Africa, India, China, and Southeast Asia) with high-income regions (North America, western Europe, and Australia), which were considered the reference.[85] The main findings revealed that the proportion of adults over 60 years who died 1 year post-emergency department (ED) attendance due to AF/flutter as primary or secondary diagnosis, was approximately double in South America (192/1132; 17%) and Africa (225/1137; 20%) compared with the reference countries (366/3800; 10%). Although these rates are unadjusted for potential confounders, such as age, the African population was approximately a decade younger than that from the high-income, while and poor outcomes were more frequently observed in Africa.[85] These findings can be partly explained by low investment in the public healthcare system and by the lack of primary prevention action within the young-middle age population in LMICs.[2,85]

Similarly, the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) study, which had more than 52 000 participants, observed markedly higher all-cause mortality rates 1 year after newly diagnosed non-valvular AF in India [7.68/100 person-years; 95% confidence interval (CI): 6.32–9.35] compared with 35 other countries worldwide from America, Europe, Africa, and Asia involved in this registry (4.34/100 person-years; 95% CI: 4.16–4.53; $P < 0.0001$). Cardiovascular mortality was also higher in Indian patients.[86]

In Latin America, the GARFIELD-AF reported 1-year mortality data focusing on four countries: Argentina, Brazil, Chile, and Mexico.[54] In this registry, all-cause mortality in Latin America (5.77/100 person-years, 95% CI: 5.06–6.56) was higher than the global rates, but lower than in India.[86,90] Considering the four Latin America countries, the highest unadjusted all-cause mortality rate was reported in Argentina (6.95/100 person-years, 95% CI: 5.43–8.90) followed by Brazil (6.19/100 person-years, 95% CI: 4.83–7.94).[54]

Also, in Latin America, a primary care-based study using an ECG database from the Telehealth Network of Minas Gerais, Brazil, reported mortality rates according to the presence of AF/flutter.[89] In that study, the highest all-cause [multivariable hazard ratio (HR): 2.59, 95% CI: 2.47–2.73] and cardiovascular disease (CVD) (adjusted HR: 2.62; 95% CI: 2.24–3.06) mortality risks associated with AF were verified in women.

Unlike most previous AF registries, two Chinese multicentre prospective cohorts reported mortality rates based on information about OAC therapy and the presence of modifiable risk factors.[84,87] In the Yang *et al.*[84] study, 1-year case-fatality (15.4% vs. 11.1%) and major adverse cardiovascular events (MACE) (22.8% vs. 17.9%) rates were higher in participants not receiving OACs. In the Jiang *et al.* study, the prognostic value of modifiable risk factors

Table 1 Fatal and non-fatal outcomes related to atrial fibrillation in low- and middle-income countries

Author	Year	Country	Sample and design	*N* (% women)	Age (years)	Results
All-cause mortality data						
Yang *et al.*[84]	2014	China	Hospital-based registry Cohort study with 1-year follow-up	2016 (54.8%)	Mean: 68.5	**1-year case-fatality rates** Total sample: 14.6 % Not anticoagulated: 15.4 % Anticoagulated: 11.1%
Healey *et al.*[85]	2016	47 countries[a]	Hospital-based registry Cohort study with 1-year follow-up	15 400 (47%)	Mean: South America: 68.3 Eastern Europe: 69.3 Middle East: 58.6 Africa: 57.2 India: 57.9 China: 68.4 Southeast Asia: 69.5	**1-year case-fatality rates** South America: 17% Eastern Europe: 9% Middle East: 13% Africa: 20% India: 9% China: 14% Southeast Asia: 9%
Sawhney *et al.*[86]	2018	35 countries from America, Europe, Africa, and Asia[b]	Hospital-based registry Cohort study with 1-year follow-up	52 014 India: 40.1% All countries: 44.2%	Mean: India: 68.5 All countries: 69.7	**All-cause mortality rate** India: 7.68/100 person-years All countries: 4.34/100 person-years
Jerjes-Sanchez *et al.*[54]	2019	Latin America	Hospital-based registry Cohort study with 1-year follow-up	4162 (47.5%)	Mean: 69.8	**All-cause mortality rate** Argentina: 6.95/100 person-years Brazil: 6.19/100 person-years Mexico: 5.91/100 person-years
Jiang *et al.*[87]	2019	China	Hospital-based registry Cohort study with 2.5-year follow-up	17 898 (38.7%)	Mean :64.4	**All-cause mortality rates** By the number of modifiable risk factor[c] No risk factors: 2.24/100 person-years 1 risk factor: 3.08/100 person-years $\geq$2 risk factors: 5.31/100 person-years
Paixão *et al.*[89]	2020	Brazil	Primary care-based ECG database Cross-sectional study	20 782[d]	Mean: 68.5	**All-cause mortality rate** 1.78/100 person-years **HR for all-cause mortality associated with AF** All: 2.10 (2.03–2.17) Men: 1.83 (1.74–1.91) Women: 2.59 (2.47–2.73)
Cause-specific mortality data						
Sawhney *et al.*[86]	2018	35 countries from America, Europe, Africa, and Asia[b]	Hospital-based registry Cohort study with 1-year follow-up	52 014 India: 40.1% All countries: 44.2%	Mean: India: 68.5 All countries: 69.7	**CVD mortality rate** India: 3.38/100 person-years All countries: 1.62/100 person-years **Non-CVD mortality rate** India: 1.46 /100 person-years All countries: 1.61/100 person-years **Undetermined cause of death rate**

(continued)

Table 1 Continued

Author	Year	Country	Sample and design	*N* (% women)	Age (years)	Results
						India: 2.84 /100 person-years All countries: 1.11/100 person-years
Jerjes-Sanchez *et al.*[54]	2019	Latin America	Hospital-based registry Cohort study with 1-year follow-up	4162 (47.5%)	Mean: 69.8	**CVD (% of total deaths)** Argentina: 44.4% Brazil: 38.7% Mexico: 50.8% **Non-CVD (% of total deaths)** Argentina: 41.3% Brazil: 40.3% Mexico: 24.6% **Undetermined (% of total deaths)** Argentina: 14.3% Brazil: 21.0% Mexico: 24.6%
Jiang *et al.*[87]	2019	China	Hospital-based registry Cohort study with 2.5-year follow-up	17898 (38.7%)	Mean: 64.4	**CVD mortality rates** By the number of modifiable risk factors[c] No risk factors: 1.17/100 person-years 1 risk factor: 1.64/100 person-years $\geq$ 2 risk factors: 2.92/100 person-years
Paixão *et al.*[89]	2020	Brazil	Primary care-based ECG database Cross-sectional study	20782[d] (45.5%)	Mean: 68.5	**HR for CVD mortality associated with AF** Men: 1.71 (1.62–1.80) Women: 2.62 (2.24–3.06)
Stroke						
Yang *et al.*[84]	2014	China	Hospital-based registry Cohort study with 1-year follow-up	2016 (54.8%)	Mean: 68.5	**Overall stroke rates** Total sample: 7.4% Not anticoagulated: 7.8 % Anticoagulated: 7.6%
Healey *et al.*[85]	2016	47 countries[a]	Hospital-based registry Cohort study with 1-year follow-up	15400 (47%)	Mean: South America: 68.3 Eastern Europe: 69.3 Middle East: 58.6 Africa: 57.2 India: 57.9 China: 68.4 Southeast Asia: 69.5	**Overall stroke rates** South America: 3% Eastern Europe: 4% Middle East: 3% Africa: 8% India: 1% China: 7% Southeast Asia: 7%
Sawhney *et al.*[86]	2018	35 countries from America, Europe, Africa, and Asia[b]	Hospital-based registry Cohort study with 1-year follow-up	52014 India: 40.1% All countries: 44.2%	Mean: India: 68.5 All countries: 69.7	**Non-fatal stroke or systemic embolism rates** India: 0.85/100 person-years All countries: 1.34/100 person-years
	2019	Latin America		4162 (47.5%)	Mean: 69.8	**Non-fatal stroke or systemic embolism rate**

(continued)

Table 1 Continued

Author	Year	Country	Sample and design	*N* (% women)	Age (years)	Results
Jerjes-Sanchez *et al.*[54]			Hospital-based registry Cohort study with 1-year follow-up			1.58/100 person-years
Jiang *et al.*[87]	2019	China	Hospital-based registry Cohort study with 2.5-year follow-up	17 898 (38.7%)	Mean: 64.4	**Non-fatal ischaemic stroke** By the number of modifiable risk factors[c] No risk factors: 0.97/100 person-years 1 risk factor: 1.28/100 person-years ≥2 risk factors: 2.16/100 person-years
Other clinical outcomes						
Kawabata-Yoshihara *et al.*[15]	2012	Brazil	Population-based Cross-sectional study	1524 (2.4% with AF)	Range: 65+ Mean: 85.6	**ORs for the association with dementia** All: 1.2 (0.4-4.0) Men: 0.5 (0.1-5.1) Women: 2.2 (0.6-8.9)
Yang *et al.*[84]	2014	China	Hospital-based registry Cohort study with 1-year follow-up	2016 (54.8%)	Mean: 68.5	**Major bleeding rates** Total sample: 1.3% Not anticoagulated: 0.7 % Anticoagulated: 3.8% **MACE rates** Total sample: 21.9 % Not anticoagulated: 22.8 % Anticoagulated: 17.9%
Healey *et al.*[85]	2016	47 countries[a]	Hospital-based registry Cohort study with 1-year follow-up	15 400 (47%)	Mean: South America: 68.3 Eastern Europe: 69.3 Middle East: 58.6 Africa: 57.2 India: 57.9 China: 68.4 Southeast Asia: 69.5	**Major bleeding rates** South America: 2% Eastern Europe: 2% Middle East: 1% Africa: 2% India: <1% China: 1% Southeast Asia: 5% **Hospital admission rates due to HF:** South America: 7% Eastern Europe: 13% Middle East: 34% Africa: 4% India: 17% China: 1% Southeast Asia: 14% **Hospital admission rates due to MI:** South America: 1% Eastern Europe: 3%

(continued)

Table 1 Continued

Author	Year	Country	Sample and design	*N* (% women)	Age (years)	Results
						Middle East: 2% Africa: 2% India: <1% China: 1% Southeast Asia: 3%
Sawhney *et al.*[86]	2018	35 countries from America, Europe, Africa, and Asia[b]	Hospital-based registry Cohort study with 1-year follow-up	52 014 India: 40.1% All countries: 44.2%	Mean: India: 68.5 All countries: 69.7	**Major bleeding rates** India: 0.31/100 person-years All countries: 0.84/100 person-years **Acute coronary syndrome rates** India: 0.38 /100 person-years All countries: 0.77 /100 person-years
Jerjes-Sanchez *et al.*[54]	2019	Latin America	Hospital-based registry Cohort study with 1-year follow-up	4162 (47.5%)	Mean: 69.8	**Major bleeding rate** 0.99/100 person-years

Odds and hazard ratios are presented with the respective 95% confidence intervals.
[a]North America, Western Europe, and Australia were used as the reference population to compare with patients from other regions.
[b]All countries were used as the reference to compare with the Indian population.
[c]Modifiable risk factors were smoking, high BMI, alcohol use, high total cholesterol, blood pressure, and fasting plasma glucose.
[d]Also includes 1 445 584 individuals without AF.

[smoking, high body mass index (BMI), alcohol use, high total cholesterol, blood pressure, and fasting plasma glucose] was evaluated in almost 18 000 AF participants, with a mean follow-up of 2.5 years. It was demonstrated that the presence of ≥2 risk factors was associated with the highest risk of CVD mortality (adjusted HR: 2.92, 95% CI: 1.16–7.36), after multivariate adjustment.[87]

Non-fatal outcomes

In the RE-LY study, although the lowest stroke rate was verified in India [20 (<1%) of 2536], the highest number of strokes occurred in patients from Africa [89 (8%) of 1137], China [143 (7%) of 2023], and southeast Asia [88 (7%) out of 1331]. Meanwhile, the rate in North America, western Europe, and Australia was 2% (94/3800). Heart failure was the main cause of hospital admission 1 year after attending the ED with the highest proportion of cases in Africa compared with other geographical regions.[85] In the GARFIELD-AF study, major bleeding rates were lower in India (0.31/100 person-years; 95% CI: 0.12–0.82) compared with the global average from the same registry (0.84/100 person-years; 95% CI: 0.76–0.92), but no significant differences were observed for stroke/systemic embolism or ACS rates.[86] In Latin America,[54] reported stroke/systemic embolism and major bleeding rates were 1.58/100 person-years (95% CI: 1.23–2.02), and 0.99/100 person-years (95% CI 0.72–1.36), respectively. A Chinese study by Yang *et al.*,[84] found a significantly lower incidence of MACE events (17.9% vs. 22.8%), although accompanied by a higher incidence of major bleeding among patients with AF receiving OAC therapy (3.8% vs. 0.7%). Finally, the relationship between AF and dementia was investigated in a Brazilian population-based study,[15] performed among the elderly living in a deprived neighbourhood in the city of São Paulo. However, after age-adjustment, the association was not confirmed in this cross-sectional analysis.

Economic burden

Another way of looking at AF burden is to consider the concept of 'societal burden' or 'economic burden'. This burden includes total costs (both direct and indirect) associated with AF symptoms, its consequences, treatment, and/or treatment-induced complications. Direct costs include hospitalization (primarily for stroke, heart failure, arrhythmia recurrence, or decompensation and bleeding events), outpatient and home visits, prescriptions, laboratory testing, and long-term care. Economic burden also includes indirect costs related to loss of productivity from missing work during complications/hospitalizations or due to permanent disability from ischaemic stroke and support provided by caregivers. Given that AF-related strokes are predominantly more severe, cause more disability and tend to occur in people with more comorbidities, they result in higher direct costs annually compared with non-AF-related stroke. Furthermore, the financial burden is higher for patients and their families in LMIC countries where there is a greater level of out-of-pocket expenditure on healthcare. Across all countries where these issues have been studied, most of the costs are related to hospitalization.[91]

The treatment of patients with AF includes prevention of thromboembolic complications (particularly ischaemic stroke) and control of symptoms.[81] Thus, it includes antithrombotic therapy, management of concomitant conditions, and various strategies for symptom relief including antiarrhythmic drugs for rate or rhythm control, electrical cardioversion, and left atrial ablation. Access to all these possible treatment strategies varies greatly across LMICs. There is limited information on the true burden of disease, current management strategies, and cost-effectiveness for managing patients with AF in LMICs.[92]

Table 2 summarizes studies that evaluated the economic burden of AF in LMICs.[60,93-97] There are very few studies in this area. As the incidence of AF in LMICs is on the rise, more studies are needed to further elucidate the ongoing and future clinical and economic burdens of AF.

An analysis by Stevens *et al.*[93] estimated the prevalence, incidence, loss of wellbeing, health system cost, and productivity losses for four heart conditions (hypertension, heart failure, myocardial infarction, and AF) in Brazil. The authors estimated the annual economic costs of AF in Brazil to be 1.2 billion USD (2018), 94% of which was attributed to healthcare costs. In contrast, only 14% of the economic cost of hypertension was attributed to healthcare costs. They also estimated an annual attributable cost of 1003 USD for each patient with AF. The impact of AF on wellbeing showed that of the 3.2 million DALYs for the four heart conditions, 9% was due to AF (298 000 DALYs). Of the 1.9 million healthy years lost due to disability (YLD), 2% was due to AF and of the 1.3 million years of life lost due to premature mortality (YLL), 14% was due to AF. In comparison, the total cost of AF care in the USA is 6.65 billion USD (2005), 75% of which was costs associated with hospitalization, and the reported annual healthcare costs of AF range from 660 to 3286 million euros across Europe,[91] which represents ~2.5% of total healthcare spending.

In Algeria, Bouame *et al.*[94] estimated the annual cost of drugs and examinations to be 4.1 million euros and 62 million euros for hospitalizations related to AF. Hu *et al.*,[95] in a hospital-based cohort of patients with AF with embolic stroke in six major Chinese cities, estimated the mean total direct cost for AF-related stroke to be ~5000 USD per person-year, the major cost driver (61.5%) being hospitalization. Total indirect cost was estimated at ~2800 USD, most of which (63%) was a result of early retirement. Wen *et al.*,[96] in a retrospective analysis of economic data from the Beijing urban health insurance database compared the economic burden of treatment-related costs of stroke patients with AF vs. those without AF. Overall inpatient costs and total healthcare costs per patient were nearly three times as high in patients with AF compared to those without, partly due to higher frequency of comorbidities in the former group. Total healthcare cost covered by health insurance and annualized total healthcare cost per patient were also higher in the patient group with AF. As a high-income country comparison, Kim *et al.*[98] evaluated 931 138 patients with AF from the National Health Insurance Service (NHIS) database in South Korea and found a 420% increase in hospitalizations for AF from 2006 to 2015 (from

Table 2 Economic burden of atrial fibrillation in low- and middle-income countries

Author	Year	Location	Sample and design	*N*	Age (years)	Results
Stevens *et al.*[93]	2018	Brazil	Community-based cohort study with cost of illness framework based on estimated prevalence	1 202 151 patients with AF in Brazil	Range: 20+	Annual economic costs: 1.2 billion USD (2018); 94% attributed to healthcare costs. 1003 USD per patient-year
Bouame *et al.*[94]	2018	Algeria	Literature review and cost estimation based on AF prevalence	Estimated Algerian population with AF: 187 686	66.7% aged 65+ (estimative)	Drug cost: 1.5 million euros Examination cost: 2.6 million euros Hospitalization cost: 62 million euros Economic burden of non-valvular AF > 65 million euros
Hu *et al.*[95]	2013	China	Economic analysis in hospital-based cohort study of patients with AF and ischaemic stroke	300	Mean: 70.2	Mean total direct cost for AF-related stroke: approximately 5000 USD per person-year
Wen *et al.*[96]	2017	China	Cost study using an urban health insurance database of individuals with ischaemic stroke	4061 (992 with AF)	Mean: 68.5	Individuals with AF-related stroke had more comorbidities and hospitalizations. They also had higher cost per hospitalization and total healthcare cost compared to individuals with stroke without AF
Silva *et al.*[60]	2020	Brazil	Retrospective cohort cost study (private health insurance database) using outpatient anticoagulation clinic data	1220	Mean: 63.9	Annual cost per patient across the entire cohort was (10679 USD); Inpatient costs represented 64% of all costs (6851 USD); Outpatient costs represented 36% (3828 USD).
Marfatia *et al.*[97]	2014	India	Multicentric cost of illness study using hospital data of patients with incident AF-related stroke	400	Mean: 61.4	Total mean direct healthcare costs per patient amounted to 8020 USD during the first year (47% due to index hospitalization)

767 to 3986 per million Korean population). There are very few studies about the economic impact of AF in LMICs, and as the incidence of AF in LMICs is expected to increase, more studies are needed to further elucidate the ongoing and future clinical and economic burdens of AF.

A hospital-based study from India[97] found that AF-related stroke had a total mean direct healthcare cost per patient of 8020 USD during the first year after the stroke, and 47% of this amount was for the index hospitalization. Other healthcare costs were related to outpatient care (40% of total), nursing care, home modifications, and informal care (13%).

Another study from Brazil[60] evaluated anticoagulation therapy in 1220 individuals with AF in a private setting. They found an annual cost of 10679 USD per patient across the entire cohort (mean follow-up of 1.5 years). Hospitalizations represented 64% of all costs (6851 USD) and outpatient costs amounted to 3828 USD (36% of total).

Discussion

To date, AF prevalence is still higher in high-income countries than in LMICs. This acknowledgment, however, should not overshadow the impact of AF on the health of LMIC populations, where 61% of global DALYs due to AF occur. Analyzing the data from the previous three decades, we may predict a progressive concentration of AF burden (including AF-related stroke) in LMICs in the coming years.

Oral anticoagulant therapy for AF-related stroke prevention is underused even in high-income countries. It is reasonable to consider this problem has a higher magnitude compared with high-income countries. Although

conflicting data exist,[99] the best system to identify individuals with AF who will benefit from OAC therapy currently is the CHA_2DS_2-VASc score.[100-102] The prevalence of risk factors for AF-related stroke (and, consequently, the distribution of stroke risk stratification score values) differs among countries, but a substantial proportion of articles included in this review does not present information about CHA_2DS_2-VASc scores. This is an important current gap in knowledge. In addition, similar CHA_2DS_2-VASc scores may be associated with heterogeneous levels of risk across populations, probably due to multiple factors, as access to healthcare, adherence to treatment, ethnic characteristics (especially in highly admixed populations), or genetic predisposition.[103] Although previous studies have studied the prediction accuracy of CHA_2DS_2-VASc scores for AF-related stroke in some LMIC settings,[104-106] information from these countries are scarcer compared with those from high-income countries.[107] This highlights the importance of future observational studies to validate and refine stroke risk prediction in LMICs.

Some LMIC features will make stroke prevention in these locations an increasingly challenging situation. First, barriers to health care access in LMICs[108] are usually greater than in high-income nations. Second, the advances brought by NOACs in long-term OAC therapy also come with an initial rise in treatment costs. The widespread adoption of a more expensive medication would represent a new cost for LMICs. Although there is evidence this is counteracted by other costs in patient care, such as visits needed to monitor VKA action and event costs,[109] this investment may be currently unaffordable for LMICs due to other pressing demands from the healthcare sector. Future patent expirations will probably change this scenario, and most likely represent an important stimulus to the adoption of NOACs. Lastly, the structure and expenditures of national health systems vary widely in LMICs which range from conflict-affected states to countries with mature health systems.[110] Currently most LMICs do not have a healthcare structure capable of managing OAC, as WHO data about healthcare coverage shows. The WHO Universal Health Coverage (UHC) index of service coverage ranges from zero to one and summarizes indicators about how health service coverage is improving across the world.[111] In 2017, this index was 0.82 for high-income countries, while upper-middle, lower-middle, and low-income countries had indexes of 0.77, 0.55, and 0.43, respectively.[112] Moreover, there are large gaps in the service capacity and access component of the index among income country groups. For example, although the score for high-income country group is over 90% for this component, the low-income country group scores slightly above 20%. An out-of-pocket cost (OPC) is a direct payment of money that may or may not be later reimbursed from a third-party source, such as a health insurance company. It is another healthcare system feature that may influence the adoption of effective strategies for AF treatment and stroke prevention. OPC also vary widely across national health systems. In general, the lower the per capita income, the higher the OPC proportion among total health costs. OPC proportions in high-, upper-middle, lower-middle, and low-income groups are 13.6%, 32.9%, 55.7%, and 51.5%, respectively. Looking at these ratios, however, masks intense differences among countries in the same groups. In 2017, OPC proportions varied from 0.9% (Nauru) to 48.9% (Mauritius) in high-income countries, 0.5% (Tuvalu) to 84.3% (Armenia) in upper-middle income countries, 0.1% (Kiribati) to 77.2% (Nigeria) in lower-middle income countries, and 6.2% (Rwanda) to 75.5% (Afghanistan) in low-income countries.[113]

Besides a low use of OAC therapy, this review reports a widespread use of aspirin for stroke prevention in LMICs, a characteristic present in high-income countries,[114] but with lower magnitude compared with LMICs. This poses an additional challenge to achieve adequate levels of OAC use for stroke prevention in LMICs. Aspirin, alone or in combination with other antiplatelets, is incorrectly perceived as a 'soft' choice for stroke prevention in patients with AF, with a combination of fair efficacy and low bleeding risk.[115,116] Both perceptions are not true, as recognized by the recent 2020 ESC guidelines.[81] Improving physician and patients' perceptions about the balance of benefits and risks of anticoagulation for patients with AF and high stroke risk is an important objective to overcome this scenario in LMICs.[117] However, this is probably not only a problem of incorrect perceptions and, eventually, lack of knowledge. Especially in LMICs, many physicians may be afraid to initiate warfarin therapy for a patient who would not have adequate follow-up to ensure INR control and a high TTR. This is potentialized by the possibility of being held accountable for harmful effects of the drug.[118] Some strategies must be considered to increase adequate OAC use in patients with AF, including educational interventions, providing adequate support for OAC management with warfarin and higher availability and access to NOAC. Future studies using both quantitative and qualitative methodologies are needed to further specify the reasons for the incorrect use of antiplatelets for stroke prevention, disclosing opportunities for effective interventions.

Therefore, local data are needed to guide the allocation of resources in countries living in similar conditions. In addition, LMICs encompass remarkably diverse ethnicities, and this affects stroke prevention strategies for patients with AF due to multiple reasons.[119] First, as discussed earlier, there is evidence that the prevalences of AF-related stroke risk factors differ, and even similar stroke risk scores may represent heterogeneous levels of risk among different populations. Second, racial disparities in health access and quality of care do exist, also explaining part of the higher stroke risk in minority groups.[120] For example, the REasons for Geographic and Racial Differences in Stroke (REGARDS) study showed that Black individuals with AF in the USA had lower odds to be aware of the diagnosis and to receive warfarin treatment, compared to White individuals.[121] Although this study was conducted in a high-income country, it is highly likely that minority or more deprived groups in LMICs face similar or worse difficulties. Third, warfarin doses to achieve the therapeutic range are influenced by some genetic variants, as in CYP2C9 and VKORC1 genes,[122,123] reinforcing the need for adequate support for VKA dose control to ensure safe OAC therapy and a high TTR.

The available data also point to a higher morbimortality per patient with AF in LMICs compared to their counterparts in high-income countries. Although data on the

consequent economic burden in LMICs are scarce, it is reasonable to consider it will follow the same trend as observed for morbimortality.

In conclusion, AF incurs in significant burden in LMICs, and this scenario is expected to become even more important in the next decades. Adequate visibility of AF as a public health problem in LMICs is necessary as a first step to overcoming the stated difficulties and to provide adequate care for these patients. Given the high heterogeneity among LMICs, it is very unlikely that a 'one size fits all' strategy would be efficient for stroke prevention in this scenario. This makes obtaining reliable local data a sensitive point to implement public health policies.

Supplementary material

Supplementary material is available at *European Heart Journal Supplements* online.

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Data availability

All data in this review were publicly available by the time of its submission. The first author may provide downloaded datasets upon reasonable request.

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