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

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KEYWORDS

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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 CHA₂DS₂-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 globally¹; 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 criteria⁵ (Supplementary material online, Appendix S1). This classification categorizes countries according to the gross national income per capita as low-income [\leq US dollars (USD) 1035], lower-middle income (USD 1036–4045), upper-middle income (USD 4046–12 535), and high-income (\geq 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

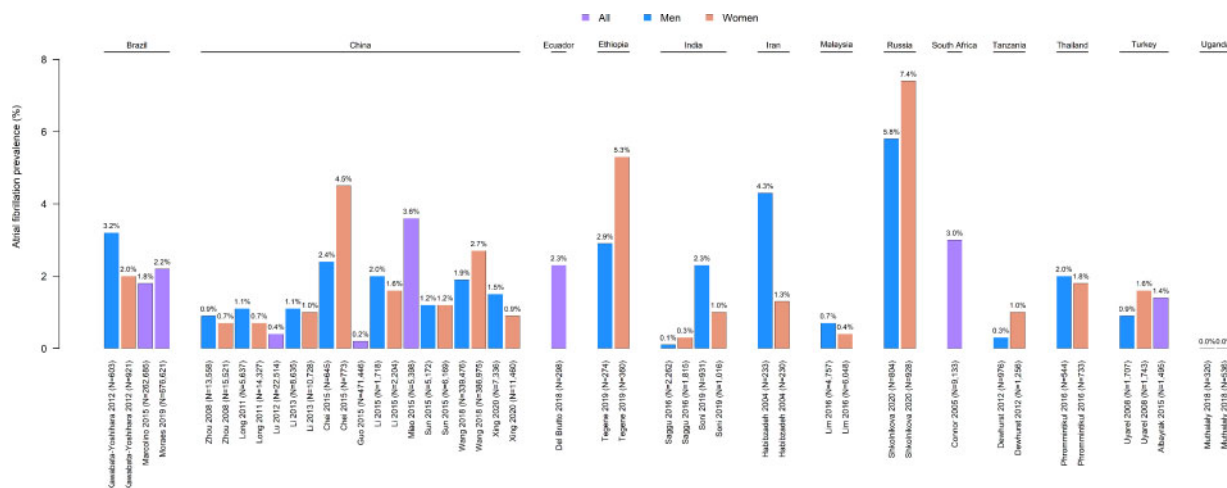


Figure 1 Atrial fibrillation prevalence rates in low- and middle-income countries, according to sex.

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 CHADS₂ or CHA₂DS₂-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 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

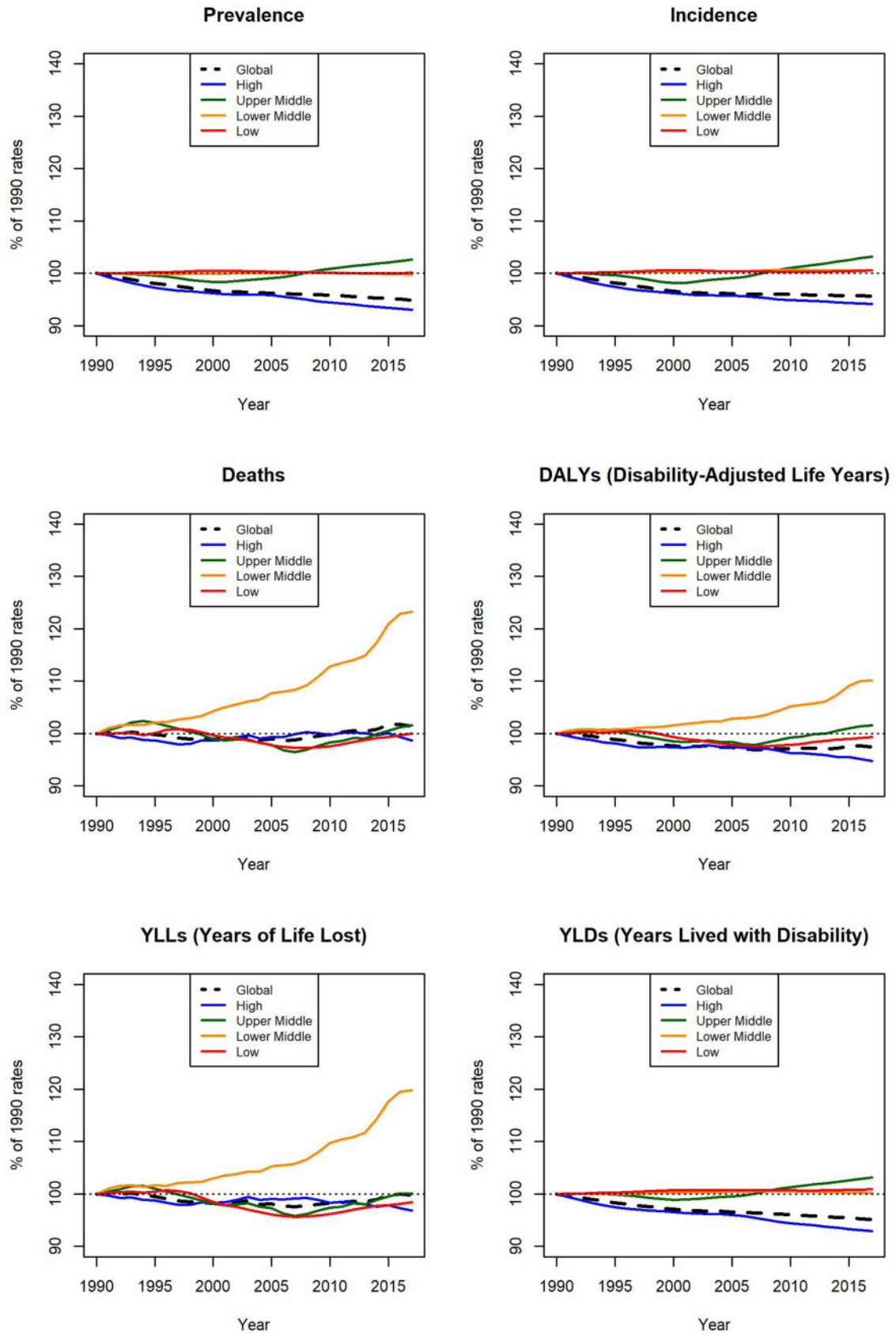


Figure 2 Epidemiological trends for atrial fibrillation, from 1990 to 2017, according to the World Bank income groups.

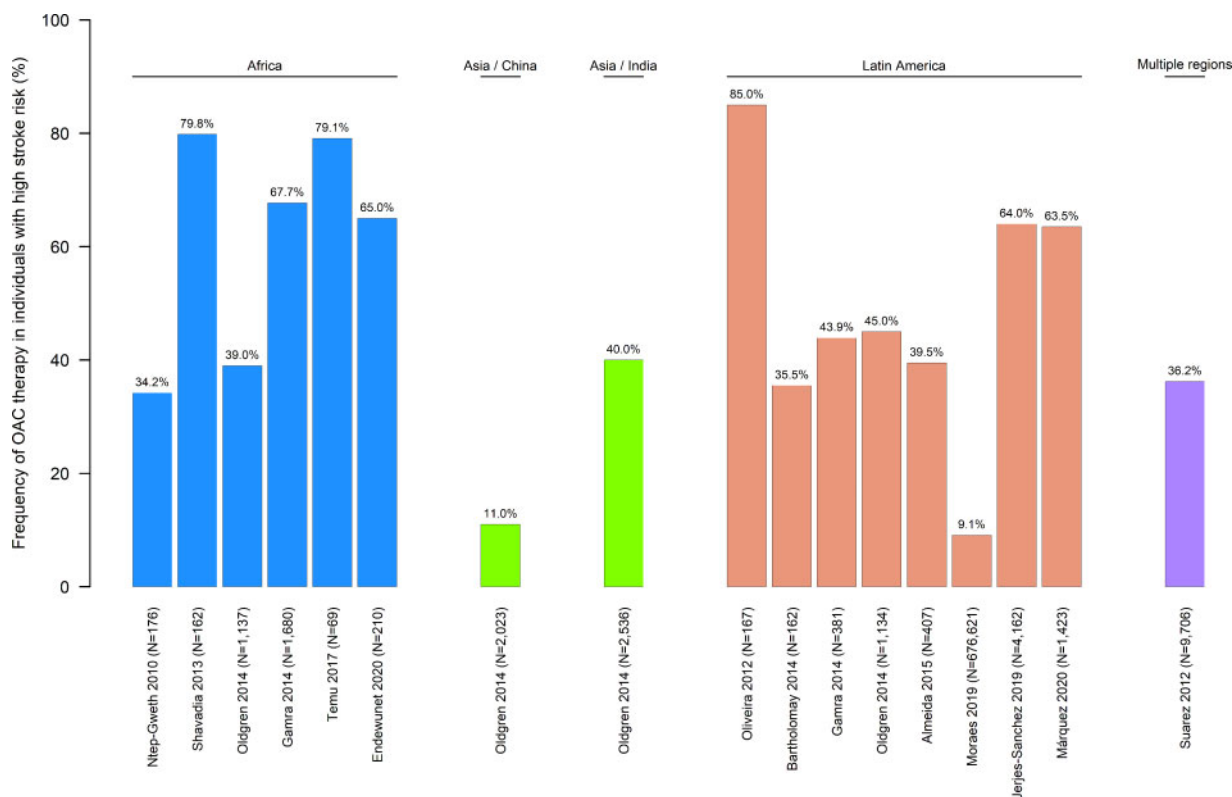


Figure 3 Oral anticoagulant therapy for high stroke risk patients with atrial fibrillation in low- and middle-income countries.

consolidated results^{54,70} and 2 have information about more than one country, with results stratified by location.^{62,72} The Realize AF Survey⁵¹ 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 Registry⁵⁷ 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 CHA₂DS₂-VASc scores ≥ 1 or women with CHA₂DS₂-VASc scores ≥ 2 . For men with CHA₂DS₂-VASc score = 1 and women with CHA₂DS₂-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' CHADS₂ or CHA₂DS₂-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 CHA₂DS₂ or CHA₂DS₂-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 CHADS₂ 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 CHA₂DS₂-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 CHADS₂ 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 (225/3800; 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 multi-centre 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 <i>et al.</i> 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 %
	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 <i>et al.</i> ⁸⁶	2018	35 countries from America, Europe, Africa, and Asia ^b Latin America	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 <i>et al.</i> 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
	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 ≥2 risk factors: 5.31/100 person-years
Paixão <i>et al.</i> 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 <i>et al.</i> 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
Jerjes-Sanchez <i>et al.</i> ⁵⁴	2019	Latin America	Hospital-based registry Cohort study with 1-year follow-up	4162 (47.5%)	Mean: 69.8	India: 2.84 /100 person-years All countries: 1.11/100 person-years 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% 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 ≥ 2 risk factors: 2.92/100 person-years HR for CVD mortality associated with AF Men: 1.71 (1.62-1.80) Women: 2.62 (2.24-3.06)
Jiang <i>et al.</i> ⁸⁷	2019	China	Hospital-based registry Cohort study with 2.5-year follow-up	17 898 (38.7%)	Mean: 64.4	
Paixão <i>et al.</i> ⁸⁹	2020	Brazil	Primary care-based ECG database Cross-sectional study	20 782 ^d (45.5%)	Mean: 68.5	
Stroke Yang <i>et al.</i> 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% Overall stroke rates South America: 3% Eastern Europe: 4% Middle East: 3% Africa: 8% India: 1% China: 7% Southeast Asia: 7% Non-fatal stroke or systemic embolism rates India: 0.85/100 person-years All countries: 1.34/100 person-years
Healey <i>et al.</i> 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	
Sawhney <i>et al.</i> ⁸⁶	2018	35 countries from America, Europe, Africa, and Asia ^b Latin America	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	
	2019			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 <i>et al.</i> ⁵⁴			Hospital-based registry			1.58/100 person-years
Jiang <i>et al.</i> ⁸⁷	2019	China	Cohort study with 1-year follow-up 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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
Sawhney <i>et al.</i> 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	Middle East: 2% Africa: 2% India: <1% China: 1% Southeast Asia: 3% 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 Major bleeding rate 0.99/100 person-years
Jerjes-Sanchez <i>et al.</i> ⁵⁴	2019	Latin America	Hospital-based registry Cohort study with 1-year follow-up	4162 (47.5%)	Mean: 69.8	

Odds and hazard ratios are presented with the respective 95% confidence intervals.

^aNorth America, Western Europe, and Australia were used as the reference population to compare with patients from other regions.

^bAll countries were used as the reference to compare with the Indian population.

^cModifiable risk factors were smoking, high BMI, alcohol use, high total cholesterol, blood pressure, and fasting plasma glucose.

^dAlso 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 anti-thrombotic 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 <i>et al.</i> 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.
Bouame <i>et al.</i> ⁹⁴	2018	Algeria	Literature review and cost estimation based on AF prevalence	Estimated Algerian population with AF: 187 686	66.7% aged 65+ (estimative)	1003 USD per patient-year 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 India⁹⁷ 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 Brazil⁶⁰ 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 CHA₂DS₂-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 CHA₂DS₂-VASc scores. This is an important current gap in knowledge. In addition, similar CHA₂DS₂-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 CHA₂DS₂-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 LMICs¹⁰⁸ 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.

References

- GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;**18**:439-458.
- Murphy A, Banerjee A, Breithardt G, Camm AJ, Commerford P, Freedman B, Gonzalez-Hermosillo JA, Halperin JL, Lau CP, Perel P, Xavier D, Wood D, Jouven X, Morillo CA. The world heart federation roadmap for nonvalvular atrial fibrillation. *Glob Heart* 2017;**12**:273-284.
- Dai H, Zhang Q, Much AA, Maor E, Segev A, Beinart R, Adawi S, Lu Y, Bragazzi NL, Wu J. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. *Eur Heart J Qual Care Clin Outcomes* 2020;doi:10.1093/ehjqcco/qcaa061.
- Global Burden of Disease Collaborative Network. *Global Burden of Disease Study 2017 (GBD 2017) Results*. Seattle, USA: Institute for Health Metrics and Evaluation (IHME), 2018. <http://ghdx.healthdata.org/gbd-results-tool> (20 August 2020).
- World Bank. World Bank Country and Lending Groups. <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups> (20 August 2020).
- Stewart S, Wilkinson D, Hansen C, Vaghela V, Mvungi R, McMurray J, Sliwa K. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. *Circulation* 2008;**118**:2360-2367.
- Alkali NH, Bwala SA, Akano AO, Osi-Ogbu O, Alabi P, Ayeni OA. Stroke risk factors, subtypes, and 30-day case fatality in Abuja, Nigeria. *Niger Med J* 2013;**54**:129-135.
- Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, Francis V, Ogendo S, Gitura B, Mondo C, Okello E, Lwabi P, Al-Kebisi MM, Hugo-Hamman C, Sheta SS, Haileamlak A, Daniel W, Goshu DY, Abdissa SG, Desta AG, Shasho BA, Begna DM, ElSayed A, Ibrahim AS, Musuku J, Bode-Thomas F, Okeahialam BN, Ige O, Sutton C, Misra R, Abul Fadl A, Kennedy N, Damasceno A, Sani M, Ogah OS, Olunuga T, Elhassan HH, Mocumbi AO, Adeoye AM, Mntla P, Ojji D, Mucumbitsi J, Teo K, Yusuf S, Mayosi BM. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015;**36**:1115-1221.
- Habibzadeh F, Yadollahie M, Roshanipoor M, Haghghi AB. Prevalence of atrial fibrillation in a primary health care centre in Fars Province, Islamic Republic of Iran. *East Mediterr Health J* 2004;**10**:147-151.
- Connor M, Rheeder P, Bryer A, Meredith M, Beukes M, Dubb A, Fritz V. The South African stroke risk in general practice study. *S Afr Med J* 2005;**95**:334-339.
- Uyarel H, Onat A, Yüksel H, Can G, Ordu S, Dursunoğlu D. [Incidence, prevalence, and mortality estimates for chronic atrial fibrillation in Turkish adults]. *Türk Kardiyol Dern Ars* 2008;**36**:214-222.
- Zhou Z, Hu D. An epidemiological study on the prevalence of atrial fibrillation in the Chinese population of mainland China. *J Epidemiol* 2008;**18**:209-216.
- Long MJ, Jiang CQ, Lam TH, Xu L, Zhang WS, Lin JM, Ou JP, Cheng KK. Atrial fibrillation and obesity among older Chinese: the Guangzhou Biobank Cohort Study. *Int J Cardiol* 2011;**148**:48-52.
- Dewhurst MJ, Adams PC, Gray WK, Dewhurst F, Orega GP, Chaote P, Walker RW. Strikingly low prevalence of atrial fibrillation in elderly Tanzanians. *J Am Geriatr Soc* 2012;**60**:1135-1140.
- Kawabata-Yoshihara LA, Sczufca M, Santos ID, Whitaker A, Kawabata VS, Bensenor IM, Menezes PR, Lotufo PA. Atrial fibrillation and dementia: results from the Sao Paulo Ageing & Health Study. *Arquivos Brasileiros de Cardiologia* 2012;**99**:1108-1113.
- Lu WH, Mu HY, Liu ZQ, Yang YC, He PY, Yan HY, Jia M, Gu L, Kong B, Shagen D. [The prevalence and distributing feature of atrial fibrillation in Xinjiang Uygur Autonomous Region Kazaks adult population]. *Zhonghua Nei Ke Za Zhi* 2012;**51**:674-676.
- Li Y, Wu YF, Chen KP, Li X, Zhang X, Xie GQ, Wang FZ, Zhang S. Prevalence of atrial fibrillation in China and its risk factors. *Biomed Environ Sci* 2013;**26**:709-716.
- Albayrak S, Ozhan H, Aslantas Y, Ekinozu I, Tibilli H, Kayapinar O, Investigators MS. Predictors of major adverse cardiovascular events; results of population based MELEN study with prospective follow-up. *Eur Rev Med Pharmacol Sci* 2015;**19**:1446-1451.
- Chei CL, Raman P, Ching CK, Yin ZX, Shi XM, Zeng Y, Matchar DB. Prevalence and risk factors of atrial fibrillation in Chinese elderly: results from the Chinese Longitudinal Healthy Longevity Survey. *Chin Med J (Engl)* 2015;**128**:2426-2432.
- Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GYH. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. *Chest* 2015;**147**:109-119.
- Li LH, Sheng CS, Hu BC, Huang QF, Zeng WF, Li GL, Liu M, Wei FF, Zhang L, Kang YY, Song J, Wang S, Li Y, Liu SW, Wang JG. The prevalence, incidence, management and risks of atrial fibrillation in an elderly Chinese population: a prospective study. *BMC Cardiovasc Disord* 2015;**15**:31.
- Marcolino MS, Palhares DM, Benjamin EJ, Ribeiro AL. Atrial fibrillation: prevalence in a large database of primary care patients in Brazil. *Europace* 2015;**17**:1787-1790.
- Miao H, Hong Y, Kabinur K, Zou T, Palida A, Zhou X. [Epidemiological survey of atrial fibrillation among Uygur and Han elderly people in Xinjiang Uygur autonomous region]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2015;**36**:1065-1068.
- Sun GZ, Guo L, Wang XZ, Song HJ, Li Z, Wang J, Sun YX. Prevalence of atrial fibrillation and its risk factors in rural China: a cross-sectional study. *Int J Cardiol* 2015;**182**:13-17.

25. Lim CW, Kasim S, Ismail JR, Chua NY, Najme Khir R, Zainal Abidin HA, Abdul Rahman E, Mohd Arshad MK, Ibrahim Othman Z, Yusoff K. Prevalence of atrial fibrillation in the Malaysian communities. *Heart Asia* 2016;**8**:62-66.
26. Phrommintikul A, Detnuntarat P, Prasertwitayakij N, Wongcharoen W. Prevalence of atrial fibrillation in Thai elderly. *J Geriatr Cardiol* 2016;**13**:270-273.
27. Saggi DK, Sundar G, Nair SG, Bhargava VC, Lalukota K, Chennapragada S, Narasimhan C, Chugh SS. Prevalence of atrial fibrillation in an urban population in India: the Nagpur pilot study. *Heart Asia* 2016;**8**:56-59.
28. Del Brutto OH, Costa AF, Cano JA, Peñaherrera E, Plaza KJ, Ledesma EA, Tettamanti D, Zambrano M. Low prevalence of atrial fibrillation in Amerindians: a population-based study in frequent fish consumers living in rural coastal Ecuador (The Atahualpa Project). *Aging Clin Exp Res* 2018;**30**:539-542.
29. Muthalaly RG, Koplan BA, Albano A, North C, Campbell JI, Kakuhikire B, Vořechovská D, Kraemer JD, Tsai AC, Siedner MJ. Low population prevalence of atrial fibrillation in rural Uganda: a community-based cross-sectional study. *Int J Cardiol* 2018;**271**: 87-91.
30. Wang X, Fu Q, Song F, Li W, Yin X, Yue W, Yan F, Zhang H, Zhang H, Teng Z, Wang L, Gong Y, Wang Z, Lu Z. Prevalence of atrial fibrillation in different socioeconomic regions of China and its association with stroke: results from a national stroke screening survey. *Int J Cardiol* 2018;**271**:92-97.
31. de Moraes ERF, Cirenza C, Lopes RD, Carvalho AC, Guimaraes PO, Rodrigues AAE, de Paola AAV. Prevalence of atrial fibrillation and stroke risk assessment based on telemedicine screening tools in a primary healthcare setting. *Eur J Intern Med* 2019;**67**:36-41.
32. Soni A, Karra S, Fahey N, Sanghai S, Patel H, Raithatha S, Thanvi S, Nimbalkar S, Freedman B, Allison J, McManus DD. Age-and-sex stratified prevalence of atrial fibrillation in rural Western India: results of SMART-India, a population-based screening study. *Int J Cardiol* 2019;**280**:84-88.
33. Tegene E, Tadesse I, Markos Y, Gobena T. Prevalence and risk factors for atrial fibrillation and its anticoagulant requirement in adults aged ≥ 40 in Jimma Town, Southwest Ethiopia: a community based cross-sectional study. *Int J Cardiol Heart Vasc* 2019;**22**: 199-204.
34. Shkolnikova MA, Jdanov DA, Ildarova RA, Shcherbakova NV, Polyakova EB, Mikhaylov EN, Shalnova SA, Shkolnikov VM. Atrial fibrillation among Russian men and women aged 55 years and older: prevalence, mortality, and associations with biomarkers in a population-based study. *J Geriatr Cardiol* 2020;**17**:74-84.
35. Xing L, Lin M, Du Z, Jing L, Tian Y, Yan H, Ren G, Dong Y, Sun Q, Dai D, Shi L, Chen H, Liu S. Epidemiology of atrial fibrillation in northeast China: a cross-sectional study, 2017-2019. *Heart* 2020;**106**:590-595.
36. Ding L, Li J, Wang C, Li X, Su Q, Zhang G, Xue F. Incidence of atrial fibrillation and its risk prediction model based on a prospective urban Han Chinese cohort. *J Hum Hypertens* 2017;**31**:574-579.
37. Chugh SS, Roth GA, Gillum RF, Mensah GA. Global burden of atrial fibrillation in developed and developing nations. *Glob Heart* 2014;**9**:113-119.
38. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**: 1789-1858.
39. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1736-1788.
40. Ezzati M, Pearson-Stuttard J, Bennett JE, Mathers CD. Acting on non-communicable diseases in low- and middle-income tropical countries. *Nature* 2018;**559**:507-516.
41. Ahmed I, Lemma S. Mortality among pediatric patients on HIV treatment in sub-Saharan African countries: a systematic review and meta-analysis. *BMC Public Health* 2019;**19**:149.
42. Meidani Z, Mahdian M, Ayan A, Mohammadzade M, Nickfarjam A, Moosavi GA. Registry Data Coordinator (RDC): a proper accessible strategy for improving road traffic injury (RTI) hospital based trauma registry systems in developing countries and low income countries. *Acta Inform Med* 2018;**26**:35-41.
43. Morillo CA, Banerjee A, Perel P, Wood D, Jouven X. Atrial fibrillation: the current epidemic. *J Geriatr Cardiol* 2017;**14**:195-203.
44. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Investigators REOL-TAT. Newly identified events in the RE-LY trial. *N Engl J Med* 2010;**363**:1875-1876.
45. Russo V, Attena E, Di Maio M, Carbone A, Parisi V, Rago A, Grieco FV, Buonauro A, Golino P, Nigro G. Non-vitamin K vs vitamin K oral anticoagulants in patients aged > 80 year with atrial fibrillation and low body weight. *Eur J Clin Invest* 2020;**50**:e13335.
46. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest* 2012;**142**:1489-1498.
47. Winkel TA, Hoeks SE, Schouten O, Zeymer U, Limbourg T, Baumgartner I, Bhatt DL, Steg PG, Goto S, Röther J, Cacoub PP, Verhagen HJ, Bax JJ, Poldermans D. Prognosis of atrial fibrillation in patients with symptomatic peripheral arterial disease: data from the REduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur J Vasc Endovasc Surg* 2010;**40**:9-16.
48. Iturralde-Torres P, Lara-Vaca S, Cordero-Cabra A, Nava-Townsend S, Mendoza C, Márquez MF, Saucedo-Sánchez N, Martínez-Flores E. [Design of a multicenter registry to evaluate rhythm versus rate control in atrial fibrillation: atrial Fibrillation Mexican Registry (ReMeFA)]. *Arch Cardiol Mex* 2011;**81**:13-17.
49. González-Hermosillo JA, Márquez MF, Ocampo-Peña S; CARMEN-AF. [Design of an atrial fibrillation and embolic risk registry in Mexico: CARMEN-AF]. *Arch Cardiol Mex* 2017;**87**:5-12.
50. Lopes RD, de Paola AA, Lorga Filho AM, Consolim-Colombo FM, Andrade J, Piva E Mattos LA, Bernardes-Pereira S, Berwanger O, de Oliveira Figueiredo MJ, Investigators RSCa. Rationale and design of the First Brazilian Cardiovascular Registry of Atrial Fibrillation: the RECALL study. *Am Heart J* 2016;**176**:10-16.
51. Gamra H, Murin J, Chiang CE, Naditch-Brülé L, Brette S, Steg PG, Investigators R. Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: insights from the International RealiseAF Survey. *Arch Cardiovasc Dis* 2014;**107**: 77-87.
52. Bartholomay E, Polli I, Borges AP, Kalil C, Arroque A, Kohler I, Danzmann LC. Prevalence of oral anticoagulation in atrial fibrillation. *Clinics (Sao Paulo)* 2014;**69**:615-620.
53. Almeida ED, Guimarães RB, Stephan LS, Medeiros AK, Foltz K, Santanna RT, Pires LM, Kruse ML, Lima GG, Leiria TL. Clinical differences between subtypes of atrial fibrillation and flutter: cross-sectional registry of 407 patients. *Arq Bras Cardiol* 2015;**105**:3-10.
54. Jerjes-Sanchez C, Corbalan R, Barretto ACP, Luciardí HL, Allu J, Illingworth L, Pieper KS, Kayani G; for the GARFIELD-AF Investigators. Stroke prevention in patients from Latin American countries with non-valvular atrial fibrillation: insights from the GARFIELD-AF registry. *Clin Cardiol* 2019;**42**:553-560.
55. Márquez MF, Baños-González MA, Guevara-Valdivia ME, Vázquez-Acosta J, de Los Ríos Ibarra MO, Aguilar-Linares JA, Jiménez-Cruz M, Matadamas-Hernández N, Camacho-Casillas R, Magaña-Magaña R, Rojel-Martínez U, Alcocer-Gamba MA, Lara-Vaca S, Rodríguez-Reyes H, Islava-Gálvez MA, Betancourt-Hernández LE, Reyes-Reyes N, Beltrán-Gómez ME, Cantú-Brito C, Baños-Velasco AZ, Del Rivero Morfin PJ, González-Hermosillo JA. Anticoagulation therapy by age and embolic risk for nonvalvular atrial fibrillation in Mexico, an upper-middle-income country: the CARMEN-AF Registry. *Glob Heart* 2020;**15**:32.
56. Gerales MFA, Darze ES, Rocha PN. Trends and predictors of oral anticoagulation in patients with atrial fibrillation: a serial cross-sectional study from 2011 to 2016. *Int J Cardiovasc Sci* 2020;**33**: 68-78.
57. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, Zhu J, Jansky P, Sigamani A, Morillo CA, Liu L, Damasceno A, Grinvalds A, Nakamya J, Reilly PA, Keltai K, Van Gelder IC, Yusufali AH, Watanabe E, Wallentin L, Connolly SJ, Yusuf S; Investigators R-LAFR. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. *Circulation* 2014;**129**:1568-1576.

58. Charanthyayil Gopalan B, Namboodiri N, Abdullakutty J, Lip GY, Koshy AG, Krishnan Nair V, Babu S, Muhammed S, Azariah JL, George R, Nambiar A, Govindan U, Zachariah G, Kumaraswamy N, Chakanalil Govindan S, Natesan S, Roby A, Velayudhan Nair K, Pillai AM, Daniel R; Kerala Atrial Fibrillation Registry Investigators. Kerala Atrial Fibrillation Registry: a prospective observational study on clinical characteristics, treatment pattern and outcome of atrial fibrillation in Kerala, India, cohort profile. *BMJ Open* 2019;9:e025901.
59. Endewunet E, Tadesse A, Adane A, Abdulkadir M. Appropriate use of anti-thrombotic therapy in patients with atrial fibrillation at single-center experience, Northwest Ethiopia. *BMC Cardiovasc Disord* 2020;20:375.
60. Silva PGMB, Szejder H, Vasconcellos R, Charles GM, Mendonca-Filho HTF, Mardekian J, Nascimento R, Dukacz S, Fusco MD. Anticoagulation therapy in patients with non-valvular atrial fibrillation in a private setting in Brazil: a Real-World Study. *Arq Bras Cardiol* 2020;114:457-466.
61. Zhang X, Zhang S, Li Y, Detrano RC, Chen K, Li X, Zhao L, Benjamin EJ, Wu Y. Association of obesity and atrial fibrillation among middle-aged and elderly Chinese. *Int J Obes (Lond)* 2009;33:1318-1325.
62. Cubillos L, Haddad A, Kuznik A, Mould-Quevedo J. Burden of disease from atrial fibrillation in adults from seven countries in Latin America. *Int J Gen Med* 2014;7:441-448.
63. Temu TM, Lane KA, Shen C, Ng'ang'a L, Akwanalo CO, Chen PS, Omonyi W, Heckbert SR, Koech MM, Manji I, Vatta M, Velazquez EJ, Wessel J, Kimaiyo S, Inui TS, Bloomfield GS. Clinical characteristics and 12-month outcomes of patients with valvular and non-valvular atrial fibrillation in Kenya. *PLoS One* 2017;12:e0185204.
64. Mandi D, Samadoulougou A, Yameogo R, Millogo G, Naibe D, Kaboré P, Kologo K, Zabsonré P. Non valvular atrial fibrillation related ischaemic stroke at the teaching hospital of Yalgado Ouédraogo, Burkina Faso. *J Vasc Med Surg* 2015;3: 171.
65. Akpa MR, Ofori S. Atrial fibrillation: an analysis of etiology and management pattern in a tertiary hospital in Port-Harcourt, southern, Nigeria. *Res J Health Sci* 2015;3:303-309.
66. Ntep-Gweth M, Zimmermann M, Meiltz A, Kingue S, Ndobu P, Urban P, Bloch A. Atrial fibrillation in Africa: clinical characteristics, prognosis, and adherence to guidelines in Cameroon. *Europace* 2010;12:482-487.
67. Jardine RM, Fine J, Obel IW. A survey on the treatment of atrial fibrillation in South Africa. *S Afr Med J* 2014;104:623-627.
68. Njovane XW, Fasinu PS, Rosenkranz B. Comparative evaluation of warfarin utilisation in two primary healthcare clinics in the Cape Town area. *Cardiovasc J Afr* 2013;24:19-23.
69. Anakwue R, Ocheni S, Madu A. Utilization of oral anticoagulation in a teaching hospital in Nigeria. *Ann Med Health Sci Res* 2014;4: 286-290.
70. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa K. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med* 2012;172: 1386-1394.
71. Jacobs MS, van Hulst M, Adeoye AM, Tieleman RG, Postma MJ, Owolabi MO. Atrial fibrillation in Africa—an under-reported and unrecognized risk factor for stroke: a systematic review. *Glob Heart* 2019;14:269-279.
72. Suarez J, Piccini JP, Liang L, Atherton JJ, Hayward CS, Krum H, Fonarow GC, Lopes RD, Hernandez AF. International variation in use of oral anticoagulation among heart failure patients with atrial fibrillation. *Am Heart J* 2012;163:804-811.
73. Freestone B, Rajaratnam R, Hussain N, Lip GY. Admissions with atrial fibrillation in a multiracial population in Kuala Lumpur, Malaysia. *Int J Cardiol* 2003;91:233-238.
74. Sliwa K, Carrington MJ, Klug E, Opie L, Lee G, Ball J, Stewart S. Predisposing factors and incidence of newly diagnosed atrial fibrillation in an urban African community: insights from the Heart of Soweto Study. *Heart* 2010;96:1878-1882.
75. Oliveira LH, Mallmann FB, Botelho FN, Paul LC, Gianotto M, Abt RB, Silva NJ, Luize CM, Nogueira FL, Carvalho RS, Paola AA, Cirenza C. Cross-sectional study of treatment strategies on atrial fibrillation. *Arq Bras Cardiol* 2012;98:195-202.
76. Shavadia J, Yonga G, Mwanzi S, Jinah A, Moriasi A, Otieno H. Clinical characteristics and outcomes of atrial fibrillation and flutter at the Aga Khan University Hospital, Nairobi. *Cardiovasc J Afr* 2013;24:6-9.
77. Yameogo AR, Kologo JK, Mandi G, Kabore HP, Christian GR, Taryetba AA, Samadoulougou AK, Zabsonre P. Use of Vitamins K antagonists in non-valvular atrial fibrillation thromboembolic risk prevention in Burkina Faso. *Pan Afr Med J* 2016;24:108.
78. Sonuga BO, Hellenberg DA, Cupido CS, Jaeger C. Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. *Afr J Prim Health Care Fam Med* 2016;8:e1-8.
79. Schapkaitz E, Sithole J. Predictors of warfarin dose requirements in South African patients attending an anticoagulation clinic. *J Vasc Nurs* 2017;35:27-30.
80. Ebrahim I, Bryer A, Cohen K, Mouton JP, Msemburi W, Blockman M. Poor anticoagulation control in patients taking warfarin at a tertiary and district-level prothrombin clinic in Cape Town, South Africa. *S Afr Med J* 2018;108:490-494.
81. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; Group ESC. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020:ehaa612.
82. Joseph PG, Healey JS, Raina P, Connolly SJ, Ibrahim, Q Gupta, R Avezum, A Dans, AL Lopez-Jaramillo, P Yeates, K Teo, K Douma, R Bohonar, A Chifamba, J Lanas, F Dagenais, GR Lear, SA Kumar, R Kengne, AP Keskinler, M Mohan, V Mony, Pa Alhabib, KFHuismann, Hlype, T Zatonska, Klismail, RKazmi, K Rosengren, A Rahman, O Yusufali, A Wei, L Orlandini A Islam, S Rangarajan, S Yusuf, S. Global variations in the prevalence, treatment, and impact of atrial fibrillation in a multi-national cohort of 153,152 middle-aged individuals. *Cardiovasc Res* 2020:cvaa241.
83. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010;123:638-645.e4.
84. Yang Y-M, Shao X-h, Zhu J, Zhang H, Liu Y, Gao X, Liu L-S, Yu L-T, Zhao L, Yu P-F, Zhang H, He Q, Gu X-D. Risk factors and incidence of stroke and MACE in Chinese atrial fibrillation patients presenting to emergency departments: a national wide database analysis. *Int J Cardiol* 2014;173:242-247.
85. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, Damasceno A, Reilly P, Grinvalds A, Nakamya J, Aje A, Almahmeed W, Moriarty A, Wallentin L, Yusuf S, Connolly SJ; Investigators R-LAFRaCS. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet* 2016;388:1161-1169.
86. Sawhney JP, Kothiwale VA, Bisne V, Durgaprasad R, Jadhav P, Chopda M, Vanajakshamma V, Meena R, Vijayaraghavan G, Chawla K, Allu J, Pieper KS, John Camm A, Kakkur AK, Kakkur AK, Bassand J-P, John Camm A, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Mantovani LG, Misselwitz F, Pieper KS, Turpie AGG, van Eickels M, Verheugt FWA, John Camm A, Kakkur AK; GARFIELD-AF Investigators. Risk profiles and one-year outcomes of patients with newly diagnosed atrial fibrillation in India: Insights from the GARFIELD-AF Registry. *Indian Heart J* 2018;70:828-835.
87. Jiang C, Lan DH, Du X, Geng YP, Chang SS, Zheng D, Chen JB, Yu RH, Sang CH, Long DY, Tang RB, Zhou YC, Min Y, Lu Y, Dong JZ, Lip GYH, Ma CS. Prevalence of modifiable risk factors and relation to stroke and death in patients with atrial fibrillation: a report from the China atrial fibrillation registry study. *J Cardiovasc Electrophysiol* 2019;30:2759-2766.
88. Paixão GMM, Lima EM, Gomes PR, Ferreira MPF, Oliveira DM, Ribeiro MH, Ribeiro AH, Nascimento JS, Canazart JA, Ribeiro LB, Ribeiro AL. Evaluation of mortality in bundle branch block patients from an electronic cohort: clinical Outcomes in Digital Electrocardiography (CODE) study. *J Electrocardiol* 2019;57: S56-S60.
89. Paixão GMM, Silva LGS, Gomes PR, Lima EM, Ferreira MPF, Oliveira, DM Ribeiro, MHRibeiro AHNascimento JS, Canazart JA,

- Ribeiro LB, Benjamin EJ, Macfarlane PW, Marcolino MS, Ribeiro AL. Evaluation of mortality in atrial fibrillation: clinical outcomes in digital electrocardiography (CODE) Study. *Global Heart* 2020; **15**:48.
90. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Mantovani LG, Misselwitz F, Ten Cate H, Turpie AG, Verheugt FW, Kakkar AK. Investigators G-A. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J* 2016; **37**:2882-2889.
 91. Velleca M, Costa G, Goldstein L, Bishara M, Boo LM. A review of the burden of atrial fibrillation: understanding the impact of the new millennium epidemic across Europe. *EMJ Cardiol* 2019; **7**:110-118.
 92. Mkojo P, Bahiru E, Ajijola OA, Bonny A, Chin A. Cardiac arrhythmias in low- and middle-income countries. *Cardiovasc Diagn Ther* 2020; **10**:350-360.
 93. Stevens B, Pezzullo L, Verdian L, Tomlinson J, George A, Bacal F. The Economic Burden of Heart Conditions in Brazil. *Arq Bras Cardiol* 2018; **111**:29-36.
 94. Bouame M, Ali Lahmar M, Bouafia MT, Hammoudi N, Chentir MT, Athmane MA, Kara S, Trancart M, Yildiz L, Cheynel J, Soualmi R. Economic burden of thromboembolic and hemorrhagic complications in non-valvular atrial fibrillation in Algeria (the ELRAGFA study). *J Med Econ* 2018; **21**:1213-1220.
 95. Hu S, Zhan L, Liu B, Gao Y, Li Y, Tong R, Wu L, Yu B, Gao S. Economic burden of individual suffering from atrial fibrillation-related stroke in China. *Value Health Reg Issues* 2013; **2**:135-140.
 96. Wen L, Wu J, Feng L, Yang L, Qian F. Comparing the economic burden of ischemic stroke patients with and without atrial fibrillation: a retrospective study in Beijing, China. *Curr Med Res Opin* 2017; **33**:1789-1794.
 97. Marfatia S, Monz B, Suvarna V, Bhure S, Sangole N. Treatment costs of stroke related to nonvalvular atrial fibrillation patients in India—a multicenter observational study. *Value Health Reg Issues* 2014; **3**:205-210.
 98. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015. *Heart* 2018; **104**:2010-2017.
 99. Xing Y, Ma Q, Ma X, Wang C, Zhang D, Sun Y. CHADS2 score has a better predictive value than CHA2DS2-VASc score in elderly patients with atrial fibrillation. *Clin Interv Aging* 2016; **11**:941-946.
 100. (Old 99,) Chen JY, Zhang AD, Lu HY, Guo J, Wang FF, Li ZC. CHADS2 versus CHA2DS2-VASc score in assessing the stroke and thromboembolism risk stratification in patients with atrial fibrillation: a systematic review and meta-analysis. *J Geriatr Cardiol* 2013; **10**:258-266.
 101. Liu FD, Shen XL, Zhao R, Li GF, Wu YL, Tao XX, Wang S, Zhou JJ, Zheng B, Zhang QT, Yao Q, Zhao Y, Zhang X, Wang XM, Liu HQ, Shu L, Liu JR. Predictive role of CHADS2 and CHA2DS2-VASc scores on stroke and thromboembolism in patients without atrial fibrillation: a meta-analysis. *Ann Med* 2016; **48**:367-375.
 102. Xiong Q, Chen S, Senoo K, Proietti M, Hong K, Lip GYH. The CHADS2 and CHA2DS2-VASc scores for predicting ischemic stroke among East Asian patients with atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol* 2015; **195**:237-242.
 103. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 2014; **11**:639-654.
 104. Guo Y, Apostolakis S, Blann AD, Wang H, Zhao X, Zhang Y, Zhang D, Ma J, Wang Y, Lip GHY. Validation of contemporary stroke and bleeding risk stratification scores in non-anticoagulated Chinese patients with atrial fibrillation. *Int J Cardiol* 2013; **168**:904-909.
 105. Siu C-W, Lip GYH, Lam K-F, Tse H-F. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. *Heart Rhythm* 2014; **11**:1401-1408.
 106. Fox KAA, Lucas JE, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Oto A, Mantovani LG, Misselwitz F, Piccini JP, Turpie AGG, Verheugt FWA, Kakkar AK. GARFIELD-AF Investigators. *BMJ Open* 2017; **7**:e017157.
 107. van Doorn S, Debray TPA, Kaasenbrood F, Hoes AW, Rutten FH, Moons KGM, Geersing GJ. Predictive performance of the CHA2DS2-VASc rule in atrial fibrillation: a systematic review and meta-analysis. *J Thromb Haemost* 2017; **15**:1065-1077.
 108. O'Donnell O. Access to health care in developing countries: breaking down demand side barriers. *Cad Saude Publica* 2007; **23**:2820-2834.
 109. de Jong LA, Groeneveld J, Stevanovic J, Rila H, Tieleman RG, Huisman MV, Postma MJ, van Hulst M. Cost-effectiveness of apixaban compared to other anticoagulants in patients with atrial fibrillation in the real-world and trial settings. *PLoS One* 2019; **14**:e0222658.
 110. Stenberg K, Hanssen O, Edejer TT, Bertram M, Brindley C, Meshreky A, Rosen JE, Stover J, Verboom P, Sanders R, Soucat A. Financing transformative health systems towards achievement of the health Sustainable Development Goals: a model for projected resource needs in 67 low-income and middle-income countries. *Lancet Glob Health* 2017; **5**:e875-e887.
 111. World Health Organization. Primary health care on the road to universal health coverage: 2019 monitoring report. https://www.who.int/healthinfo/universal_health_coverage/report/uhc_report_2019.pdf (10 October 2020).
 112. World Health Organization. UHC index of service coverage (SCI). <https://www.who.int/data/gho/data/indicators/indicator-details/GHO/uhc-index-of-service-coverage> (10 October 2020).
 113. World Bank. Out-of-pocket expenditure (% of current health expenditure). <https://data.worldbank.org/indicator/SH.XPD.OOPC.CH.ZS> (10 October 2020).
 114. Hsu JC, Maddox TM, Kennedy K, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Aspirin instead of oral anticoagulant prescription in atrial fibrillation patients at risk for stroke. *J Am Coll Cardiol* 2016; **67**:2913-2923.
 115. Ben Freedman S, Gersh BJ, Lip GY. Misperceptions of aspirin efficacy and safety may perpetuate anticoagulant underutilization in atrial fibrillation. *Eur Heart J* 2015; **36**:653-656.
 116. Sabir IN, Matthews GDK, Huang CLH. Antithrombotic therapy in atrial fibrillation: aspirin is rarely the right choice. *Postgrad Med J* 2013; **89**:346-351.
 117. Tse HF, Wang YJ, Ai-Abdullah MA, Pizarro-Borromeo AB, Chiang CE, Krittayaphong R, Singh B, Vora A, Wang CX, Zubaid M, Clemens A, Lim P, Hu D. Stroke prevention in atrial fibrillation—an Asian stroke perspective. *Heart Rhythm* 2013; **10**:1082-1088.
 118. Pritchett RV, Clarke JL, Jolly K, Clarkesmith D, Bem D, Turner GM, Thomas GN, Lane DA. Clinicians' views and experiences of prescribing oral anticoagulants for stroke prevention in atrial fibrillation: a qualitative meta-synthesis. *PLoS One* 2020; **15**:e0232484.
 119. O'Neal WT, Alam AB, Sandesara PB, Claxton JS, MacLachlan RF, Chen LY, Bengtson LGS, Chamberlain AM, Norby FL, Lutsey PL, Alonso A. Sex and racial differences in cardiovascular disease risk in patients with atrial fibrillation. *PLoS One* 2019; **14**:e0222147.
 120. Nanda A, Kabra R. Racial differences in atrial fibrillation epidemiology, management, and outcomes. *Curr Treat Options Cardio Med* 2019; **21**:85.
 121. Meschia JF, Merrill P, Soliman EZ, Howard VJ, Barrett KM, Zakai NA, Kleindorfer D, Safford M, Howard G. Racial disparities in awareness and treatment of atrial fibrillation. The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Stroke* 2010; **41**:581-587.
 122. Perera MA, Cavallari LH, Limdi NA, Gamazon ER, Konkashbaev A, Daneshjou R, Pluzhnikov A, Crawford DC, Wang J, Liu N, Tatonetti N, Bourgeois S, Takahashi H, Bradford Y, Burkley BM, Desnick RJ, Halperin JL, Khalifa SI, Langae TY, Lubitz SA, Nutescu EA, Oetjens M, Shahin MH, Patel SR, Sagreia Y, Tector M, Weck KE, Rieder MJ, Scott SA, Wu AH, Burmester JK, Wadelius M, Deloukas P, Wagner MJ, Mushiroda T, Kubo M, Roden DM, Cox NJ, Altman RB, Klein TE, Nakamura Y, Johnson JA. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. *Lancet* 2013; **382**:790-796.
 123. Aasiime IG, Zhang EJ, Osanlou R, Krause A, Dillon C, Suarez-Kurtz G, Zhang H, Perini JA, Renta JY, Duconge J, Cavallari LH, Marcato LR, Beasley MT, Perera MA, Limdi NA, Santos PCJL, Kimmel SE, Lubitz SA, Scott SA, Kawai YK, Jorgensen AL, Pirmohamed M. Genetic factors influencing warfarin dose in Black-African patients: a systematic review and meta-analysis. *Clin Pharmacol Ther* 2020; **107**:1420-1433. Jun