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Long-term oral anticoagulation for atrial fibrillation in low and middle income countries

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ABSTRACT

With increasing life-expectancy and changing demographics, non-valvular atrial fibrillation (AF) is currently the most common indication for long-term oral anticoagulation (OAC) in low and middle income countries (LMICs). Due to a decreasing trend in the prevalence of rheumatic heart disease (RHD), valve disease as a primary cause of AF now constitutes a small fraction of all people with AF. Moreover, emerging data also indicate that, patients with significant valve disease and AF may have a risk of stroke similar to, if not lower than, those with non-valvular AF. Previous trials of anticoagulation for AF excluded people from LMICs partly because valvular AF constituted a large proportion of those with AF, and it was thought to confer a prohibitively high risk of stroke. Trialists should therefore be less reluctant to include patients with AF from LMICs in general, and those with valve disease in particular, in future trials of anticoagulation. The quality of vitamin K antagonist based oral anticoagulation remains poor in LMICs to a large extent because of poor monitoring. The widespread use of the direct oral anticoagulants (DOAC) presents a practical approach to improve anticoagulation quality. Randomised trials of DOACs in valvular AF are particularlycriticalto bridge the knowledge gap in this area.

Discussions regarding oral anticoagulation (OAC) use in low and middle income countries (LMICs) have historicallybeendominated by severallong-held beliefs. The first is that the quality of vitamin K antagonist (VKA) based anticoagulation is poor in these countries. The veracity of this assumption is supported by a large number of studies documenting both lower prescription of OACs, and a lower proportion of international normalised ratio (INR) values in the therapeutic range.[1]The second is that a large proportion of patients receiving OAC in LMICs have atrial fibrillation (AF) related to valvular heart disease, and rheumatic mitral stenosis in particular. This assumption, perhaps valid several decades ago, is no longer supported by the data. Finally, patients with valvular heart disease and AF (specifically those with moderate or severe valve lesions), are thought to be at prohibitively high thromboembolic risk. [2] However, recent evidence suggests that this risk may have been overestimated.[3] [4]Nevertheless, the aforementioned assumptions continue to contribute to the underrepresentation of patients from LMICs in clinical trials of oral anticoagulation. Knowledge of the characteristics of contemporary patients in LMICs who are eligible for long-term OAC, estimates of their stroke risk, and a better understanding of the drivers of poor anticoagulation quality, may help guide research and clinical practice. In this review, we seek to provide an evidence-based perspective on OAC use in patients with AF living in LMICs and China.

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1. What are the common indications for OAC use in LMICs?

Contrary to popular belief, the most common indication for long-term OAC in LMICs and China is likely to be non-valvular AF. As populations in these countrieshave continued to age, increasing numbers of people nowhave AF, and are eligible for long-term OAC (Fig. 1). Though earlier population-based estimates of AF prevalence were low,[1] more recent estimates suggest that age-stratified

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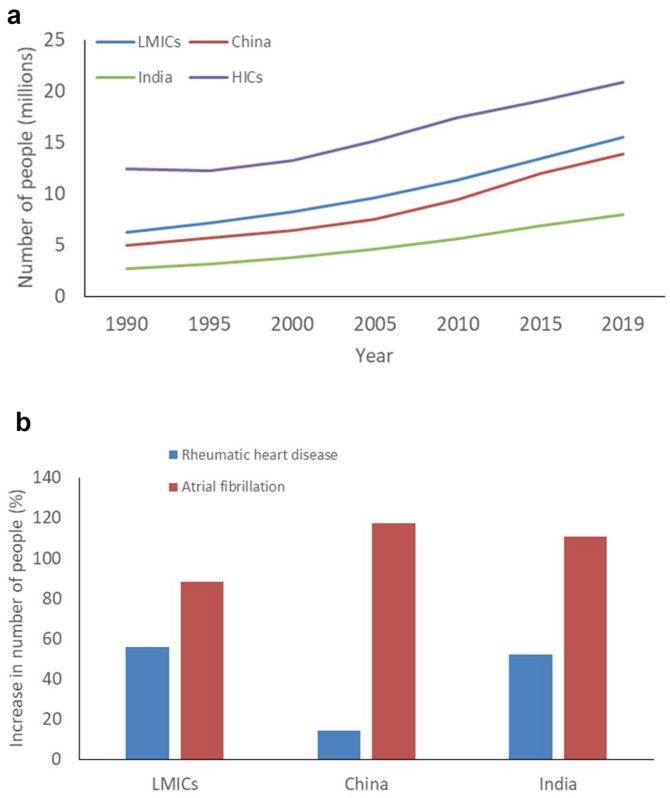

Fig. 1. Trends in the prevalence of atrial fibrillationand rheumatic heart disease between 1990 and 2019.

prevalence may be approaching that seen in high-income countries.[5] The Global Burden of Disease (GBD) Study estimates that the number of people living with AF in LMICs has increased by 147% since 1990. This translates to over15 million people with AF in 2019, many of whom may benefit from OAC (Fig. 1, panel A). In addition, the estimated number of people with AF in China (an upper middle income country) was nearly 13.9 million in 2019. Combined, this exceeds the cumulative number of people with AF in all the 58 high income countries (Fig. 1, panel A).

There are no direct estimates of the proportion of individuals with rheumatic heart disease (RHD) among those with AF in the community. The absolute number of people with RHD and AF can be estimated indirectly from the available data. The GBD estimates suggest that there were about 1.2 million patients with RHD and concomitant heart failure (HF) in 2015.[6] Hospital-based studies from countries in which RHD is endemic indicate that about a fifth of patients with RHD present with AF, and about a third with HF.[7]Since age-standardized prevalence of RHD has stabilized in most large LMICs, the increase in the number of people with RHD has been relatively smaller than for AF in general (Fig. 1, Panel B). Therefore, the total number of people with RHD in AF is likely in the range of 0.75–1 million, constituting a fraction of all people with AF in LMICs and China. These figures are consistent with recent hospital admission data indicating that, even among symptomatic AF patients presenting with heart failure (where patients with concomitant valve disease are likely to be overrepresented), nonvalvular AF was the commonest cause, accounting for three-fourth of the patients.[8]

2. Stroke-risk among people with AF in LMICs

Estimation of strokerisk is essential to inform optimaldecision-making about long-term oral anticoagulation. The risk of stroke among people with nonvalvular AF is generally estimated using scoring systems based on clinical parameters, such as the CHA_2DS_2VASc score. The use of these scores for risk-stratification in LMICs poses a challenge because of the younger age of patients with AF. In LMICs, though the age-stratified prevalence of AF is similar to that in high income countries,[5] because of the younger age of the population, the average age of people with AF tends to be substantially lower.[1]People in LMICs are nearly a decade younger at the time of suffering their first stroke.[9] In the INTERSTROKE study, patients from high income countries were about 66 years of age on the average, compared to those from India, South-East Asia and Africa, who wereabout 58 years old.[9]Since age is a critical determinant of strokerisk, the validity of scores such as CHA_2DS_2-VASc in risk-stratifying younger populations is unclear. There are some data to suggest that lowering the age threshold to 50 years in the CHA_2DS_2-VASc score may improve risk prediction in some Asian patients.[10,11] However, these results have not been replicated in LMIC populations.

2.1. Patients with valvular heart disease and AF

Stroke-risk in patients with AF and valvular heart disease (mainly rheumatic in etiology in LMICs), and their risk-stratification, are less clear. Patients with rheumatic heart disease (RHD) and AF (most of whom have mitral stenosis) have historically been considered to be at very high risk of stroke, mainly based on clinical impression and data from retrospective studies.[2,3,12]This impression was further reinforced by the widespread reporting of very large *relative risks* of stroke among these patients (compared to age, and risk-factor matched controls), despite similar absolute risks of stroke compared to patients with non-valvular AF. For example, the much cited data from the Framingham study found similarabsolutestroke risk among patients with RHD and AF, and those with non-valvular AF (4.5 and 4.2 per 100 patient-years), but emphasised the ~18-fold increase in risk among patients with RHD, compared to a population of similar age and prevalence of risk factors such as hypertension.[13] A careful review of the literature confirms that patients with RHD and AF are likely to have a stroke-risk similar to patients with non-valvular AF.[3,4] This is mainly because of their younger age and the lower prevalence of traditional risk factors such as hypertension, diabetes and coronary artery disease. It is plausible that there may be other important variables which may have a role in the pathogenesis of stroke in this population.[14] In an ongoing randomised trial, patients with RHD and AF were two decades younger than those with non-valvular AF enrolled in the four pivotal direct oral anticoagulation trials, and had a low prevalence of other traditional risk factors (hypertension 23%, diabetes 6%, and coronary disease 0.5%).[15-19] (Table 1).

These observations may have implications for decision-making regarding oral anticoagulation use in these patients in LMICs. While older patients with milder degrees of valve disease may be reliably stratified using the CHA_2DS_2VASc score, this approach may not be optimal for patients with RHD. Other factors such as the severity of mitral valve obstruction may have important predictive value.[14,20] More data on stroke-risk and predictors are urgently needed.

Table 1
Differences in characteristics of patients with rheumatic atrial fibrillation from LMICs, and patients with atrial fibrillation and valve disease in the direct oral anticoagulation studies.

Characteristics	INVICTUS-VKA[15] (n = 4565)	Kim et al[41] (n = 2230)	ROCKET-AF[16] (n = 2003)	ARISTOTLE[17] (n = 4808)	RE-LY[18] (n = 3950)	ENGAGE-AF[19] (n = 2824)
Valve disease	RHD MS MVA ≤2.0 cm^2 (>80% of patients)	Patients with any degree of MS	90% MR, 25% AR, <5% had RHD	73% MR, 18% AR, 2.7% mild MS	79% MR, 21% AR, 5% mild MS	80% MR, 13% AR, no MS
Median age (years)	50	70	75	71	74	72
Female gender (%)	72	69	39	40	41	42
CHA_2DS_2VASc score (mean)	1.9		3.5	2.2	2.0	2.9
History of stroke or systemic embolism (%)	12	47	48	19	22	24
Hypertension (%)	23	97	89	85	77	93
Diabetes mellitus (%)	6	68	40	23	23	32
History of myocardial infarction (%)	<0.5	56	24	17	33	40
Heart failure (%)	39	75	70	49	40	74
Creatinine clearance (mL/min)	77	NA	62	NA	66	70

RHD - Rheumatic heart disease, MS - Mitral stenosis, MVA - Mitral valve area.

3. Poor anticoagulation quality in LMICs

It is well known that fewer patients with AF and an indication for anticoagulation receive a prescription for OAC in LMICs and China.[1] And among those on OAC, fewer than half of the international normalised ratio (INR) values are in therapeutic range. For example, in a large international registry, only 11% of patients from China with AF and a CHA_2DS_2VASc score ≥2 were on OAC, compared to about 63% of patients from Western Europe. About 40% of Indian patients were on OAC.[21] Moreover, among those already on OAC, the proportion of INR values in therapeutic range was 35 and 36% among Indian and Chinese patients, compared to 67% for patients from Western Europe.[21] More recently, among a deprived population in rural India, 34% of INRs were in therapeutic range, and the time in therapeutic range (TTR) was only 13%.[22]The main reasons for poor anticoagulation quality in LMICs are the lack of patient awareness, and fewer facilities for, and poor access to INR testing, and OAC management. Among poor populations, the direct and indirect costs incurred in the process of obtaining INR tests may be a further major impediment.[22]An important, but less often discussed reason for sub-therapeutic INRs in LMICs is systematic under dosing of warfarin or other VKAsbyphysicians.

3.1. Systematic under dosing: is it just poor practice?

Many physicians in LMICs and some high-income East Asian countries systematically under dose patients on OAC, as a result of which INR values are more often below the recommended therapeutic range of 2.0–3.0. Data from an international randomised trial of AF patients showed that geographic region was one of the key predictors of TTR, with the poorest anticoagulation quality was seen in India and the East Asian region.[23] More pertinently, these data showed that the variation between geographic regions was largely attributable to the variation in the proportion of people with INRs below 2.0. On average, patients in India and those from East Asia were more likely to have INR values < 2.0 (44 and 37%) compared to those from North America or Western Europe (20% in either region).[23] Dangerously sub-therapeutic INR values (<1.7) were also far more common (India 31%, East Asia 19%) compared to North America and Western Europe (8%).[23]These findings are mirrored by other recent data from India.[24]This skewed distribution of INR values indicates that physicians in these regions systematically target lower INR values, most likely because of a fear of major bleeds.

There are no data from LMICs indicating a higher risk of bleeding with therapeutic anticoagulation with VKAs. Therefore, the use of a lower target INR in patients with AF, may simply reflect physicians' risk-aversion to bleeding.[25] However, this risk-aversion may not be without basis. Observational data from East Asia, particularly from Japan, suggest thattherisk-benefit trade-off with vitamin K antagonist (VKA) based anticoagulation is most favourable at an INR range of 1.6–2.6, both for non-valvular and valvular AF.[26 27]These observations are supported by laboratory studies in Japanese patients which showed that indices of coagulation activity and fibrinolytic activity were not different between patients whose INRs were 1.5–1.9 and those with INRs over 2.0.[28]This sensitivity to VKAs may extend to other ethnic groups as well. Data from multi-ethnic cohorts in the United States showed a consistently higher risk of intracranial bleeding among Asians, Hispanics, and African-American patients, than among Caucasians, which were not fully explained by differences in achieved INR values.[29]However, the extent to which these ethnic differences are attributable to genetic variation in warfarin metabolism[30] or the prevalence of other risk factors for intracranial bleeding such as hypertension,[31]is not known. The role of warfarin dosing guided by knowledge of individual patient pharmacogenetics is uncertain.[32 33] However, given the differences in age, prevalence of traditional stroke risk factors, and sensitivity to VKAs, between patients with AF in LMICs and other countries, differences in stroke-risk, bleeding risk, and the risk-benefit trade-offs with OAC are likely to exist. But, until the time morerobustdata on bleeding risk in LMICpopulations become available, the general recommendations for OAC indication and INR targets should be preferred over those that recommend lower INR targets.[34]Educational interventions targeting physicians should emphasize the lack of reliable data from LMICs indicating a greater sensitivity to VKAs.

4. Improving anticoagulation quality

In well-resourced settings, self-monitoring and self-management by patients improves the quality of anticoagulation, and may reduce the risk of ischemic stroke. A systematic review found that self-testing with or without self-management by patients may reduce the risk of thromboembolic events by nearly half.[35]But there was considerable heterogeneity both in the proportion of patients who were found eligible for self-monitoring, and in the observed reduction in thromboembolic events.[35]Moreover, the willingness of patients to self-monitor varies greatly even among high-income countries, and may not exceed

20%.[35]Dedicated anticoagulation clinics are also common in high-income countries. While they may improve patient satisfaction and INR control, their effect on clinical outcomes is less certain.[36-] Given resource constraints, lower levels of patient education, and different healthcare priorities and delivery systems, these strategies are unlikely to be of practical value in LMICs.

Educational interventions targeted at closing gaps in knowledge and raising patient awareness may yield significant and sustainable benefits. Recently, a cluster-randomised trial involving several middle income countries (including China and India), showed that a complex educational intervention, targeted both at patients and their healthcare providers, improved OAC use, and resulted in a large reduction in stroke.[37]The use of non-physician health care workers to provide patient education and deliver primary care, are attractive options, but remain to be tested in the context of anticoagulation.[38] Moreover, the cost and scalability of such complex interventions to entire populations in LMICs may be challenging.

4.1. Wider adoption of the direct oral anticoagulants

The most practical strategy for improving anticoagulation quality in LMICs may be the widespread adoption of direct oral anticoagulants (DOAC).[36] These drugs provide consistent levels of anticoagulation without the need for monitoring, and have been shown to be effective and safe for stroke prevention in non-valvular AF.[39] Benefits are also consistent among patients with valve disease of mild to moderate severity, enrolled in the pivotal randomised trials.[40] Recent observational data suggest that DOACs may be more effective than VKAs for stroke prevention in elderly patients with significant mitral stenosis (MS).[41]Though this study had several methodological limitations, and the patients studied were elderly (unlike patients in LMICs), the results are broadly consistent with the data on older patients with valve disease and AF in the pivotal DOAC trials. While data on the use of DOACs among patients with RHD from LMICs are lacking, there are no *a priori* pathophysiologic reasons to believe that their response to anticoagulation with DOACs will be any different from other patients with valve disease, or those with non-valvular AF.[3] [15]Moreover, the strong recommendations for anticoagulation with VKAs in patients with MS are also based on observational data.[42] Applying the same criteria, it appears illogical to proscribe DOACs in these patients. Nevertheless, data from randomised trials among patients with RHD in LMICs, particularly those with significant MS, are needed to guide practice. At least one such trial is ongoing.[15]

An important impediment to the widespread use of DOACs is their higher cost compared to VKAs. Though licensing agreements with pharmaceutical companies based in LMICs have considerably reduced costs, DOACs remain more expensive than VKAs. But drug acquisition costs capture only a fraction of the total cost of long-term OAC.[43] This may be especially true in LMICs, where the direct and indirect costs incurred due to frequent INR testing and physician consultations for dose-adjustment, and the opportunity costs due to lost wages, may greatly increase the total cost of VKA therapy. Formal evaluation of cost-effectiveness of DOACs compared to VKAs in LMIC settings are urgently needed.

There are reasons other than efficacy and ease of use, tofavour the use of DOACs over VKAs in LMICs. Because of more predictable and consistent levels of anticoagulation, DOACs may be associated with greater benefits among patients with poor INR control.[44] Moreover, the net benefit due to anticoagulation with VKAs begins to accrue only when baseline stroke risk increases above approximately 2 per 100 patient-years,[45] [46] while the threshold with DOACs may be lower.[46]Given that a larger proportion of patients with AF in LMICs are young, and possibly have a lower stroke risk, DOACs may present a more effective stroke prevention strategy compared to VKAs.

In summary, over the last several decades, patients with AF in LMICs have become similar to those living in high-income countries. Contrary to common belief, most of them have non-valvular AF. Those with underlying valve disease represent only a small subset of patients with AF. Importantly, concomitant valve disease may not confer an excessive risk of stroke as previously believed. Consequently, there should be less reluctance to include these patients, and patients from LMICs in general, in future trials of anticoagulants involving patients with AF. The quality of oral anticoagulation with VKAs in LMICs continues to be poor. Broader access to, and wider use of DOACs may present the most practical solution to providing effective anticoagulation in these countries.

Disclosure

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Declaration of competing interest

None of the authors report any conflicts of interest.

With increasing life-expectancy, the number of persons living with atrial fibrillation (AF) and flutterin the LMICs and China shows a steady increase. In 2019, there are more people living with AF in India and China alone when compared to all the high income countries put together (Panel A) The proportional increase in the number of people with rheumatic heart disease (RHD) is smaller than the increase in AF(Panel B) Note that these estimates are for all patients with a diagnosis of RHD including those with mild disease detected by screening. Only a fraction of patients with RHD develop AF. Even among patients with RHD and significant valve disease requiring hospital care, the prevalence of AF is about 22%.[7]

Data are from the Global Burden of Disease study accessed at https://vizhub.healthdata.org/gbd-compare/.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2021.02.003.

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