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

Venkatakrishnan Ramakumar a, Alexander P. Benz b, Ganesan Karthikeyan a, *

a Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India
b Department of Cardiology, Cardiology I, University Medical Center Mainz, Johannes Gutenberg-University, Mainz, Germany

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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 particularly critical to bridge the knowledge gap in this area.

Discussions regarding oral anticoagulation (OAC) use in low and middle income countries (LMICs) have historically been dominated by several long-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. 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. However, recent evidence suggests that this risk may have been overestimated. 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.

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 countries have continued to age, increasing numbers of people now have AF, and are eligible for long-term OAC (Fig. 1). Though earlier population-based estimates of AF prevalence were low, more recent estimates suggest that age-stratified...
prevalence may be approaching that seen in high-income countries. 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 over 15 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. 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 concomitant valve disease are likely to be overrepresented), non-valvular AF was the commonest cause, accounting for three-fourth of the patients.

2. Stroke-risk among people with AF in LMICs

Estimation of stroke risk is essential to inform decision-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 CHA2DS2-VASc 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, because of the younger age of the population, the average age of people with AF tends to be substantially lower. People in LMICs are nearly a decade younger at the time of suffering their first stroke. 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 were about 58 years old. Since age is a critical determinant of stroke risk, the validity of scores such as CHA2DS2-VASc in risk-stratifying younger populations is unclear. There are some data to suggest that lowering the age threshold to 50 years in the CHA2DS2-VASc score may improve risk prediction in some Asian patients. 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. 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 similar absolute stroke 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. 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. 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. 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%). More data on stroke-risk and predictors are urgently needed.
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. For many East Asian patients, than among Caucasians, which were not fully explained by differences in achieved INR values. However, the extent to which these ethnic differences are attributable to genetic variation in warfarin metabolism or the prevalence of other risk factors for intracranial bleeding such as hypertension, is not known. The role of warfarin dosing guided by knowledge of individual patient pharmacogenetics is uncertain. 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 morerobust data on bleeding risk in LMIC populations become available, the general recommendations for OAC indication and INR targets should be preferred over those that recommend lower INR targets. 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.34 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. Moreover, the willingness of patients to self-monitor varies greatly even among high-income countries, and may not exceed...
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.\(^{27}\) The use of non-physician healthcare workers to provide patient education and deliver primary care, are attractive options, but remain to be tested in the context of anticoagulation.\(^{36}\) 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.\(^{38}\) 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.\(^{3}^{\text{15}}\) 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.\(^{35}\)

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.\(^{61}\) 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, to favour the use of DOACs over VKAs in LMICs. Because of more predictable efficacy and ease of use, 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 flutter in 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.ijh.2021.02.003.

## References


