

STATE-OF-THE-ART REVIEW

Global Health Inequities in Electrophysiology Care



A State-of-the-Art Review

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ABSTRACT

This state-of-the-art review examines disparities in the diagnosis, management, and outcomes of cardiac arrhythmias globally. These arrhythmias include atrial fibrillation, ventricular tachyarrhythmias underlying sudden cardiac death, and bradyarrhythmias associated with sinus node and atrioventricular node disease. Arrhythmias in low- and middle-income countries often result in higher mortality rates due to complex and poorly documented risk factors, lack of clinical expertise among health care personnel, lack of sufficient infrastructure, and challenges in access to care. Innovative approaches like repurposing pacemakers, mobile clinics, use of digital technology, and training initiatives are being explored to address these issues. This article highlights the importance of diagnosis of arrhythmias in varying resource settings, access to care in those settings, and ongoing efforts to expand access to care. (JACC Adv. 2024;3:101387) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Cardiovascular disease (CVD) remains the leading cause of mortality globally.^{1,2} Current projections indicate that by the year 2030, CVD will account for more than 25 million deaths worldwide.³ Reports on CVD typically focus on conditions such as ischemic heart disease and stroke, while data on mortality and morbidity arising from cardiac arrhythmias are often underreported or unknown.

Cardiac arrhythmias contribute significantly to the burden of total CVD, but limited diagnostic and reporting capabilities within many low- and middle-income countries (LMICs) make it likely that the true incidence, consequences, and cost of cardiac arrhythmias are underrepresented.⁴ In high-income countries (HICs), inequality in care is linked to inequitable distributions of structural, social, and environmental determinants across racial, ethnic, and

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**ABBREVIATIONS
AND ACRONYMS**

AF	= atrial fibrillation
CVD	= cardiovascular disease
CPR	= cardiopulmonary resuscitation
DOAC	= direct oral anticoagulant
ECG	= electrocardiogram
EP	= electrophysiology
HIC	= high-income country
ICD	= implantable cardiac defibrillator
LMICs	= low- and middle-income countries
SCD	= sudden cardiac death
SSA	= sub-Saharan Africa
RHD	= rheumatic heart disease

social class groups. In low- and middle-income nations, inequality in care may arise from additional causes, including lack of diagnostic equipment, access to trained health care professionals, and disease-based guidelines tailored to high-income regions, with potential unsuitability for practice patterns and pathologies that are more prevalent in LMICs.⁵ This review summarizes the existing data on health inequities related to cardiac arrhythmias globally and addresses possible opportunities for improving care.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting roughly 46.3 million people worldwide and contributing significantly to morbidity and mortality from strokes, heart failure, cognitive decline, and hospitalizations.^{6,7}

DIFFERENCES IN EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF AF. There are many factors contributing to changing rates of AF globally. In 2017, the international incidence rate of AF had risen by 31% in 20 years.⁸ The greatest burden is seen in countries with high sociodemographic indices, an index that includes fertility, income, and education and is considered representative of a country's health outcomes.⁸ However, by the year 2050, it is projected that countries with historically lower sociodemographic indices will have twice as many people living with AF than in countries with high sociodemographic indices.⁹ In addition to changing sociodemographic factors, a major contributor to rising global burden of AF is increased survival with other chronic diseases.¹⁰ In sub-Saharan Africa (SSA), for example, while the reported prevalence of AF in the general population is currently low at <1%, its prevalence is increasing as the population ages and chronic disease prevalence rises.¹¹

Risk factors for AF in the United States include older age, hypertension, diabetes, obesity, structural heart disease, vascular disease (both coronary and cerebrovascular), obstructive sleep apnea, and thyroid disease. While these risk factors are increasing in prevalence in LMICs as the global population ages and lifestyles in LMICs begin to approximate those in HICs, in LMICs, risk factors such as valvular heart disease may play an outsized role in AF pathogenesis.¹¹

In regions such as India and Africa, rheumatic heart disease (RHD), and its valvular sequelae including

HIGHLIGHTS

- Cardiac arrhythmias contribute significantly to morbidity and mortality from cardiac disease globally.
- Treatment and diagnosis of cardiac arrhythmias is limited in low- and middle-income countries due to lack of available technology, trained personnel, and lack of epidemiological and clinical data regarding disease pathology.
- To improve care in low- and middle-income countries, there needs to be increased investment in training of local personnel, expansion of regulations and infrastructure related to reutilizing implantable cardiac devices, and region-specific databases to tailor guidelines and therapies.

mitral and aortic stenosis, are significantly more prevalent than in the United States and Europe. There are an estimated 33 million people living with RHD, with 95% of patients with RHD living in LMICs.¹² One-third of patients with RHD develop incident AF.¹² AF is a factor for the progression of heart disease in RHD and the incidence of AF in this population rises with advanced heart failure and duration of disease.¹² Patients with RHD who develop AF are typically younger, female, and have advanced valvular heart disease.^{11,13,14} In SSA, tuberculosis, pericarditis, and pregnancy with structural heart disease have a high prevalence of associated AF.¹¹ Studies highlight a notable contrast in epidemiology of AF in SSA compared to the United States. In SSA, females demonstrate a higher prevalence of AF as compared to males, which may be attributable to distinct differences in the etiology of AF in these regions, often related to infectious diseases and pregnancy.¹¹ As people living with HIV are now living longer, the risk for CVD related to HIV has become clearer. Asia and SSA experience a larger portion of the global burden of disease for HIV-associated CVD.¹⁵ Even when controlling for overlapping risk factors for AF, HIV infection is associated with an increased risk for AF (HR: 1.46; 95% CI: 1.38-1.55; $P < 0.0001$).¹⁶ Further characterization of the burden of HIV-related AF globally remains limited due to a paucity of data.

Current methods of predicting stroke are tailored to high-income regions with specific risk factor profiles. Novel methods of stroke risk stratification should be developed, or existing methods should be

validated, to appropriately risk stratify patients with AF with different etiologies including but not limited to RHD, HIV, and pregnancy with structural heart disease.

AF presents later in the disease course in SSA, with higher rates of permanent and persistent AF at the time of diagnosis, as compared to the earlier detection of paroxysmal AF which is seen more in HICs.¹¹ This has important treatment ramifications. Paroxysmal AF responds relatively well to rhythm control strategies including anti-arrhythmic drugs or catheter ablation. Successful restoration and longer-term maintenance of sinus rhythm in patients presenting with more persistent forms of AF is often significantly more challenging. Later diagnosis may be related to the lack of infrastructure for tests such as screening electrocardiograms (ECGs) and Holter monitors and has a crucial impact on the ability to meaningfully intervene on disease progression of AF.

REGION-SPECIFIC TREATMENT DIFFERENCES AND DISPARITIES. Despite the rising burden of disease globally of AF, the adoption of effective treatment strategies remains slow and sparse.

ANTICOAGULATION. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) registry found that rates of anticoagulation in appropriate patients were 65.7% in the United States compared to 11.2% in China ($P < 0.001$).⁴ Moreover, patients in India, China, and Africa who were treated with warfarin for oral anticoagulation spent less time in the therapeutic range compared to warfarin-treated patients in other countries.⁴ In Kenya, patients with valvular AF due to RHD were significantly less likely than patients with non-valvular AF to be taking an anticoagulant.¹⁷ The GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) demonstrated a lower rate of direct oral anticoagulant (DOAC) utilization in Latin America and Asia than in Europe and North America.⁴ In a subgroup of the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) registry of 4 Latin American countries, 36.9% patients who were at moderate to high risk for stroke (excluding patients with mitral stenosis) were not receiving anticoagulation therapy; of those who were at low risk for stroke (and who, by international guidelines did not have an indication for anticoagulant therapy), 49.9% in the GARFIELD-AF registry were prescribed anticoagulants.¹⁸ Significant heterogeneity existed within the regions and within each country. While Brazil was one of the highest utilizers of DOACs in this registry, it also had one of the highest proportions of patients

not receiving appropriate anticoagulation therapy. In the PASCAR (Pan-African Society of Cardiology Annual Report), in which 33 of the 55 African countries were surveyed, only 14 countries had DOACs available (despite being a World Health Organization essential medicine) and anti-arrhythmic drugs were limited primarily to digoxin, amiodarone, and beta-blockers with limited intravenous formulations available.¹⁹

Guidelines have not recommended the use of DOACs in RHD-related AF due to limited evidence. The use of warfarin in LMICs is often limited by lack of requisite infrastructure for drug monitoring. To address this issue, the INVICTUS (INVESTigation of rheumatic AF Treatment Using [VKAs]) trial investigated the use of rivaroxaban for AF in RHD.^{20,21} This study found that warfarin therapy led to lower composite rates of cardiovascular events compared to rivaroxaban.²¹ Notably, rates of thromboembolic events were low in the trial, reflecting the relatively low CHADS-VASC profile of study participants and possibly different comorbidities predicting stroke in RHD-related AF.²¹ In contrast, a prospective cohort in Korea found that in patients with mitral stenosis, DOACs were associated with lower rates of thromboembolic events compared to warfarin.²² These differing findings highlight the need for further investigation of stroke risk factors in AF and different pathologic states, and whether the rigorous international normalized ratio monitoring performed in a clinical trial setting can be translated effectively, both cost and logistically, to the general community.

RHYTHM CONTROL AND OUTCOMES. Digoxin and amiodarone remain the most widely used drugs for AF in SSA, despite known mortality and toxicity profiles.¹⁹ Only 5 of the 33 countries had access to catheter ablations and about half to electrical cardioversion.^{19,23} In Latin America and Africa, <50% of countries have dedicated electrophysiology (EP) labs.⁴

Due to limited therapies and access to optimal treatments for AF, AF-linked mortality is higher globally in comparison to White patients in the United States.¹¹ In SSA, despite lower prevalence of AF, the presence of disease is associated with higher rates of stroke, heart failure, and 10 to 15% higher mortality.^{11,17} In the 4 Latin American countries in the GARFIELD-AF registry, combined mortality was higher than all the other GARFIELD-AF sites.¹⁸ Despite the fact that rhythm control strategies significantly improve morbidity and mortality, SSA predominantly applies rate control strategies due to lack of access to rhythm control medications and

procedures (cardioversions and catheter ablation); widespread adaptation of rhythm control approaches in the near future seems unlikely in SSA due to lack of resources and training.¹¹

SUMMARY. Globally, AF has a variable epidemiology due to the prevalence of underlying etiologies like RHD, pregnancy, and other causes. Treatment for AF is severely limited due to lack of anticoagulant and anti-arrhythmic drugs as well as the lack of trained staff and infrastructure for basic and advanced EP care including cardioversions and ablation. All of these factors contribute to excess AF-related morbidity and mortality. Improving care for AF requires expanding access to screening ECGs and Holters, tailored stroke assessments for different pathologies, expanded access to medications, and trained personnel to manage anticoagulation, cardioversions, and ablation therapies.

SUDDEN CARDIAC DEATH AND IMPLANTABLE CARDIAC DEFIBRILLATORS

DIFFERENCES AND CHALLENGES IN EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH GLOBALLY. In the United States and Europe, sudden cardiac death (SCD) accounts for over half the deaths related to heart disease. Russia, India, China, and most countries in Africa (except for Egypt) do not have SCD registries to verify and substantiate statistics related to SCD.⁴ In the few published studies of SCD in SSA, the mean age of SCD is lower than in HICs, ranging from 35 to 60 years old.¹¹ This difference may reflect the nature of CVD seen in SSA which, while heterogenous, includes RHD, HIV, valvular heart disease, and hypertensive heart disease. Genetic causes of SCD including hypertrophic cardiomyopathy, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, and Brugada syndrome have all been reported within SSA, but correlation with SCD is limited in this region.¹¹ In a single-center registry of 5,000 patients in Egypt, 246 patients experienced SCD from January 2010 till January 2020, in ages 2 to 40 years old, the most common causes of SCD were hypertrophic cardiomyopathy followed by dilated cardiomyopathy, congenital long QT, congenital complete heart block, and least frequently Brugada syndrome.²⁴ This is in stark contrast to the dominant role of coronary heart disease in SCD in the United States.¹¹ Given the younger age of SCD in LMICs, this disease disproportionately impacts the economically productive members of society.²⁵ HIV, highly

prevalent in SSA, is associated with higher incidence of sudden death from arrhythmia as determined by postmortem data from the United States (incidence rate ratio: 1.87; 95% CI: 0.93-3.78).²⁶ Patients in LMICs are disproportionately impacted by environmental toxins and climate change, and while not well categorized, climate change and air pollution have been linked to cardiac arrhythmias.²⁷ The burden of arrhythmias from these causes will continue to grow as capacity to handle the evolving environment is most limited in LMICs.²⁷

MANAGEMENT OF SCD IN LMICs. Treatment for malignant arrhythmias leading to SCD includes immediate cardiopulmonary resuscitation (CPR), primary or secondary prevention with implantable cardiac defibrillators (ICDs), genetic and structural heart evaluations, and ablation procedures. In LMICs, ICD therapies are often not available due to lack of centers and trained operators. In SSA, while ICDs were implanted in 29% of the PASCAR countries, most of these were from visiting humanitarian teams.¹¹ Rates of centers that perform ICDs were 0.02 to 1.59 per million population.¹¹ Rates of ICD implantation have slowly risen in recent reports by PASCAR. Twenty-two percent of countries in PASCAR are increasing rates of implantation by utilizing reconditioned devices.¹¹

The Douala study, the first population-based cohort survey on SCD in SSA, shed light on the numerous challenges associated with SCD management in the region.²⁸ Out-of-hospital cardiac arrest in the Douala cohort was associated with 100% mortality rates due to no attempted CPR outside of the hospital setting. The primary mode of transportation to a hospital for patients with witnessed out-of-hospital cardiac arrest was by taxi, and the remaining patients were directly taken to a mortuary.²⁹ In the SSA region, CPR is incredibly variable, with out of hospital CPR rates as low as 3.7%.¹¹ For in-hospital cardiac arrest, CPR is only attempted 50% of the time.¹¹ Based on self-reports, physicians in the region are often not certified in basic life support, advanced life support, or external defibrillator use.¹¹ South Africa is one of the select areas that emergency medical services are available in the region, and in this setting only 25% of emergency medical services personnel were qualified per local standards.¹¹

Due to limited data, it is challenging to understand the true prevalence of SCD in the Asian Continent due to regional variability. East Asian countries generally

underreport the SCD incidence and South and Southeast Asia lack comprehensive data for reporting.^{30,31}

The economic burden of death from CVD, estimated at \$3.7 trillion dollars in economic losses over 6 years, contributes to half of the noncommunicable disease burden and 2% of the gross domestic product in LMICs.³² Given this economic burden and the impact of SCD on economically productive individuals, financial investment into infrastructure for monitoring and treatment of SCD remains economically prudent. Investment avenues include investing in further diagnostic evaluation, registries, training programs for CPR, and ICD implantation training and monitoring.

BRADYARRHYTHMIAS AND PACEMAKERS

While the global prevalence of heart block is estimated at 0.04%, understanding pacemaker implantation rates in LMICs is limited due to lack of registries. Implantation rates are significantly lower in LMICs than in the United States and European nations.⁴ Pacemaker implantations rates are <1 per 100,000 people in LMICs, in contrast to the United States where the rate is 62 per 100,000 people.⁴ Inability to implant pacemakers was reported by 18% of African countries that were able to provide data.⁴ Rates of pacer implantation in Nigeria are 4,000 times less than in Germany.¹¹ The 11th World Survey of Cardiac Pacing and ICDs reported that in Asian countries, only 10 new cardiac implantable electronic device implants per million were placed compared to 750 per million in Western countries.³³ Furthermore, an estimated 2.5 million people die annually in SSA due to lack of access to pacemaker implantation.⁴ In India, only 1 in 5 patients with sinus node dysfunction receive the indicated pacemaker.³³ In the program Africa-Pace, a European-based program that provides pacemakers in 14 African countries, over half of patients died while waiting for pacemaker therapy.^{4,11} In low resourced settings, post pacemaker implantation monitoring is extremely limited due to cost, access to reliable power and internet, however, as usage of smart phones grows, this may begin to change.⁴

While selecting appropriate pacemaker therapies in different regions, different forms of pacing may also have an impact. Conduction system pacing is significantly more cost-effective as compared to traditional biventricular pacing, and utilizing this technology in resource limited settings may result in more affordable therapies.³⁴ As different pacing modalities emerge, selecting carefully in differently

resourced regions could be beneficial to ensuring access to care.

FUTURE DIRECTIONS

Many countries are still falling short of governmental expenditure on health care relative to levels demanded by World Health Organization (WHO) guidelines.¹¹ Even with appropriate expenditure, major barriers remain to the widespread and appropriate use of EP therapies in LMICs that need to be addressed.¹¹

MONITORING AND POLICIES. Global communities, and particularly those in LMICs, are currently hindered in addressing the health challenges posed by arrhythmic disease by simple lack of data about the breadth and depth of the problem. Investment in large registries focusing on AF, SCD, and bradyarrhythmias will enable tailored therapies that would address regional differences in pathophysiology of disease and facilitate a better understanding of needs. Creating SCD registries has demonstrated efficacy in case studies across communities in Japan, Mexico, Australia, and the United States by allowing state, municipal, and regional governments to implement interventions and track outcomes based on these interventions. Other simple policy interventions have included advocating for policy change related to availability of automated external defibrillators in public places and raising funds to provide those automated external defibrillators. Teaching CPR is also a simple, but widely used intervention for improving outcomes for SCD. Utilizing novel approaches to monitoring that take advantage of available resources can be also be implemented, including the use of community health workers to perform verbal autopsies as a way to contribute to medical registries for SCD.²⁵

INFRASTRUCTURE. Apart from monitoring and reporting, arrhythmia care is greatly limited by access to ECGs, Holter monitors, EP labs, and trained personnel. To expand care to rural areas, India has created mobile vans that can complete ECGs and transmit them to central hospitals for evaluation by trained physicians.³⁵ To help minimize the supply and demand mismatch of these scarce resources, countries like Pakistan, Nepal, and Sudan are creating systems to prioritize patients by severity of disease, and categorizing which patients will most benefit for treatment, such as those with the most unstable rhythms.⁴ In order to deliver antiarrhythmic therapy and anticoagulants to low-resourced areas, differential or tiered pricing can be utilized to make therapy

more affordable in LMICs as well as careful selection of important medications to the essential WHO medication list.⁴ International programs for specific treatments are not novel, and programs such as President's Emergency Plan for AIDS Relief (PEPFAR) have been shown to improve number of patients treated, increase workforce capacity, and improve infrastructure.³⁶ Utilizing historical models for public health, much can be learned on how to build and optimize infrastructure for different diseases. While historic models may be useful, novel methods of utilizing technology are also being leveraged, and care is expanding within Africa through the use of smart phones to consult with experts.

Several philanthropic programs have worked to provide the services not currently available in LMICs. Programs will travel with medical brigade teams often with donated and recycled pacemakers and aim to freely implant pacemakers in regions like Bolivia, South America, and French-speaking African Nations. These efforts, however, often do not develop local expertise and do not offer sustainable solutions.³⁷ Other solutions have been proposed in "south-south" collaboratives, such as through the African Heart Rhythm Association, in order to funnel financial resources to geographically centrally located centers where trained electrophysiologists can perform procedures and provide care, and systems can be set up in which patients can be transferred from the region to these centers in order to expand care.

TRAINING. To address training gaps in low-resource environments, proctorship-based programs allow clinicians to receive training on cardiac arrhythmia management in their home environments and provide the technology to do so.⁴ The Africa-Pace program, initially a medical mission program, has now expanded to distance training and telemedicine, enabling local teams to grow from handling 3% of device implantations to 98% of device implantations in 2018.³⁸ Other regional programs, such as the Pan-African Society of Cardiology Fellowships in Cardiac Pacing, select African physicians for 6 months of training at the University of Cape Town for pacemaker training, with a goal of having at least 1 trained implanter in every African country.³⁹ The Egyptian ministry of health now offers a 3-year pacing and EP program to train both Egyptian and other African fellows in order to increase trained professionals on the continent. However, EP fellowships in LMICs

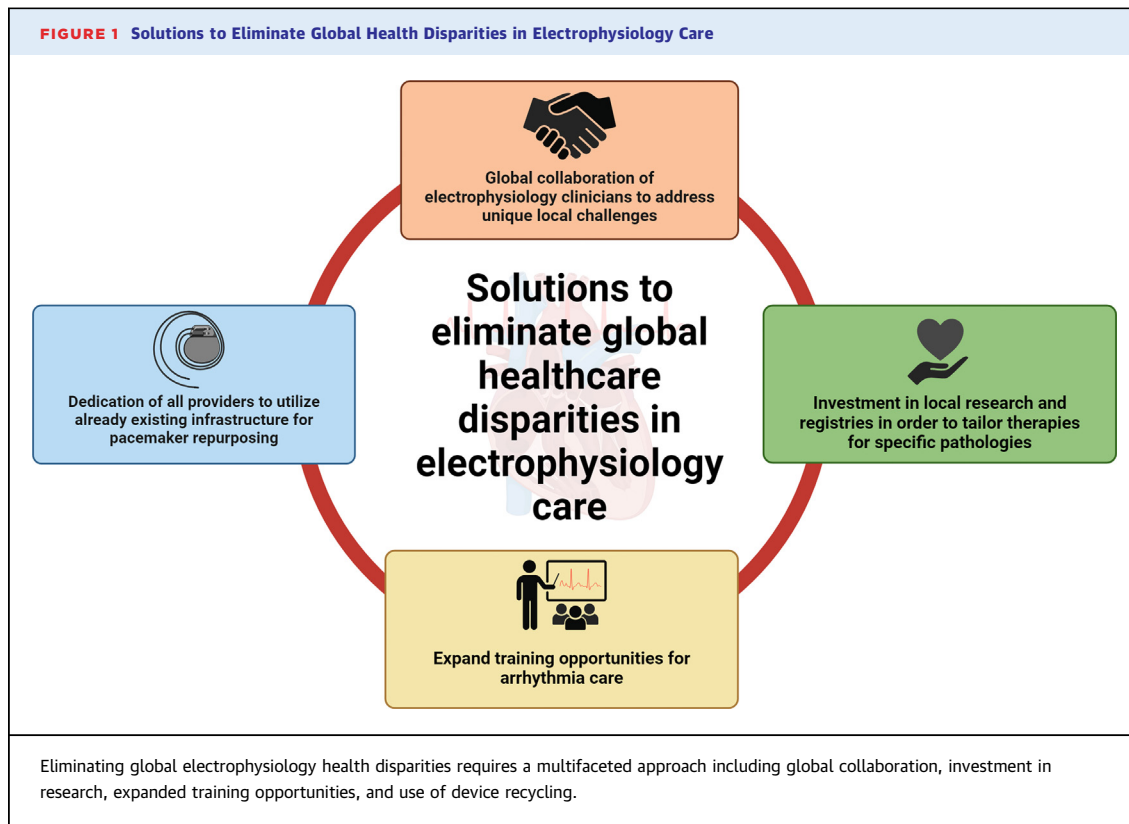
remain limited despite the ongoing efforts to increase opportunities. The Africa Heart Rhythm Association has launched a 30-week online foundation course in EP to address these needs and is working on building more accreditation opportunities.³⁷ Such ongoing work to be able to train local expertise is required to improve access to therapy.

DEVICE REPURPOSING. Device recycling originated in the 1970s and 1980s when many countries including Canada, Australia, France, Sweden, Norway, began systems in order to sterilize and reuse devices.⁴⁰ The Food and Drug Administration (FDA) subsequently issued a statement in 1980 in a compliance document, which they have since maintained, that "pacemaker reuse is an objectionable practice" due to concerns over adequate sterility.^{40,41} University of Michigan published sterilization techniques in 2017 that met industry standards of sterility.⁴² Many studies and meta-analysis have demonstrated the safety and efficacy of device reuse. In an earlier meta-analysis in 2011 there was noted to be low rates of infection and device malfunction and later meta-analysis in 2018 demonstrated that there were no significant differences in rates of infection, device malfunction, or battery depletion when using resterilized devices.^{43,44} Pacemakers that are removed in hospitals from living patients due to infection or during device revisions are considered to have the most longevity.⁴⁵ Devices that are sourced from funeral homes and crematoriums can also be used, though the safety considerations for this continue to be investigated. There are now many programs helping bring reconditioned devices to places like SSA, including My Heart Your Heart, Project Pacer, STIMUBANK, and Pace 4 Life.^{11,33} While the FDA has not changed its stance on domestic reuse of devices, it has collaborated with these organizations to legally export devices to LMICs.^{40,46} Despite this, current industry representatives do not recommend reuse of the device, in accordance of the FDA's original recommendations.

Despite the acknowledgment by international societies of the safety of this practice, many such reusable devices are unfortunately still discarded as medical waste.⁴

CALL TO ACTION

Small actionable steps are required at each and every center around the world in order to address the

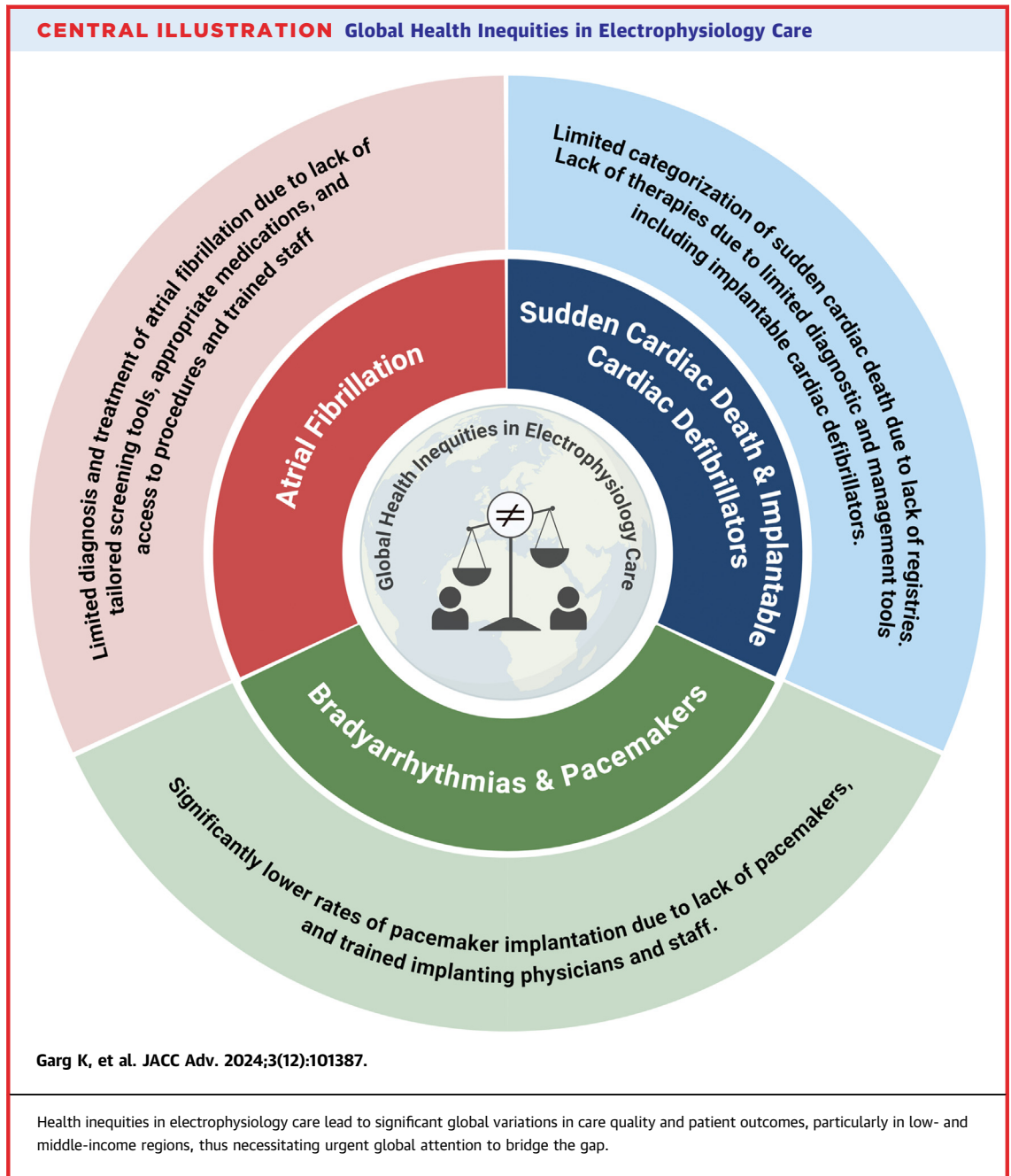


mortality and morbidity experienced globally due to lack of equitable arrhythmia care (Figure 1). Uniting as a global EP community requires collaboration and cohesion to raise awareness of unique regional challenges so that we may address them together. International collaboration such as the HRS Africa Summit, and other similar regional meetings, allow global EPs to come together to address challenges. Device repurposing still faces challenges given historic and outdated recommendations and national EP societies from around the globe must unite to call for updated guidelines from the FDA and other international regulatory bodies. However, given the legality of the practice, awareness must be changed so that both industry and providers utilize current avenues available for device reuse and push for expansion of this practice. Device repurposing programs require only an online submission form and will send prepaid shipping to hospitals, funeral homes, and even private citizens attempting to repurpose devices. Clinicians must take responsibility for utilizing these simple methods to reduce medical waste that could

save lives. Industry must also take responsibility for making technology affordable and available to all patients. As novel technology is developed, such as left bundle area pacing, it is crucial to apply those techniques in regions that would most benefit. Availability of essential medicines by the WHO must be enforced to reduce the variability of use of medications like DOACs. Finally, investment in research in LMICs must be prioritized to better understand disease pathology, so that patients may be better screened, diagnosed, and treated according to region-specific guidelines.

CONCLUSIONS

Worldwide, particularly in resource-constrained settings, patients suffer premature mortality and exacerbated morbidity from cardiac arrhythmias due to several factors including access to care and lack of tailored therapies (Central Illustration). While strides have been made to create programs that are working to address these gaps, adoption of existing resources



such as anticoagulants, repurposed pacemakers, and ICDs needs to increase, as well as novel tailored solutions for complex problems. Utilizing HIC guidelines for differently resourced regions, with different disease pathology, will fail to appropriately diagnose and treat patients who were not originally encompassed in those HIC specific guidelines. Funding research in order to better understand needs in LMICs will pave the road for being able to create tailored solutions for each unique populations' needs.

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