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Bio-Imaging and Subclinical Cardiovascular Disease in Low- and Middle-Income Countries

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Abstract

Cardiovascular disease (CVD) is the leading cause of mortality worldwide and also exerts a significant economic burden, especially in low- and middle-income countries (LMICs). Detection of subclinical CVD, before an individual experiences a major event, may therefore offer the potential to prevent or delay morbidity and mortality, if combined with an appropriate care response. In this review, we discuss imaging technologies that can be used to detect subclinical atherosclerotic CVD (carotid ultrasound, coronary artery calcification) and non-atherosclerotic CVD (echocardiography). We review these imaging modalities, including aspects such as rationale, relevance, feasibility, utilization, and access in LMICs. The potential gains in detecting subclinical CVD may be substantial in LMICs, if earlier detection leads to earlier engagement with the health care system to prevent or delay cardiac events, morbidity, and premature mortality. Thus, dedicated studies examining the feasibility, utility, and cost-effectiveness of detecting subclinical CVD in LMICs are warranted.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and loss of disability-adjusted life years (DALYs) worldwide.[1] In addition to the health burden, CVD will exert a significant economic burden, on the order of approximately \$15 trillion over the next 20 years.[2] While high-income countries have experienced a substantial decline in CVD mortality over the past several decades,[3,4] many low- and middle-income countries (LMICs) have higher age-standardized CVD mortality rates than high-income countries. [4,5] Rapid urbanization, mechanization of transport, and increasingly sedentary jobs in LMICs have led to a rise in CVD burden.[6] In combination with a persistent infectious and

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nutritional disease burden, this has led to a challenging “double burden of disease” in many countries.[7,8] Furthermore, CVD in LMICs affects younger individuals than in high-income countries, which has severe adverse effects for household income, livelihood, and functionality.[9,10,5]

CVD in LMICs manifests as both atherosclerotic and non-atherosclerotic disease, with significant geographic heterogeneity with respect to relative burden of these broad categories of disease.[11–14] Atherosclerotic manifestations of CVD, including ischemic heart disease and stroke, have emerged as the principal causes of death and disability in many parts of Eastern Europe, South Asia, East Asia, North Africa/Middle East, and Latin America.[15–20] On the other hand, non-atherosclerotic CVD, such as rheumatic heart disease and non-ischemic cardiomyopathy, are disproportionately burdensome in sub-Saharan Africa, Southeast Asia, and parts of South Asia.[21,22,16]

Detection of subclinical CVD, before an individual experiences a major event, may therefore offer the potential to prevent or delay morbidity and mortality, if combined with an appropriate care response. Moreover, detection of asymptomatic vascular disease may lead to adoption of risk-mitigating therapies or healthy lifestyles that might lower subsequent CVD risk.[23,24] The full spectrum of cardiovascular imaging technologies exist in many LMICs.[25] However, in this review, we will limit our discussion to carotid ultrasound, coronary calcium scan using computed tomography, and echocardiography, which can be used to detect subclinical atherosclerotic and non-atherosclerotic CVD.

Atherosclerotic Cardiovascular Disease

The two bioimaging technologies that we will discuss for detection of subclinical atherosclerotic CVD are carotid ultrasound and coronary calcium scan using computed tomography.

Carotid Ultrasound

Atherosclerosis is a diffuse process and requires a systematic approach to medical and risk factor management. Since detection of atherosclerosis in the carotid vasculature is associated with coronary atherosclerosis,[26,27] it is a valuable approach to assessing an individual for subclinical atherosclerotic CVD. Although multiple imaging-based modalities exist to assess extra-cranial carotid disease, the most commonly used method in primary prevention settings remains carotid ultrasound (cUS). Measuring carotid intima-media thickness (cIMT), most commonly performed at the carotid bifurcation, has been linked in numerous studies to an increased and independent risk for cardiovascular events.[26] Thus, cIMT has long been considered a marker of atherosclerosis. However, recent studies have shown that approximately 80% of the cIMT complex is comprised of media rather than intima. As atherosclerosis is largely a sub-intimal process, cIMT is no longer considered a reliable marker of atherosclerosis but rather a phenotypic response to aging or hypertension.[28–30] In contrast, cUS may also be used to directly visualize and quantify carotid atherosclerotic plaque (Figure 1).[27,31] Compared to cIMT, carotid plaque-based metrics demonstrate stronger associations with thrombotic events.[32,33,31] To date, most studies evaluating carotid plaque have used either semi-quantitative or binary (present/absent)

approaches to measure disease.[34,35] In contrast, a novel approach to quantify carotid atherosclerosis was introduced by the High-Risk Plaque (HRP) BioImage study, a longitudinal cohort of approximately 6,000 asymptomatic United States adults who underwent multimodality vascular imaging.[36] In this study, cUS was used to interrogate the entire length of both right and left common and internal carotid arteries from the angle of the jaw to the clavicle. The cross-sectional areas of all visualized plaques were summed to calculate the overall carotid plaque burden (cPB) for each individual (Figure 2). The overall prevalence of carotid atherosclerosis in this cohort (78%) was much higher than previously reported in other studies using less sensitive methods to detect atherosclerosis.[27] In terms of risk prediction, preliminary findings from the HRP study show that cPB demonstrates a strong and graded association with cardiovascular events over 3 years. Specifically, three-year rates of adverse events among those without any carotid plaque and first, second and third tertiles of cPB were 1.7%, 3.3%, 4.5% and 5.2%, respectively ($p<0.001$).[37]

Emerging data suggest that cUS may be a feasible method to screen for subclinical atherosclerotic CVD in LMICs. The multinational HAPPY (Heart Attack Prevention Program for You) initiative examined the utility of cUS, performed by non-experts after a single 4-hour training session, in a relatively young (mean age 40 years) rural cohort from Northern India.[38] Each examination took approximately three minutes, and cUS studies were performed in 771 asymptomatic volunteers over a three-day period. Carotid plaques were detected in 69 subjects (8.9%) with a higher prevalence in men compared to women (10% vs. 4%, $p=0.02$). Although these results highlight the feasibility to train, perform and interpret cUS in a LMIC setting, these findings should be considered within the context of the cohort studied. Specifically, participants were young and tended to be physically active with a healthy diet, which may limit the generalizability of these findings to other populations with less healthy lifestyles. In addition, associations between atherosclerosis detected by cUS and longitudinal outcomes in LMIC cohorts have not been examined in detail. Moreover, whether or not such an imaging-based approach for subclinical atherosclerotic CVD screening will be more cost-effective than traditional CVD risk factor assessment alone remains unknown.

Coronary Calcium Scan

Deposition of calcium within the coronary arteries is considered pathognomonic for coronary artery atherosclerosis, and may be directly quantified with a coronary calcium scan using computed tomography.[39] With the Agatston method,[40] the measurement of coronary artery calcium (CAC) has been largely standardized allowing comparisons across populations and time periods. While the prevalence of CAC varies by gender, age, and race, the absolute amount of CAC is a consistent and independent correlate of adverse events. [41,42] Results from the Multi-Ethnic Study of Atherosclerosis, which can be applied with caution to LMIC populations of similar ethnic backgrounds, have shown that both the extent and progression of CAC are strong and independent predictors of adverse events as compared to other modalities such as cIMT.[43,44] The utility of this method as a screening tool for atherosclerosis is reflected in recent guidelines—no other imaging-based modality, with the exception of coronary calcium scanning, was recommended for use in recent American College of Cardiology/American Heart Association lipid-lowering guidelines

(Class IIb).[45] Although previous studies have shown the utility of CAC in predicting long-term events,[41] the HRP study demonstrated the impact of CAC for near-term risk prediction. Over an average follow-up of 2.7 years, the extent of CAC among HRP participants was independently associated with a graded risk for adverse events, even after controlling for concomitant carotid atherosclerosis.[37]

Despite the clear epidemiologic links between CAC and adverse events in primary prevention populations in high-income countries, similar data from cohorts in LMIC remain sparse.[46,47] One report from a large urban teaching hospital in Pakistan examined the correlation between CAC scores and coronary luminal obstruction based on CT angiography.[47] Consistent with findings from cohorts in high-income countries, the authors found that low CAC scores (< 10) were associated with a low frequency of obstructive CAD while a majority of subjects (74%) with CAC scores exceeding 400 had severe coronary stenosis.[48] Another study from India found that presence of CAC in an asymptomatic population was associated with traditional atherosclerotic risk factors, such as age, hypertension and diabetes mellitus.[46] These findings notwithstanding, the feasibility, cost implications and predictive utility of CAC in LMIC cohorts remain unknown. For example, while measuring CAC is a largely automated and standardized process, detecting CAC requires large scanners that emit radiation are not portable. Given that coronary calcium scanning involves ionizing radiation, and that CVD affects a relatively younger population in LMICs, the issue of radiation exposure at younger ages may also be another limitation for its widespread use in LMICs.

Non-Atherosclerotic Cardiovascular Disease

Echocardiography is the primary imaging technology for the detection of subclinical non-atherosclerotic CVD.

Echocardiography

Cardiac ultrasound, or echocardiography, has advantages over other cardiovascular imaging modalities and has become the dominant technology in LMICs. There is no ionizing radiation, so there are no radiation safety issues. Echocardiography can be used for a broad range of non-atherosclerotic cardiovascular indications, beyond ischemia evaluation alone, and is already the most commonly used diagnostic imaging tool in cardiology.[49] Because of the fewer infrastructure requirements, it is more adaptable to low-resource settings, and compared to other imaging modalities (i.e. nuclear imaging, magnetic resonance imaging, computed tomography), it is imminently more portable. Echocardiography is well-suited for the epidemiology of CVD in many LMICs, which face a substantial burden of non-atherosclerotic CVD.[21,22,16,50] Given the relative predominance of valvular heart disease, cardiomyopathies, and hypertensive heart disease in many LMICs, echocardiography is the primary bio-imaging technology for these regions.

Rheumatic heart disease (RHD), a dominant cause of valvular heart disease in LMICs, is a disease for which echocardiography can help with management. The worldwide prevalence of RHD is estimated to be 15.6 million cases, with 233,000 deaths per year.[51] However, these estimates may underestimate the true prevalence of subclinical RHD, as recent

echocardiography-based screening studies have demonstrated.[52] Although the valvular lesions of RHD have classic and distinctive auscultatory patterns detected by stethoscope, even highly trained specialists vary in their ability to detect RHD with the stethoscope alone, compared to echocardiography with low levels of training.[53] Effective image quality has been demonstrated, even by individuals with no prior training in echocardiography, prior to mass RHD screening.[54] Multiple studies have demonstrated its effectiveness in the mass screening setting.[55,56] Earlier detection of RHD can lead to treatment that may delay progression to advanced disease, although the link between early detection of RHD and impact on prognosis is still debated.[57,58] The World Heart Federation has proposed criteria for echocardiographic diagnosis and recommends screening in high-prevalence regions.[59]

Handheld echocardiography has recently been developed and numerous studies have demonstrated feasibility and applicability in low-resource settings with studies performed by non-cardiologists, especially as these devices have become smaller while maintaining some of the sophistication of larger machines (Figure 3).[60–62] Early studies from the 1990s required portable generator use,[63] by the 2000s, ultrasounds were hand-carried and battery-operated,[64] and in the 2010s, these devices can now fit in the same pocket that once would carry a stethoscope.[65]

Because of the potential for misapplication or incorrect interpretation of echocardiographic images by non-expert imagers,[66] remote interpretation has been evaluated to provide greater access to accurate interpretation.[67] In the past, such consultation has required dedicated satellite connections and custom wireless transmitters.[68] However, with the expansion of access to broadband internet connectivity, this kind of teleconsultation is now no longer prohibitively resource-intensive, and rapid remote interpretation can be provided on a mass scale.[69] This may be especially useful if local expert interpretation is not available. For example, the World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease are complex and may require expert interpretation,[59] which could be facilitated by this type of remote image interpretation.

In summary, echocardiography can be a powerful tool to direct treatment pathways for non-atherosclerotic CVD. For instance, in sub-Saharan Africa, 90% of cardiomyopathy cases are non-atherosclerotic in etiology. Thus, simple parasternal and subcostal views to quickly establish right ventricular size, left ventricular systolic function and the existence of any valvulopathy can effectively differentiate between cardiomyopathy, right-sided heart failure, rheumatic disease, or congenital heart disease.[50]

Access to Imaging and Clinical Services in Low- and Middle-Income Countries

Bio-imaging for subclinical CVD may be technically feasible and available in many LMICs, but there exist marked disparities in utilization (Figure 4).[25] Limited resources and lack of available health care infrastructure in LMICs may introduce unique challenges in widespread implementation of these technologies. Cardiovascular imaging is concentrated in capital cities,[70] with higher use in border states of “high user” nations.[71] However, these

services are often provided on a fee-for-service basis with the cost prohibitive for all but the highest echelons of wealth in those countries. For example, stress SPECT MPI in India costs \$180, which is a significant burden in the context of an average monthly middle-class income of \$500.[72]

Even when imaging technologies are available, in many LMICs they may not be sufficiently utilized. For example, although cUS is mobile and relatively inexpensive, acquisition and interpretation of images requires experienced technicians and readers, particularly when making precise measurements of area. Training for technicians is nearly non-existent in most LMICs,[67] leading to more than half of installed equipment being not utilized secondary to inadequate servicing or lack of operators.[73] When these technologies are used, problems are further compounded by lack of accreditation processes which may lead to patient and operator safety oversights.[74]

Health care delivery systems also need to be developed alongside the implementation of imaging to detect subclinical CVD. The benefit of early detection would be lost if there was no means to seek additional medical attention after an abnormality is found. For example, in West Africa there are no pediatric cardiac surgery centers, and in Ghana only 20 percent of children diagnosed with congenital heart disease could afford surgery within one year of echocardiographic diagnosis.[75] In Brazil, the mean waiting time for coronary artery bypass graft surgery was 23 months with a 6% annual mortality rate on the waiting list; for heart valve surgery, the wait time was reported at 32 months with a 13% annual mortality.[76] Surgical missions funded by international charities cannot meet the overwhelming demand in LMICs for those with surgical CVD, and are also not sustainable long-term solutions. Instead, building local capacity (physical, technical, and human) is critically important. In addition to surgical treatment options, access to medicines remains a formidable challenge.[77] Among patients with atherosclerotic CVD, less than 25% have been found to use evidence-based medicines such as antiplatelet drugs, beta blockers, and statins,[78] with correspondingly worse statistics in LMICs. The development of care delivery systems, both surgical and medical, must dovetail with diagnostic referrals if bio-imaging for subclinical CVD is to actually aid the population to prevent or delay events, morbidity, and premature mortality due to CVD. The potential promise of earlier detection of subclinical CVD can be realized if preventive, lower-cost, and early therapeutic measures could slow progression to later stages that require prohibitively costly intervention.

In part, this will require funding for CVD control that needs to be re-aligned in order to correspond to the burden on LMIC populations. Development assistance for health that is allocated to CVD and other non-communicable diseases is very low relative to the burden of these diseases in LMICs.[79–81] In fact, many donor countries have policy bans against funds for non-communicable diseases.[82] These trends must change in order to improve the alignment of health financing and disease burden. Efforts to promote universal health coverage and healthy life expectancy have the potential to improve efforts at CVD prevention and control, but this would also require careful attention to structures of global governance that impact health and related sectors.[83]

In summary, issues related to access, feasibility, and integration within a comprehensive care delivery system need to be addressed in the context of implementation and utilization of bio-imaging for the detection of subclinical CVD in LMICs. In addition to the issues described above, further documentation and experience is required to demonstrate that these bio-imaging technologies can be equitably utilized and accessed outside of research settings. Policymakers at all levels—global, national, and local—need to take these issues into account when considering the expansion of these technologies in LMIC settings.

Conclusions

There are many potential challenges and issues that need to be addressed regarding the consideration of using bio-imaging for the detection of subclinical CVD in LMICs. However, the potential gains in detecting subclinical CVD may be substantial in LMICs, if earlier detection leads to earlier engagement with the health care delivery system in a fashion that prevents or delays subsequent cardiac events, morbidity, and premature mortality. Thus, dedicated studies examining the feasibility, predictive utility, and cost-effectiveness of detecting subclinical CVD in LMICs are warranted.

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Abbreviations (in alphabetical order)

CAC	Coronary artery calcium
cIMT	Carotid intima-media thickness
cPB	Carotid plaque burden
cUS	Carotid ultrasound
CVD	Cardiovascular disease
DALY	Disability-adjusted life years
HRP	High-Risk Plaque
LMICs	Low- and middle-income countries
RHD	Rheumatic heart disease

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Figure 1.

Measurement of carotid plaque vs cIMT using ultrasound imaging. The right carotid of the individual (37-year-old male) is scanned in the transversal plane (short-axis view) from the base of the common carotid up through the bifurcation. An atherosclerotic plaque is seen in the bulb region and marked up as illustrated (A). The far-wall IMT of the common carotid approximately 1 cm from the flow divider is measured and recorded in the longitudinal plane (long-axis view) (B). Reproduced with permission from Singh et al.[38]

Figure 2.

Calculation of the overall carotid plaque burden using carotid ultrasound. Segment of carotid artery with a plaque (orange), which is scanned with a linear array transducer as a series of image slices in transverse section (top). Each image is analyzed with semi-automated software to quantify plaque area, plaque grayscale statistics, percent stenosis, and other metrics of interest. Plaque areas from all images in the entire image sequence were summed as “plaque burden”. Lower left: Common carotid artery with no plaque. The blue border represents the lumen/intima border; the red border represents the media-adventitia boundary. Lower right: Common carotid artery with plaque. The red and blue borders are the same as in previous image, but the orange border represents the boundary of the plaque. Reproduced with permission from Sillesen et al.[27]

Figure 3. Photograph of the Vscan handheld ultrasound (GE Healthcare, Wauwatosa, WI) being used in a medical mission to Honduras where patients were screened for cardiovascular disease. Used with permission from Monica Mukherjee, M.D.[84]

Figure 4.
Illustration of worldwide utilization of nuclear cardiology procedures (per 100,000 population). Reproduced with permission from Vitola et al.[71]