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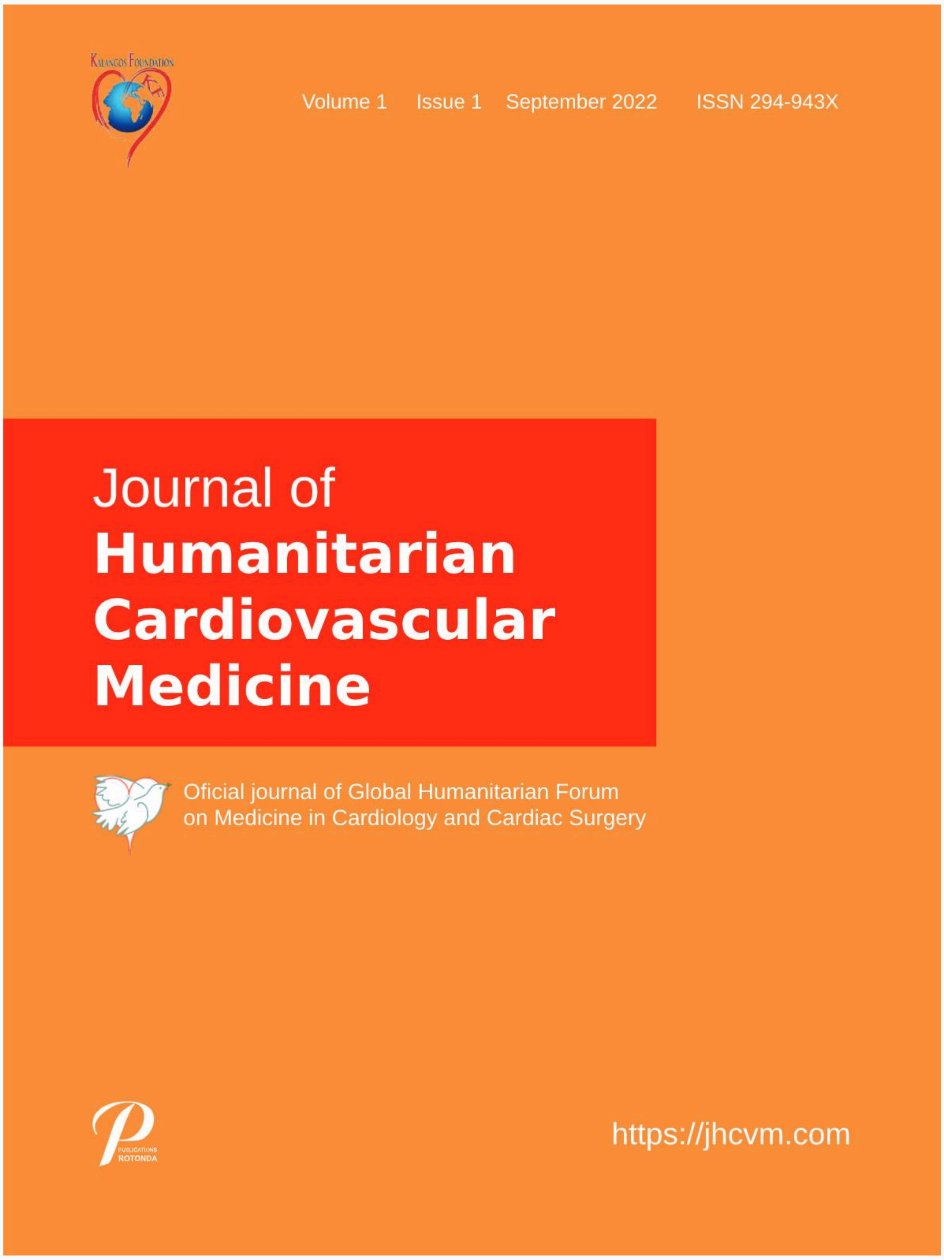

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Official journal of Global Humanitarian Forum on Medicine in Cardiology and Cardiac Surgery

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The Journal of Humanitarian Cardiovascular Medicine (JHCVM) is a Four-month, peer-reviewed scientific journal dedicated to report the clinical, epidemiologic, public health and basic research studies focused on Cardiovascular Medicine in Low-and Middle-Income countries.

It is the official journal of the Global Forum on Humanitarian Medicine in Cardiology and Cardiac Surgery (GFHM) whose Mission is to close the disparity between the medical care facilities of the North and those of the South by developing programs & projects related to education, research, facilities, quality improvement and training in these countries.

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Health inequalities between the developing and developed world as one of the persistent challenges of our globalizing world

A specific focus on cardiovascular diseases, the impact of global humanitarian forums, and potential solutions

Professor Afksendiyos Kalangos

President of "Kalangos Foundation"

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Editorial

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Humans with different demographic, geographical, cultural, and ethnic characteristics and various levels of development and wealth presents clear gaps in health care. Complex historical, geographical, socioeconomic, cultural, climatic, adaptive genetic, and behavioral mechanisms can explain why humans' collective work since the beginning of their first communities was not and is not equally distributed. Nevertheless, this unequal distribution of global economic resources between developing and developed countries leads to inequalities in many levels of social life which are, at the same time, responsible for the unequal exposure to the factors determining health problems as well as the unequal ability to benefit from basic and qualified health services.

Cardiovascular medicine is one of the most affected fields of health services by these inequalities. In 2001, there were 13 million cardiovascular diseases (CVD) related-deaths in low and middle-income countries compared to 3 million in high-income countries[1] with a burden in the percentage of all deaths due to CVDs from 23% in 1990 to 28% in 2001[1,2].

Non-communicable diseases (NCDs) account for 73.4% of all deaths due to CVD, with ischemic heart disease and strokes related to atherosclerosis being the most frequent causes in the 2017 Global Burden of Disease study[3]. With 35% of all deaths, NCDs are located at the second position among the different causes of death in sub-Saharan Africa following an assembly of communicable, maternal, neonatal, and nutritional diseases. Since early twenties, this assembly of diseases is in a progressive decline with regard to their contribution to overall mortality. NCDs might rise to the first position with more than half of all deaths by 2030 in sub-Saharan Africa[4].

Concurrently in low and middle-income countries, rheumatic heart disease, congenital heart diseases, the endemic endomyocardial fibrosis, and Chagas' heart disease remain unsolved common public health problems[5-7].

The incidence of acute rheumatic fever (ARF) varies from 5 to 80 per 100,000 inhabitants in most low and middle-income countries[8]. Rheumatic heart disease caused by repeated episodes of ARF affects about 20 million young people and is at the origin of 250,000 premature deaths each year in low and middle-income countries[9].

In 2017, 12 million people were suffering from congenital heart diseases worldwide, with nearly half of them in low and middle-income countries[10]. Each year between 500,000 and 1.5 million newborns with congenital heart defects are added to this total population. Although the birth prevalence of congenital heart diseases varies between 8 to 12 per 1000 live births, it is very difficult to know the true prevalence of congenital heart diseases at birth in the majority of low and middle-income countries due to unreliable public health statistics, the lack of perinatal diagnostic and major specialty structure facilities. The high frequency of deliveries at home and geographic barriers for families living in rural areas to reach a specialty center are additional factors leading to more undiagnosed cases that die within the first weeks after birth. The low incidence rate of 1.9 per 1000 live births in Africa reflects this multifactorial reality[11].

Chagas' disease, more endemic in Latin America, caused by Trypanosoma Cruzi usually affects children living in poor rural areas and can result in left ventricular systolic and/or diastolic dysfunction and arrhythmias during its chronic phase. Although the risk of new contaminations persists in many children in endemic countries, disease prevention programs continue to be effective in reducing the infected people number. This number was estimated to be between 16 and 18 million in the early nineties versus between 10 and 12 million in the early twenties[12].

The management of all these above-mentioned heart diseases in low and middle-income countries needs a traditional humanitarian platform focusing on the alleviation of health inequalities and its potential solutions adapted to the conditions of the national health system and the demographic, geographical, cultural, ethnical, socioeconomic, behavioral specificities of each country. These country-related specificities are determinant factors because they directly influence the establishment of a stronger national political will to invest more in national health systems, the reinforcement of moral imperatives, and the implementation of an appropriate political model to adequately intervene on the socioeconomic determinants of health conditions. For this reason, we have launched in 2003 the *"Global forum on humanitarian medicine in cardiology and cardiac surgery"* in Geneva to serve as a bridge from thought provoking discussions to concrete actions on site adapted to the above-mentioned specificities of the country in need for long term assistance in their national cardiac care programs. On an international level, these global forums have instigated the relationship and networking between NGOs and low or middle-income countries and reinforced the global coalition against the lack of health care services for cardiac patients by promoting awareness of the consequences of lack of appropriate medical and surgical treatment.

These forums have also implemented actions for searching country-specific solutions and have rallied a large number of NGOs for precise policies on research, prevention and health care reinforcement, by including international organizations, foundations and the community of cardiovascular health professionals who in the majority of high income countries was initially quite skeptical. Some low and middle-income countries were also concerned by the same skepticism because of the lack of ownership of these aid policies and the reaction against the myth of Western superiority, which consists of "We talk, you listen; We recommend, you obey; We give, you receive; We teach, you learn...

These forums allowed us to change our approach and make our counterparts involved in cardiovascular health care more self-confident and permit them to take complete responsibility for taking care of their patients. I always strongly believe that we also have plenty of things to learn from them as well; as partners agreed to work together, coordinate and harmonize procedures, and respect our various specificities, homegrown strategies, and priorities.

I will never forget the intensity of the debates during these global forums over the fact how we must recommit ourselves to prevent the fleeing and draining of the local human medical capacities of low and middle-income countries and rather make them more accountable to their patients, thus permitting them to exercise leadership in their regions (as India and Brasil do actually). One of the most spectacular achievements of these forums was also the process of how we must concentrate on intensifying our efforts through economic policies to enable them to mobilize additional domestic financial resources to sustain their medical reforms. Many health institutions in India accomplish the most impressive part of this vision by making healthcare affordable for everybody not only across India but at the same time across the globe. The entrepreneurship of Doctor Devi Shetty from Bangalore who introduced a micro health insurance scheme with a monthly premium of Rs 5-7 in his province has to be mentioned as an efficient policy to mobilize the mandatory domestic financial resources to increase the accessibility to heart surgery in India which needs 2.5 million heart operations a year and yet there are only 90 000.

I still believe that the global trends in low and middle-income countries call for optimism. Since economic progress has overcome the demographic explosion over the last decade, in the near future, we can expect more low and middle-income countries to achieve their medical goals on target. Their individual success stories may further stimulate other countries to accentuate international and regional "networking" and collaboration through sustainable programs established by international NGOs.

As social determinants of health play a crucial role in the etiology of all cardiovascular diseases, in 2005 the World Health Organization has created a commission in an attempt to determine the actions aiming at promoting equity in health at global level. In its final report in 2008, this commission recommended improving daily living conditions, fighting against the unequal distribution of money, power, and resources, and evaluating the dimension of the problem and the impact of actions undertaken by all world governments.

Although the individual success stories of some low and middle-income countries especially in cardiovascular health care reflecting the appropriate actions undertaken by their governments impress us, the improvement of general health conditions in low and middle income countries is unfortunately still a slow-acting process with an estimated 800 million people being chronically hungry worldwide, with limited access to food although the global food production can easily cover 120% of global food needs, with unacceptable slight decrease of life expectancy rates' gap between developing and developed countries, with more than 6 million children under the age of 5 years dying on a yearly basis due to preventable causes in low-income countries, with infectious diseases such as diarrhea, respiratory infections, malaria, tuberculosis and HIV continuing to be the first cause of death in children in low-income countries, with an evidence showing that about 80% of non communicable diseases related deaths -such as cardiovascular diseases, cancer, diabetes, chronic respiratory diseases-, occur in low and middle-income countries and with higher death rates related to various forms of violence, in low and middle-income countries.

Despite all these arguments, unfortunately, the political motivation in favor of implementing concrete actions as part of public health policies by national governments is still failing. For this reason, health inequalities between developed and developing countries perhaps require an international leadership capable of formulating specific health policies adapted to the specificities of each low or middle-income country, coordinating them in different sectors such as labor, education, social protection etc and supervising their positive effects on health determinants[13].

As we have started timidly doing for our environmental and climatic problems, a global governance able to collaborate in harmony with the health authorities of low and middle-income countries, various international organizations, intergovernmental agencies and NGOs may be one of the ideas to deploy in actions, the target being to ensure the sustainable development of our global human society in the area of health.

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New Knowledge from Research - Can Global Congenital Cardiac Surgery Play a Part? A Call for International Collaboration

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humanitarian, congenital heart defect, heart surgery

Abstract

Over 1.3 million babies are born each year with congenital heart defects (CHD), with the highest incidence in low-income countries (LIC) and low-middle income countries (LMICs)[1]. The Lancet Commission on Global Surgery found that surgically treatable conditions make up 28-32% of the total global burden of diseases, of which most are cardiovascular diseases[2]. Currently, high-income countries (HICs) undertake mission trips to LICs and LMICs to provide surgical care for those who otherwise would not have access. These trips also provide an opportunity to train the local surgical teams. It has been proposed that there should be a shift in thinking from 'humanitarian surgery' to 'global surgery', as this benefits both the provider and the receiver. With this change, we should address several limitations in our current infrastructure, including but not limited to, the lack of international research collaboration, the need for globalising and scaling up the paediatric cardiac surgical workforce, offsetting greenhouse gas emissions from mission trips, and opportunities for mentorship and training in LICs.

Why We Do What We Do

Firstly, there exists the moral axiom for providing surgical care to LICs and LMICs - 'to heal' should have no borders. Current inequalities, conflicts, and disasters continue to disadvantage those living in the poorest of countries. Even with interventions from the World Health Organisation (WHO) and other international bodies, the issue persists. The right to health is a global issue. COVID-19 has only strengthened this argument. The pandemic is a paragon in highlighting the co-operation between countries when the situation warrants. Surgery is as essential a treatment option as any pharmaceutical on the WHO Model List of Essential Medicines. Though it is deemed indispensable in any healthcare model in HICs, it is still considered a luxury elsewhere in the world - a therapeutic available only with the help of philanthropic organisations and insurance. Only 6% of the world's total number of surgical interventions take place in the poorest third of the world's population, compared to 74% of all major surgeries performed in the wealthiest third[2]. There ought to be a substantial leap from the current infrastructure to ensure every child has access to appropriate medical and surgical care. The cost of 'not doing' is too catastrophic, and reneges on the core undisputed promises of the UN Convention on the Rights of the Child including the right to life and provision of necessary medical assistance and health care to all children[3].

Meeting these challenges requires clinical evidence pertinent to the local settings, an adequate number of well-trained personnel, improvement in nursing and medical education, research, and quality improvement activities[4]. All of these requirements are financially demanding and therefore can be extremely difficult for LMICs to achieve. 58% of the burden of disease of CHDs could be averted by scaling up selected surgical care in LMICs through various mechanisms[5]. Patients suffering from CHD are significantly more likely to achieve lower education and are more often unemployed than their counterparts[6]. With the globalisation of industries and sectors, there exists an economic argument as to why the entire global cardiac community should intervene and do so immediately. Even with an increase in surgical workforce, the continuous increase in CHDs warrants a demanding ask to reduce gaps given the current resource allocation.

The Need for A Paradigm Shift

There have been major advancements within global surgery in the past few years. However, substantial gaps remain in merging humanity and surgery. Lockdowns due to the pandemic have only exacerbated current disparities in service delivery. Cardiac screening, check-ups, and mission trips came to a halt, allowing existing conditions to worsen, paving way for further deterioration in health. The pandemic has unreservedly changed the way we conduct business.

With the use of telehealth monitoring for check-ups to the utilisation of virtual MDT meetings, the internet has paved way for alternative ways of service delivery without compromising on quality. With this, we limited the carbon emissions from transport modalities required to attend meetings and conferences, and to encourage cross-country research collaboration, which was unfathomable prior to the pandemic without, for example, attending a large international symposium.

Mission trips provide an opportunity for those who do not have the luxury of accessing cardiac surgical care. However, with the pressing dangers of global warming and climate change, it is becoming harder to justify cross-continental trips for a handful of operations. A carbon-conscious humanitarian effort will have to balance the travel-related emissions with sustained efforts to reduce CO_2 in all surgical settings, at home and abroad. A recent eco-audit performed in France highlights that on average a heart operation emits 124.3kg of CO_2, 89% of which come from disposable plastics[7]. This is the equivalent to driving 2,273 miles in an averaged sized petrol-powered car. Almost all operations in LMICs utilise significantly less resources whilst maintaining excellent quality of care, compared to their HIC counterparts. HICs can better understand how to reduce plastic usage and surgical carbon emissions by studying how such operations are performed in LMICs with reduced costs, optimising resources, and minimising reinterventions.

Vervoort et al.[8] proposed a collaborative framework required for safe, timely and affordable cardiac surgical care for all children in need. With this initiative, the global cardiac surgical community still need to bridge the gap from good intentions to reportable outcomes. Currently, there exists limited open-sharing international database which provides real-world data on the number of operations performed in LICs and LMICs, and the different characteristics of such operations. The International Quality Improvement Collaborative (IQIC) is one of such organisations that has a registry of outcomes of CHD surgical programmes operating in LICs and LMICs. The IQIC data has shown a negative correlation of gross domestic product (GDP) and health expenditure per capita to mortality[9]. This calls for more data collection at a regional and local level to identify the exact the reasons of such outcomes. Vervoort et al.[10] has already investigated the current state of paediatric cardiac surgical service provisions in LMICs and HICs. We add to this by determining new issues presented to global surgery, and potential benefits and solutions for both HICs and LMICs. **Table 1.** states the key messages and potential benefits and solutions encountered in global paediatric cardiac surgery.

More Data for Better Decision Making

Currently, several databases exist which aims to collect various data points from mission trips and surgery in LMICs. However, there exists no global repository with a minimum dataset requirement for global cardiac surgery. Even with such databases, language barriers and interchangeable terms warrants no uniformity in data collection. For example, cardiac surgery is also known as cardiovascular surgery, cardiothoracic surgery, CT surgery, chest surgery etc. The inception of the common diagnostic code allowed clinicians to jump semantic barriers to uphold the integrity of key terminologies used to manage patients and their conditions. Such utility for data collection on a global scale will limit the issue of language barriers when cross-country audit and research collaboration are required.

Is it too ambitious to think that a common effort can now generate a minimum dataset for humanitarian surgery, which will then inform data-driven practice in this area? To our knowledge, the IQIC database is the main database that aims to collect data to aid the development of global paediatric cardiac surgery. More unique repositories such as the IQIC database, or a combined effort within IQIC, are needed to go from an idea to a measurable outcome. Such databases in other fields are not uncommon - the British Heart Foundation (BHF) Data Sciences Centre[11], or the aortic valve insufficiency and ascending aorta aneurysm international registry (AVIATOR)[12] are examples of starting grounds for research by providing granular data on what exactly needs to be done in LICs[13], other than just the need for ‘operating more’.

Table 1. Table outlining key messages of global paediatric cardiac surgery and potential benefits and solutions for HICs and LICs

Key Messages	Potential Benefits & Solutions
New issues in global paediatric cardiac surgery	New age of frugality Climate change and travel barriers Overshadowed by infection, public health and economic issues
Potential opportunities	Recognition that global surgery is a ‘two-way street’ Mutual benefits for LICs and HICs Reduction of surgical carbon footprint is a common goal Education and research can be done in a more global framework New developments are best informed by data
Research opportunities	Reviving old concepts for new treatments (e.g., central shunts for pulmonary hypertension) Reviewing indications in late diagnosis and late treatment scenarios Creation of a unique dataset for global congenital surgery with a data sharing framework Follow-up via routinely collected data Simple studies of new technologies and interventions

The shift from humanitarian surgery to global cardiac surgery provides a framework for which both HICs and LICs benefit. Currently, there are only 0.07 congenital cardiac surgeons per million paediatric population in LICs, compared to 9.51 congenital cardiac surgeons per million in HICs[14]. We postulate that HICs should acknowledge the benefits of global cardiac surgery. The opportunity for additional training, most of which would not be possible in Western surgical training programmes are one of such key opportunities for HICs. The recent paper by Vinck et al.[15] only highlight this further. With the globalisation of the paediatric cardiac surgical workforce, globally coordinated training programmes including those in LMICs will enable the next generation of global surgeons to understand the disease process in a broad spectrum of patients and support research development.

Such collaboration will not only aid overall surgical training but provide a platform where surgeons worldwide can discuss cases, offer support, collaborate on research on an international scale, team-build to resolve limitations that currently exist within congenital cardiac surgery, and ultimately pave way for the globalisation of congenital cardiac surgeons to ensure every child has access to appropriate and quality surgical care.

Research Initiatives

Transfer of know-how to LMICs rests on data science, surgical education, and healthcare economics. HICs can benefit from understanding how LICs provide surgical care with limited resources by reducing waste, providing real-world data on choice of clinical strategy, and improving overall service delivery. Gouton et al.[16] offers an example on the late management of truncus arteriosus from twenty years of humanitarian experience. Such articles set a precedent on clinical benefits to HICs with the existence of a global network of researchers. **Table 2** outlines examples of previous studies that were conducted, with key messages to highlight the benefit for both HICs and LICs in service delivery and research.

The first study by Lim et al.[18] aimed to evaluate the utility of diuretics post-coronary surgery. The endpoint was assessing if patients achieved pre-operative weight post-operatively. The second study by Lim et al.[19] aimed to assess the clinical significance of pleurotomy-associated morbidity during internal mammary artery harvesting. The patients were divided into a pleurotomy group and an intact pleurae group. It was observed the left pleurotomy was not associated with adverse clinical outcomes. These trials shine a light on the character of research that could take place in LICs, the results of which can aid management in HICs and LICs.

Table 2 outlines examples of previous studies that were conducted which could benefit both HICs and LICs

Study	Author	Year Published	Key Message
Midterm outcomes of the Potts shunt for paediatric pulmonary hypertension, with comparison to lung transplant	Lancaster et al.[17]	2020	Revising old concepts such as central shunts for treating pulmonary hypertension
Late management of truncus arteriosus: 20 years of humanitarian experience	Gouton et al.[16]	2018	Reviewing management of truncus arteriosus for patients who present late in LMICs due to lack of antenatal screening. Can this be used to aid management of such patients in HICs?
Evaluating routine diuretics after coronary surgery: a prospective randomised controlled trial A prospective study on clinical outcome following pleurotomy during cardiac surgery	Lim et al.[18] Lim et al.[19]	2002 2002	Simple prospective single-centre or multicentre studies could be replicated in LICs to assist in transfer of trial 'know-how', whilst gaining support from industry
Assessing long-term outcome after atrial correction of TGA over arterial switch	Turina et al.[20]	1998	Circumstances which do not allow for arterial switch operations can by managed by favouring atrial correction for older children with TGA

The Next Steps

To progress, we must first acknowledge and enhance the mutual benefit global cardiac surgery delivers. Service delivery provides benefit for the provider, as well as the receiver. QI projects and audits ensures health professionals constantly assess, evaluate, and improve current standards. International collaboration, especially with the current climate on 'work from home', aims to subside the barriers of culture, language, and distance for improved surgical care. Cross-country research extends the possibilities of new discoveries, and fostering to more enhanced data collection, sharing, and partnerships.

Additionally, there needs to exist an international repository of data of all mission trips and local training programmes in LMICs. No meaningful change can be made without data, as this outlines what the exact limitations are, and how we can help resolve them. Uniform data collection from all charitable organisations and surgical teams can be used to conduct localised audit programmes to allow for more personalised strategic decisions. Mission trips are effective but not sustainable. The need for setting up local units, and if needed, the ability for online mentorship ensures patients have access to excellent care with compromising on quality. The Cape Town Declaration has been a pivotal turning point in global cardiac surgery[21]. We support its aims and encourage all HICs, including the UK to take part in this global initiative. We have highlighted the next steps in what we think is required for global cardiac surgery in **Figure 2.**

Limitations exist in our current practice which should be addressed. We cannot deliver adequate services and treatments in LICs, and now HICs due to the challenges presented by the pandemic. Additionally, further research will be difficult without first prioritising service delivery in both HICs and LICs. The lack of congenital cardiac surgeons and a global paediatric workforce prevents the cross-country collaboration that is required to achieve the goals of the global cardiac surgery. The heterogeneity in data collection, lack of a central database, and lack of support from industry and local workforces still presents as a challenge in the road for deliverable outcomes.

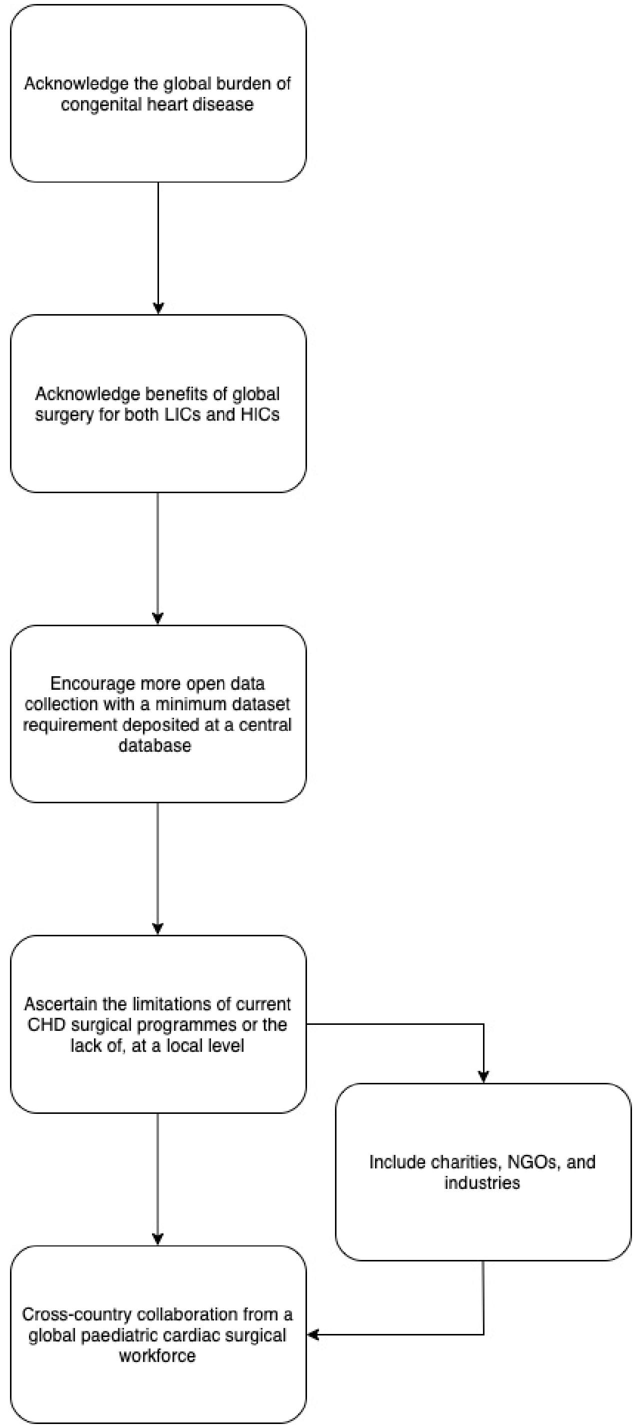

Figure 2. Highlights the steps required for the establishment of Global Paediatric Cardiac Surgery

Finally, there exists a financial burden in maintaining a high-level surgical team and ICU infrastructure necessary for successful CHD surgery. The stark contrast in surgeries performed and surgeons available between HICs and LMICs attests to this[22]. Furthermore, the medical network required to successfully maintain a cardiac centre is extensive and complex; and requires logistical planning. In LMICs, such convenience is not a readily available commodity, and patients find that they cannot access the care available to them, and that the care they receive may not be adequate for survival. Mission trips provide temporary support with travelling surgeons, anaesthetists, and nursing staff. However, when such trips come to an end, the local surgeons are held responsible for less-than-optimal results.

In light of COVID-19, we know change is possible. With the new problems presented by climate change, the pandemic, and the globalisation of all aspects of society, it is important that we too adapt our practices to ensure no child is left helpless. Recent advancements by cardiac surgical organisations have identified the vast surgical inequalities that exist between our borders. The way forward is more enhanced data collection and data sharing, the utilisation of which will allow for workforces to identify limitations at a local level and provide solutions to yield sustainable contributions to further bridge the gross inequalities our neighbours feel.

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Prevalence of Critical Congenital Heart Disease During Surgical Mission Trips to Low-Middle Income Countries. What to Expect

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Abstract

Background: The incidence of congenital heart disease (CHD) is nearly 8 per 1000 live births and about 20% of those patients diagnosed with CHD will present early after birth with signs of Critical Congenital Heart Disease (CCHD) requiring a catheter-based or surgical intervention during the neonatal period.
These numbers are based exclusively on Western literature and Western countries. Little is known about the actual prevalence of CCHD at the time of clinical assessment and treatment during surgical missions in low- and middle-income countries (LMICs).

Methods: This is a retrospective study comparing the prevalence of CCHD at the time of presentation for surgery during humanitarian missions in LMICs. We compared the results to published data for similar cohorts in the USA. Proportions were compared using OR and 95% CI and significance was set at $p<0.01$
We discuss potential causes for epidemiological discrepancies. Classification of CCHD was in 4 groups according to the number of functional ventricles (2 or 1) and the presence of Aortic Arch Hypoplasia (No and Yes)

Results: Between February 2008 and June 2019, our organization operated on 5767 patients in 27 countries. Of these, 243 Neonates were presented to our cardiologists with CCHD. After excluding simple PDA ligations in Preterm newborns, 239 neonates surgically treated for their CCHD, or 4% of the total. Most of our patients were in Group I (2 ventricles and normal aortic arch), while the USA predominant group was IV (1 ventricle and arch hypoplasia)

Conclusions: The prevalence of Critical CHD is significantly lower during humanitarian missions to LMICs than the one observed in Western Countries (4% vs. 20%).
Conditions on the ground such as pregnancy termination laws, gender bias, geographic bias, and length of short-term missions play a strong influence on types of CHD diagnosis seen during humanitarian surgical missions.

Introduction

Congenital heart disease (CHD) accounts for at least 50% of congenital malformations.[1] About 20% of those children born with CHD will present early after birth with what is known as Critical Congenital Heart Disease (CCHD).[2] This severe form of CHD presentation has been described as the specific group of cardiovascular malformations that will likely result in the death of a child in the first year of life unless some type of invasive intervention (catheter or surgery based) takes place.[3]

The expected prevalence of diagnoses among patients presenting with CCHD in the newborn period has been thoroughly described in the Western literature, but it is solely based on the statistics of Western countries. Very little is known about the actual prevalence of CCHD and its variants at the time of clinical assessment and surgical treatment during humanitarian missions to low- and middle-income countries (LMICs).

Objectives

This observational study attempts to assess the prevalence of different diagnoses in newborns with CCHD presenting to surgery during surgical mission trips to LMICs with limited cardiology/cardiac surgery services. We also compare CCHD prevalence during surgical humanitarian missions to the published data for similar cohorts in the USA and discuss potential causes for epidemiological discrepancies.

Methods

All newborns screened, diagnosed, and treated for CCHD during surgical missions to low-and middle-income countries by a single specialized NGO were included in this retrospective analysis.

The proportion of patients diagnosed with specific CCHD diagnosis at the time of assessment for treatment are compared to Western published data. We used Odds Ratio calculations with 95% confidence intervals to assess any differences between patients. Significance was set at $p<0.01$

Classification of Critical Congenital Heart Disease

Critical congenital heart disease encompasses several cardiac defects: Hypoplastic left heart syndrome, pulmonary atresia, transposition of the great arteries, tricuspid atresia, truncus arteriosus, total anomalous pulmonary venous return, coarctation of the aorta, double outlet right ventricle, Ebstein's anomaly, interrupted arch, single ventricle, aortic stenosis and some critical presentations of Tetralogy of Fallot and pulmonary stenosis.

While a clear diagnosis is the basis for an accurate estimation of the true incidence of CCHD, when confronted with over a dozen different entities, a way to cluster them by similarities becomes necessary to facilitate the comparative effort.

We elected to group our patients utilizing the CCHD classification published by Schultz[3] and Clancy[4]. This simple form of classification considers the number of ventricles (1or 2) combined with Aortic Arch obstruction (Yes/No) resulting in a CCHD classification consisting of 4 categories. Class I (Biventricular, no arch obstruction); Class II (Biventricular with arch obstruction); Class III (Single ventricle, no arch obstruction) and Class IV (Single ventricle with arch obstruction).

Results

Between Feb 2008 and June 2019 our organization, in collaboration with our local colleagues, diagnosed and surgically treated 5767 pediatric patients born with CHD at 27 pediatric heart centers distributed among 17 LMICs (Ukraine, North Macedonia, Belarus, Honduras, Iraq, Russia, Libya, Iran, Ecuador, Pakistan, Egypt, Paraguay, China, India, Dominican Republic, Kuwait, Morocco).

Among all the patients operated on, there were only 256 neonates (4.2% of the total) presenting with critical congenital heart disease. After excluding all pre-term newborns diagnosed with hemodynamically significant isolated patent ductus arteriosus, data on the remaining 243 neonates (M/F: 151/92) were collected for this epidemiological review, with 238 of them matching within the four categories of CCHD used for comparison. The overall surgical mortality among the 243 neonates operated in LMIC for their CCHD was 19.7% (n=48).

The first significant finding was in the proportion of neonates diagnosed with CCHD in our cohort when compared to published data (4.2% vs. 20% respectively). There were also discrepancies in the proportion of cases in each sub-group, particularly in Classes 1 and 4. For instance, Class 1 patients in our cohort represented 63% of all CCHD treated, while Class 4 neonates represented only 4.2% of our total.

Several cyanotic (e.g., Tetralogy of Fallot and Hypoplastic Right Ventricle in all its variants) as well as non-cyanotic diagnoses (e.g., Critical Aortic Stenosis) were less common among our patients than usually described. (**Tables 1** and **2)**. There was an over-representation of transposition of the great arteries (TGA) (n=106/243 cases) in our cohort of patients with CCHD. Furthermore, 32.7 % of all our transposition diagnoses were from a single center (Nasiriyah, Iraq). **Table 3**.

Table 1. Comparison between our data (NCA) and Schultz published data[3]

CHD Class	Schultz et al. (n)	%	NCA (n)	%	OR (95% CI)	P-Value
I	159	32.5	150	63	**3.55** (2.57-4.91)	**<0.0001**
II	90	18.4	38	15.8	**0.84** (0.56-1.28)	0.42
III	73	14.9	40	16.8	**1.15** (0.76-1.76)	0.51
IV	168	34.3	10	4.1	**0.084** (0.043-0.16)	**<0.0001**
	490		239			

Table 2. Comparison between our data (NCA) and Clancy published data[4]

CHD Class	Clancy et al. (n)	%	NCA (n)	%	OR (95% CI)	P-Value
I	102	32.1	150	63	**3.61** (2.53-5.14)	**<0.0001**
II	28	8.8	38	15.8	**1.97** (1.17-3.31)	0.01
III	8	2.5	40	16.8	**7.83** (3.59-17.1)	**<0.0001**
IV	180	56.6	10	4.1	**0.034** (0.017-0.066)	**<0.0001**
	318		239			

Table 3. Our cohort by country and CCHD Class prevalence. The last column shows the prevalence of Transposition of the Great Arteries in each country and overall.
CCHD= Critical Congenital Heart Disease
TGA= Transposition of the Great Arteries

Country	Total Patients Operated	CCHD	CCHD as % of Total	Class 1	Class 2	Class 3	Class 4	TGA (as % of all CCHD operated)
Ukraine	765	57	7.4	31	16	6	4	14
Russia	354	31	8.7	18	6	6	1	12
Libya	856	20	2.3	10	5	5		8
Iraq	1151	47	4	45	1	1		44
Macedonia	209	15	7.1	6	2	6	1	3
Pakistan	164	7	4.2	6		1		6
India	228	7	3	5	1	1		2
Honduras	606	12	2	8	4			3
Ecuador	431	7	1.6	7				3
Dominican Republic	454	7	1.5	5		2		3
Belarus	89	11	12.3	8	1	2		2
China	222	2	0.9	1		1		1
Morocco	46	3	6.5	1		1	1	0
Egypt	56	3	5.3	2		1		2
Kuwait	11	2	18	2				0
Paraguay	7	1	14.2	1				1
Iran	118	10	8.4	8	1		1	5
Total	**5767**	**242**	**4.1**	**164**	**37**	**33**	**8**	**109 (45%)**

Discussion

According to an ongoing series of peer-reviewed publications by Hoffman et al. [5,6,7] focusing exclusively on the incidence of congenital heart disease in the previous decades, there has been a steady upward trend in the diagnosis of CHD and CCHD worldwide. Going from as low as 4 or 5 per 1000 live births in the 1960's up to 12 to 14 per 1000 live births in 2002.

The reasons for this upward trend seem to be multifactorial, with the most significant influence arising from improved diagnostic methods and the growing availability of specialists worldwide. The same authors conclude "there is no evidence for significant differences in the incidence of CCHD in different countries or times."[6] This concept seems to be somewhat in conflict with published data showing that the prevalence of CHD varies around the world, but what remains constant is the proportion of the different types of diagnoses within a given region.[2] Along those lines, a systematic meta-analysis on the prevalence of CHD at birth worldwide seems to be in agreement with the constant increment of CHD prevalence over time.[8] Bringing into question the concept of geographic uniformity, by showing a significantly higher prevalence of CCHD at birth in Asia, followed by Europe, North America, South America, Oceania and Africa. Whether these differences are due to the lack of diagnostic technology and specialists, particularly in Africa, it remains to be proven.

Critical congenital heart disease has a widespread occurrence with an estimated prevalence of 19 per 10,000 births [2] with geographic variations in prevalence but not in proportions of diagnoses. While variations do happen, they are likely related to local diagnostic capabilities and expertise, the methodology used to assess the diagnoses and factors foreign to the incidence of CHD per se, such as the ability to early terminate pregnancies in the country in question.[2] Further variations in incidence may be due to regional genetic predisposition, maternal diabetes or malnutrition and the use of alcohol and teratogenic drugs.[9]

The setting in which CHD is first recognized (diagnosed prenatally, after birth but before discharge from the hospital, or diagnosed after discharge home) does seem to exert an influence on preoperative condition.[10] Paradoxically, patients diagnosed with CCHD later in life (beyond day one of life or after discharge) seem to fare better[11] likely because more serious conditions tend to either be recognized immediately after birth and either be rapidly treated or die, depending on resources available.

There are several ways to cluster the universe of CCHD into comparable sets of lesions.

A commonly used classification system, different from the one we used in this study, is based on a combination of 3 major sub-group types (LVOT obstruction, RVOT Obstruction and Cono-truncal anomalies) and two isolated diagnoses (Single ventricle and Total anomalous pulmonary venous return) encompassing a total of five categories of CCHD.[10, 12] We chose the classification based on number of ventricles and the anatomy of the aortic arch purely based on the ease of comparison with previously published sets of data.

Potential causes for the prevalence of discordance

Neonatal cardiac surgery is an uncommon occurrence during humanitarian surgical trips, at least in our experience, and when it happens is ~~likely~~ due to chance rather than planning. Survivability beyond the first month of life while waiting for treatment constitutes a severily limiting factor regarding the chances of surgical treatment for most children born with CCHD in LMICs without fully functioning cardiology/cardiac surgery programs. This is particularly patent when even prolonged palliation with Prostaglandin cannot be secured in many centers.

When confronted with significant discordance between published data on CCHD among newborns in Western countries and those found in LMICs, we must first recognize that clinical prevalence of CCHD in Western countries closely follows prevalence at birth. Many, if not most, are antenatal or early after birth diagnosis. The continuum of cardiac care in those countries is well established and few patients, ~~if any,~~ are lost to the healthcare system. It would be difficult to know the true prevalence of CHD diagnoses at birth in most LMICs due to the unreliability of their public health statistical system, the unavailability of antenatal diagnosis, the frequency of deliveries at home and the geographic barriers presented to families that live far from a major specialty hospital when available, all conditions conductive to an early demise of the patient.

We believe variations in prevalence among different centers in low- and middle-income countries to be multifactorial. In some cases~~, just~~ the length of our team's presence in the country or the frequency of the surgical mission trips completely changed our ability to deal with newborns diagnosed with CCHD. Another decisive factor that seems to play a role is whether there was an established functioning program in place before our arrival. Undoubtedly many circumstantial reasons beyond the scope of this study also contribute to the differences. While neonatal cases are an uncommon occurrence during surgical trips lasting one or two weeks, a quite different picture arises when the assistance is provided on a more regular basis, such ~~it~~ was the case of our annual programs. For instance, nearly 20% of all our neonatal patients were diagnosed and treated at a single center (Nasiriyah, Iraq) where we were providing almost uninterrupted surgical and educational support to the local staff for 42 weeks a year.

Gender Bias

In contradiction to the accepted fact regarding stating that CHD prevalence among newborns is gender-neutral, only 37.8 % of our patients diagnosed with CCHD were female. While lacking a verifiable explanation, we can only speculate that there were strong gender biases at work, perhaps due to cultural beliefs. Selective abortion of otherwise normal female fetuses is a well-documented occurrence in a few low-income countries.[13] Another plausible explanation could be a somewhat lesser effort on the part of families to search for a center and travel great distances to treat the heart-compromised female newborn.

Prenatal Diagnosis and Pregnancy termination

As prenatal ultrasound screening has increased globally, there has been a documented increase in early terminations of fetuses diagnosed with CHD.[14] In many ~~of the~~ countries where we work, we also confront the indiscriminate early termination of pregnancy in cases of inaccurate prenatal prognosis for some types of CHD. While accurate prenatal echocardiographic diagnosis is not widely disseminated in LMICs, in many instances routine pregnancy follow-up ultrasounds revealing a heart other than normal will trigger a reaction leading to early termination. In many cases, the specialist making the diagnostic is not clinically qualified to discriminate very simple forms of CHD with the result of fetuses that could have had a normal delivery and a normal life after surgical repair are being terminated. Pregnancy termination laws, Gross Domestic Product per Capita and Human Development Index for each country included in the study have been included as an **Appendix** to provide a better perspective.

Appendix

Country	GDP PER CAPITA (Median 2008-2019) ¶	Human Development Index Ø	Pregnancy Termination Law
Russian Federation	USD* $11 392	0.824	On-Demand
Libya	USD* $7 781	0.724	Allowed with Exceptions 1
Iraq	USD* $5 450	0.674	Allowed with Exceptions 1
North Macedonia	USD* $5 195	0.774	On-Demand
Pakistan	USD* $1 229	0.557	Allowed with Exceptions 2
India	USD* $1 515	0.645	Allowed with Exceptions 4
Honduras	USD* $2 159	0.634	Unlawful
Ecuador	USD* $6 058	0.759	Allowed with Exceptions 2
Dominican Republic	USD* $6 423	0.756	Unlawful
Belarus	USD* $6 368	0.823	On-Demand
China	USD* $7 020	0.761	On-Demand
Morocco	USD* $ 2 973	0.686	Allowed with Exceptions 2
Egypt	USD* $2 905	0.707	Allowed with Exceptions 2
Kuwait	USD* $38 074	0.806	Allowed with Exceptions 3
Paraguay	USD* $5 354	0.728	Allowed with Exceptions 1
I.R. Iran	USD* $5 647	0.783	Allowed with Exceptions 3
Ukraine	USD* $3 100	0.779	On-Demand 5

¶ World Bank Data: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD
Ø Human Development Index: https://hdr.undp.org/en/countries
* USD = United States Dollars
1 Allowed when risk to mother's life
2 Allowed when risk to mother's life or health
3 Allowed when risk to mother's life, health, or fetal defect
4 Allowed when risk to mother's life, health, fetal defect, or poverty
5 With restrictions after the 20th week

We have made the organization wide decision not to treat patients diagnosed with hypoplastic left heart syndrome (HLHS) except where the programs we are assisting fulfill the following criteria; 1- Serves as the sole source of pediatric cardiac surgery for the country, 2- Has a robust neonatal program with a survival for the arterial switch operation of 90% or more, 3- Has a critical care transport system capable of hospital to hospital transport of less than 6 hours, 4- Has historical birth records of at least 12 HLHS annually, and 5- There is country-wide availability of prostaglandins . The reasons behind this decision are multiple. Surgery for HLHS and ~~the~~ subsequent care is considered among the most demanding in neonatal cardiac surgery. Nowhere is the concept of total team excellence more apparent in our field. A major issue regarding treating children born with HLHS during a humanitarian mission is the limited assistance provided by the visiting team (one or two weeks), leaving a significant portion of the postoperative care to the local, unexperienced team. Another ethical consideration is the diversion of resources (material and human) taken away from children with other defects with relatively low operative mortality. To date, we have helped four heart centers with their HLHS management program, but only two continue to provide this surgery.

Transposition of the Great Arteries bias in our cohort

Several factors are likely contributing to this unbalance. Environmental issues such as oil and uranium contamination (see below) of soil and water, as well as public health issues~~,~~ (Nasiriyah Heart Center being the only fully functioning pediatric cardiac unit between Baghdad and Basra)~~,~~ are likely contributors to our biased experience in this center.

Use of Depleted Uranium ammunition in conflict zones and CCHD

This is an area of the world that has suffered prolonged and intense armed conflicts. Due to the type of ammunitions used, particularly during the second invasion of Iraq, the concentration of uranium in the soil is excessively high, particularly in areas of the country where the fight was the heaviest. This is the case in Fallujah, a town located west of Baghdad and about 400km north of Nasiriyah, where uranium contamination has been well documented.

The uranium concentration in the area surrounding Fallujah is around 1000 times the international allowed maximum uranium concentration in soil and 27 times higher than the international allowed uranium concentration in water.[15] The concentration of Uranium, among other heavy elements, in the hair of parents of children born with congenital defects in that area are several folds above the levels found in individuals of similar age in other countries.[16]

The number of congenital birth defects in general and congenital heart disease around Fallujah is much higher than international values. For instance, out of 6049 children born during an 11-month period at Fallujah General Hospital, 113 were diagnosed with congenital heart disease, which represents an incidence of 1.86%.[17] This could ~~well~~ be a strong contributing factor to the high numbers of neonates requiring surgical services for CCHD in the Iraq central area. It is not clear whether the specific incidence of transposition of the great arteries as a prevalent diagnosis is also directly related to this local phenomenon. However, it is certainly deserving of further investigation.

Conclusion

Our cohort of patients diagnosed and treated for critical congenital heart disease in low- and middle-income countries represent a small fraction of the total number of patients born with CCHD in these countries, yet some lessons can be drawn.

The prevalence of CCHD during humanitarian missions is always low since most patients are lost within weeks of birth. Consequently, while surgical missions may contribute in many ways to alleviate in part the heavy toll CHD places on society, they are unlikely to prevent significant losses from its most critical forms. Sustainable programs, with long-term assistance by international NGOs at least until fully established local services are a reality, are the only way to decrease the neonatal mortality related to CCHD in LMIC.

Discrepancies in specific diagnoses and prevalence between LMIC and their high-income counterparts are likely multifactorial, and management should be adapted to the conditions of each country and health system.

Proper prenatal diagnosis, specialized critical neonatal transportation systems, countrywide availability of Prostaglandins, and at least one highly functioning heart center are some of the most basic needs required to revert the current natural history of CCHD in countries with limited resources settings.

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Cost-Effectiveness Analysis: Small Country Pediatric Cardiac Surgery Program Development

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Pediatric Cardiac surgery, Cost-Effectiveness analysis, Outsourcing Healthcare

Abstract

Objectives: The cost-effectiveness of sending children abroad for treatment of their congenital heart disease (CHD) in small population countries versus developing a local program should be carefully considered. From the purely economic viewpoint, we investigated, the cost-effectiveness of developing such program in a small Eastern-European country.

Methods: Calculated costs during different stages in developing a program in North Macedonia were obtained from the Ministry of Health. All patients diagnosed and surgically treated between 2010 and 2017 were included in three distinctive periods.
2010-2012 - *Outsourcing* (All patients sent abroad for surgical treatment)
2013-2016 - *Foundational* (Program development with assistance from a global charity organization)
2017 - *Tutelage Period* (Semi-Independent program)
Cost-Effectiveness is provided in US$ per Disability Adjusted Life Years (DALY) a unit of health value.

Results: Between January 2010 and December 2017, 384 patients diagnosed with CHD underwent surgical treatment at government expense. The breakdown was: 125, 204, and 55 patients in each period.
The cost-effectiveness of the intervention was $315, $297, and $251 per DALY averted, respectively.

Conclusions: Surgical treatment of patients born with CHD is a highly cost-effective intervention, irrespective of the approach taken. Even after accounting for the initial capital investment costs, developing a local pediatric cardiac surgery program seems to be slightly more cost-effective than outsourcing.

Introduction

With a documented rate for CHD of 7,669 new cases per million live births[1] and a daily global birth rate of 353,000 live births[2], we could estimate a global incidence of nearly 980,000 new CHD patients born every year. Most of these patients are born in low- and middle-income countries (LMIC), lacking the most basic infrastructure to deal with the diagnosis of CHD, let alone its surgical treatment[3,4,5].

Some LMIC, with sufficient funding for a public health system capable of providing primary and secondary healthcare, may lack the systematic approach, equipment, or the knowledge to deal with the complexities of CHD diagnosis and treatment safely. Instead, they may resort to some form of outsourcing of cardiac services to reduce their infant mortality rate.

When resources are lacking, the cost-effectiveness of alternative management strategies should be carefully considered to secure an equitable allocation of the limited public health system resources. We investigated the cost-effectiveness comparison between different CHD management strategies implemented by the public health system of North Macedonia.

Methods

An Institutional Review Board waiver was granted for this study by the IRB Committee of the University of Tennessee.

Every patient diagnosed with CHD and surgically treated with funding provided by the Republic of North Macedonia Ministry of Public Health between January 2010 and December 2017 was included in the study.

Data obtained from the Ministry of Health of North Macedonia database was used to account for the patients diagnosed and treated and to calculate total expenditures during the period. Patients were divided into three groups, according to the strategy used.

2010-2012 - *Outsourcing period*

All patients were sent abroad (Sofia, Bulgaria) for surgical treatment

2013-2016 - *Foundational period*

In-country program development with help from a specialized global charity organization utilizing existing University hospital facilities and reassigned local personal

2017 - *The Tutelage Period*

A semi-independent program with its own local human resources and the monthly assistance from a small group of specialized professionals from Belgrade, Serbia.

Costs

During the *Outsourcing Period,* the referral of patients abroad was based on a capitation system (fixed payment per patient treated independently of diagnostic complexity and including up to 20-day hospital admission). The treating hospital billed extra charges incurred beyond the 20-days capitation period on a case-by-case basis. Neither the costs beyond the 20-day capitation for the handful of complex cases that required it nor the transportation and lodging costs for the patient and companion family member were available, therefore are not included in our calculations.

The *Foundational Period* costs included: Capital equipment, disposable materials, selected medications, administrative service fees, and travel and lodging expenses for a large team of foreign specialists sent by an established foundation (The William Novick Global Cardiac Alliance) specialized in this type of program support and development.

During the *Tutelage Period,* the costs included limited capital equipment, disposables, medications, service fees, and lodging expenses for a smaller team of specialized professionals from Belgrade, Serbia.

All costs are presented in 2018 US Dollars and with a 3% discounting

Cost-Effectiveness Calculations

Cost-Effectiveness of the interventions was expressed in 2018 US Dollars per DALY averted and it was calculated on a patient-by-patient case by applying a formula used for different congenital heart defects in a previous publication by the authors.[6] Once the individual cost-effectiveness of surgical treatment for each patient in each period was calculated, it was then averaged among all patients treated within a period. Mortalities during each period, with their negative effect on the DALYs averted, were properly discounted.

Results

Between January 2010 and December 2017, 384 patients diagnosed with CHD underwent surgical treatment for their congenital heart disease at the expense of the North Macedonia Ministry of Health. The breakdown was: 125 patients treated during *Outsourcing* (2010-2012), 204 during *Foundational (2013-2016),* and 55 patients during the first year of the *Tutelage period* (2017). Mortality between 2013-2017 was 8%. Mortality during the *Outsourcing* period was never reported back to the Ministry of Health therefore a standard mortality of 5% was used in the calculations for that period.

Total global costs were: $1,826,791; $2,813,112 and $639,812 for each period, while costs per patient operated were $14,614, $13,789 and $11,632 respectively.

Using our previously published average of 46.3 DALYs averted per patient operated[6], the cost-effectiveness for the different management strategies was estimated to be $315, $297, and $251 per DALY averted during each corresponding period. Itemized costs for each period can be found in **Table 1,** and the surgical case mix by risk category is presented in **Table 2**.

During the Foundational period, the charity in charge of program development realized nineteen trips a 2-week duration each, adding up to 38 weeks of in-country presence. The median size of the international team of specialists participating on each trip was 15 members (range 12-19) and included surgeon, perfusionist, scrub nurse, intensive care specialists, nurses, anesthesiologist, respiratory technician, cardiologist and nurse practitioner or nurse educator. The costs of airfare and lodging for each team member, as well as the charity administrative fee charges, were included in the estimates.

During the *Tutelage Period*, the surgical visiting team (one week per month) was significantly smaller (7-8 members) consisting of a senior surgeon, cardiologist, anesthesiologist, perfusionist, an intensive care specialist and two critical care nurses. All team members were from Tirshova Hospital with a 30-year-old program and experienced in all aspects of congenital heart disease management. The visiting team during this period traveled only 400 kilometers, allowing for minimal travel expenses while providing close collaboration, consistency, and continuity of care.

Table 1. Costs per period, costs per patient, and costs per DALY Averted

Period	Capitation	Capital Equipment	Disposable Materials /Meds	Service Fees	Travel /Lodge	Total	Patients operated	Cost per patient treated	Cost per DALY Averted (Averaged 46.3 DALY/patient)
Outsourcing (2010-12)	$1,826,791					$1,826,791	125	$14,614	$315/per DALY Averted
Foundational (2013-16)		$664,874∆	$938,832	$680,000	$610,406	$2,813,112	204	$13,789	$297/per DALY Averted
Tutelage (2017)		$126,101•	$311,000	$178,000	$24,711	$639,812	55	$11,632	$251/per DALY Averted

All costs in 2018 dollars and at 3% discounting

∆ Includes: Bedside Monitors; Cardiopulmonary Bypass Machine; New X-Ray System; ACT Machine; Temporary Pacemakers; Surgical Instruments (2 sets); Pediatric Cardio-probe for ultrasound machine.

• Includes: Syringe pumps; Ultrasound equipment.

Table 2. Number of patients in each risk adjusted categories between January 2010 and December 2017 RACHS-1 (Risk Adjusted Congenital Heart Surgery)[7]

RACHS-1	Outsourcing	Foundational	Tutelage
Risk 1	23	37	10
Risk 2	59	96	26
Risk 3	34	55	15
Risk 4	9	14	4
Not RACHS case	0	1	0
Adult Congenital	0	1	0
	125	204	55

Not RACHS-1 classifiable patients and adult congenital patients were included in order to accurately calculate the costs-per-surgery but excluded from the DALYs averted calculations

Discussion

Most published cost-effectiveness analyses related to cardiac surgery are circumscribed to answering very specific questions, such as the cost-effectiveness of using a particular device[7] or to compare alternative ways of performing a procedure[8].

We are unaware of a published study investigating the cost-effectiveness of opening a sustainable pediatric cardiac surgery program.

Outsourcing may take different formats.[7] Health authorities may choose to send complex patients for treatment to an outsourced public or private healthcare center abroad (contracting-out), or they may decide to redirect those patients towards a specialist provider in the private sector within country borders (contracting-in).

Outsourcing may be of a mixed format, by exploiting idle capacity in public health facilities while hiring the know-how abroad (NGO or specialized charity) for organizational, clinical and educational tasks. This alternative form of "in-country outsourcing" may be favored when local specialists are unavailable, but there is a strong interest in treating complex patients within the country, near their families and social support network.

Contracting-out is not a new concept, and its use is not limited to LMICs. Some of the earliest adopters of contracting-out were western health systems, and its implementation goes beyond clinical interventions (e.g., food services, materials management, pharmacy services, and others)[8]

Contracting-out healthcare services from government to non-state providers in LMIC may improve the delivery of a particular service,[9,10] and in some cases, it may represent the only available option for the delivery of primary care, as is the case in so-called "fragile states."[11]

Contracting-out of health services has been documented across several European Union countries (Ireland, UK, Norway, Netherlands, Germany, Denmark)[12], New Zealand[13] and more specifically regarding cardiac surgical services at the Canada - USA border. [14,15]

The contracting-out of primary care services to foreign charities is a simple alternative solution with good results in many LMIC. [16,17]

In this case, the development of a de novo service for pediatric cardiac surgery at a state-owned hospital was driven by local stakeholders interested in providing higher complexity services within the capital, with the hope of a lesser emotional toll on the families of the patients and the goal of reducing healthcare expenses in some critical areas. An element not found in the literature, and certainly not a factor during the decision-making process, at least in this case, is the unexpected benefit associated with the "spill-over" effect of the development of pediatric cardiac surgery program over other areas of the hospital. Several clinical and support services are likely to be positively influenced in their care delivery from working in proximity to a new tertiary specialty. Not much has been published in this respect, and an accurate quantification of hospital wide benefits of developing a pediatric cardiac surgery program is long overdue.

Current status

Nine years after the inaugural development trip, program's status is as follows. While the program has been moved from the public University hospital into a private hospital, it continues to provide free cardiac surgery care for all children born in North Macedonia and their families. The capitation payment continues as it was, adjusted for the cost of living. Most patients diagnosed with congenital heart disease at birth are managed by this program, with a total volume of between 100-120 cases a year, including hybrid management of hypoplastic left heart syndrome with mortality similar to that of other Eastern European countries. The program does not treat patients in need of a heart transplant yet.

Conclusions

The decision between outsourcing and developing expensive health services in a small country is always difficult and subjected to the willingness to pay by the public health authorities. We attempted in this study to present a clear view of the costs-effectiveness options to facilitate an informed decision by other countries in a similar situation.

All three management strategies proved to be highly cost-effective. Despite the significant initial capital costs, the development of a pediatric cardiac surgery program seems to become a more cost-effective intervention by the fourth year.

Potential Shortcomings of this Study

Arguably, a potential critique of our study would be the absence of patient's clinical data (diagnosis, age, weight, etc.) following the argument that by not knowing such critical information, no equivalent comparison between the cost for each period could be drawn.

The logic behind such reasoning would be correct in a Fee-for-Service type of healthcare system, but under a Capitation system such as the one described here, where every surgery is paid a global fee regardless of the diagnosis, risk stratification, age and outcome, we believe the absence of specific clinical data, becomes practically irrelevant.

The intention of this manuscript was to study the political decision process and the economic analysis behind the decision as to whether developing a pediatric cardiac surgery program from scratch in this small country would be beneficial. There are no clinical implications meant to be drawn from our study.

As with most cost-effectiveness analysis, several assumptions were made. For instance, the calculated averted DALYs for the cohort of patients in each period were averaged among all the patients regardless of diagnosis or operation. Otherwise, the DALYs averted per patient would vary significantly between simple and highly complex diagnoses. The purpose of this paper was not to speculate whether some surgeries are more cost-effective than others but whether having a program is more cost-effective than not having one.

During our calculations of the DALYs averted, we decided to avoid using age-weighting and health discounting, understanding that if applied, both principles would lessen our cost-effectiveness results. We based our decision on published opinions underscoring the highly controversial nature of these adjustment tools in calculating DALYs.[18,19] The concept of age-weighting seems, from a purely ethical position, debatable given the fact our interventions were specifically targeted towards the least "productive" members of society, neonates, and children.

While we used discounting at 3% per year on the costs of the intervention, we refrained from using discounting in DALYs calculation since we believe "unlike money, health cannot be invested to produce future gains".[20]

The exclusive use of Cost-Effectiveness thresholds to decide allocations of public health resources can be contentious and may induce public debate.[21] The mere definition of what constitutes cost-effectiveness in LMIC[22] is not enough to guide public health policy and, a few non-economic factors may have to be taken into consideration. For instance, the unmeasurable benefits of family closeness and know-how transfer should also play a meaningful role in these decisions.

Our situation in North Macedonia was unique. During the Foundational and Tutelage periods, all needed vacant positions to eventually provide the services autonomously were pulled from existing hospital staff and re-trained, consequently lowering costs. We do realize that to create an entirely independently functioning pediatric cardiac surgical unit, all of these positions would need to be filled permanently, thereby affecting the final financial cost. However, given the actual salary costs in North Macedonia at the time of the intervention, the high cost-effectiveness of the intervention would not have been greatly affected by including new personal costs.

Finally, a case could be constructed favoring outsourcing services to a foreign regional program, increasing its volume while maintaining or even improving their morbidity and mortality. While the idea of regionalization of pediatric cardiac surgery programs argues in favor of reaching a minimum volume of cases per hospital and per surgeon at which mortality would be theoretically lower, [23] the many positive effects of developing an in-country solution, including but not limited to the family-social ones should not be overlooked.

An understandable concern about the decision-making process is, why not use a team like the one used during the Tutelage period throughout the entire development, hence augmenting savings.

Starting the first pediatric cardiac surgery program in a country with no history of pediatric cardiac surgery in the public sector and no history of neonatal cardiac surgery at all (and no public adult cardiac surgery program for that matter either) is a complex process. From training the human resources in every aspect of the specialty to the decisions on equipment purchasing or clinical space modifications and functionality, everything had to be planned de novo. While one-time teams coming into a country to do cardiac surgery are easily found, few alternatives exist to develop a de novo program. Our organization specializes in such endeavors. Once the program, the equipment, and the human resources were in place, the clinical spaces were functioning, and most importantly, the know-how became routine, it was much easier for the political decision makers to find a less expensive alternative. Lastly, there is the question of *Service Fees*. When developing a program at a location where no human resources are available and training of these resources is paramount, we normally resort to bringing a full line of specialists on every trip (surgeon, anesthesiologist, intensive care specialist, perfusionist, respiratory technician, critical care nurse practitioner and several nurses).

With that in mind, and while we welcome volunteers to participate in our program development trips, our organization counts on several staff members who are salaried and work full time traveling and participating in the care of our patients and the systematic training of the local specialists. As an organization dedicated to developing sustainable pediatric cardiac surgery programs, we cannot afford to have vacant positions when arriving at a site. Our ongoing commitments and frequent concomitant trips make relying exclusively on volunteers unreliable.

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Key Points

- The treatment of children born with CHD in small countries lacking cardiac surgery services presents a social, economic, and health policy challenge.
- Surgical treatment of these patients is highly cost-effective, regardless of the approach.
- The decision to develop a sustainable in-country program seems to be slightly more cost-effective than outsourcing health services.

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Ten years follow-up under atorvastatin therapy of patients with carotid artery stenosis: the prognostic impact of oxidised low-density lipoprotein on carotid plaque progression and restenosis

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Abstract

Background: Atorvastatin reduces oxidized low-density lipoprotein (oxLDL) levels and reduces the rate of plaque progression in patients with and without prior carotid angioplasty. The aim of our study was to investigate the durability of this effect and to explore the possible prognostic impact of oxLDL levels on carotid stenosis and plaque stability.

Methods: 106 patients (71 males, mean age 64.82±7.26 years) were studied. They were divided into two groups. Group 1 included patients with carotid stenosis >70% (n=50) who underwent carotid angioplasty prior to enrolment. Group 2 included those with <70% stenosis who were treated medically and were given atorvastatin with a dose adjusted to maintain LDL cholesterol <100mg/dl. Anthropometrics, complete lipid profile, oxLDL, and ultrasonography were performed at baseline, 1, 3, 6, 12 months, and yearly thereafter for 10 years.

Results: oxLDL levels significantly decreased from 53.3±10.91 mg/dl at baseline to 8.31±2.08 mg/dl at 12 months (p<0.001) and remained stable until the 10th year. In group 1, restenosis (>70%) was noticed in four patients, yet no further intervention was needed due to plaque morphology (echo-grade IV). In group 2, carotid stenosis was initially reduced (6th month - 4th year) and later relapsed (5th - 10th year), yet plaque morphology was recorded as type III or IV in almost all patients of group 2 (53=95%), indicating a significantly lower risk for stroke.

Conclusion: Atorvastatin treatment to a target of LDL <100 mg/dl in patients with carotid stenosis is associated with marked, and durable reduction of lipid levels, especially oxLDL and LDL and reduction in the rate of stenosis progression, improved plaque stability, and decreased stroke risk.

Introduction

Oxidized low-density lipoprotein (oxLDL) has a central role in the pathogenesis of atherosclerotic plaques. Circulating oxLDL is considered an indicator of atherosclerosis[1], coronary heart disease (CHD), and cardiovascular disease (CVD)[1-3]. Increased circulating oxLDL levels lead to the accumulation of lipids in the vessel wall, thus causing endothelial dysfunction[4] and contributing to atheromatous plaque instability[2,5,6]. LDL remains in the intima for a prolonged period of time, thus giving the opportunity to be oxidized by free radicals derived from the endothelial cells, the smooth muscle cells and the macrophages.[7]. Oxidized LDL then acts as a chemotactic agent for monocytes and smooth muscle cells through binding to scavenger receptors[8], leading to the formation of foam cells. Oxidized LDL also modifies the secretory activity of endothelial cells[8], inhibits the nitric oxide-mediated vasodilatation, induces adhesion of monocytes to intima through the expression of adhesion molecules on the endothelium[8], and enhaces the expression of inflammatory cytokines[9], a chronic inflammatory process which promotes atherosclerosis[10].

The statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce mostly total cholesterol (TC), LDL cholesterol, and apolipoprotein B (apoB); they also have a minor effect on triglycerides (TG) and lipoprotein a (Lp-a) levels. Unquestionably, statins reduce the incidence of coronary events and are used for primary and secondary prevention of CHD[11]) Statins also have pleiotropic effects[12], among which remarkable is the modification of cell-mediated LDL oxidation[13,14]. These mechanisms contribute to the reversion of atherosclerosis. In a previous study we have shown that statin therapy reduces the oxLDL levels and reverses carotid artery stenosis independently from their lipid lowering effect during a follow-up period of one year.

The present study aimed to investigate the long-term efficacy of atorvastatin to slow down the progression of carotid stenosis and to provoke such plaque characteristics changes leading to stability of plaques. Also, to investigate the long-term effect of atorvastatin on oxLDL levels in such patients. We hypothesized that atorvastatin therapy would confer reduction of oxLDL levels in vivo, resulting in a significant change in the type of atherosclerotic plaque, delayed atherosclerotic plaque growth or even durable stenosis regression and therefore long-term prophylaxis against stroke.

Patients & Methods

This was a prospective open-label cohort study with a 10-year follow-up period. A total of 725 patients with hyperlipidemia and symptomatic and asymptomatic carotid atherosclerosis were screened, of which 127 fulfilled the inclusion criteria and were included in the study. The local and national ethics committee approved the study protocol.

Eligible were patients with hyperlipidemia, defined as total cholesterol levels ≥ 200 mg/dl, low-density lipoprotein (LDL) ≥ 150 mg/dl or 130 mg/dl in the presence of other cardiovascular risk factors and/or triglycerides ≥ 150 mg/dl up to 350 mg/dl as well as carotid artery stenosis defined as ≥ 50% restriction of the lumen diameter and/or ≥ 50% decrease of the vessel blood flow. Exclusion criteria included: acute coronary disease, unstable angina pectoris, clinically evident cardiac failure, severe arrhythmias, recent stroke, recent surgical procedures, inflammatory diseases, active liver disease or liver impairment, excessive alcohol consumption (>4 units/day), known allergic reaction to statins, poorly controlled diabetes mellitus as defined by a hemoglobin A1c (HbA1c) level of >7%, past history of thromboembolism, bleeding disorders, serum triglyceride levels above 350mg/dl, history of thyroid dysfunction, use of systemic corticosteroids, pernicious anemia, impaired vitamin B12 or folic acid levels, pregnancy or lactation, and end-stage renal disease.

Patients after signing informed consent were divided into two groups according to the degree of carotid artery stenosis: Patients with >70% stenosis (n=61) of common or internal carotid vessel (Group 1) underwent percutaneous carotid angioplasty and stenting with brain protection systems followed by statin administration. Those with stenosis <70% (n=62, Group 2) were treated conservatively with statins, without invasive procedures. In both groups, patients were encouraged to exercise and follow the American Heart Association step II diet. Clopidogrel or acetylsalicylic acid was additionally administered. Out of the 127 patients, four patients died soon after the initiation of the study due to reasons that did not relate to the study protocol, such as cancer, renal insufficiency, and accidental death. Of the remaining 123 patients, 17 (11 from group A and 6 from group 2) asked to be excluded or were lost to follow-up opting out of the study due to change of address or difficulty in commuting to the center. In total,106 patients completed the 10-year follow-up period and were included in the analysis.

Patients in both groups were placed on atorvastatin once daily at bedtime in individualized doses, with a goal to achieve and maintain serum LDL-cholesterol levels of <100mg/dl or <70mg/dl, if hypertension, renal impairment, smoking, symptomatic peripheral arterial obstructive disease, symptomatic coronary artery disease or diabetes mellitus were present. Usual doses were between 20 and 40 mg. Other medications that might cause elevation of CPK or frank rhabdomyolysis were discouraged during the time that patients were receiving statins. Possible adverse events were assessed during each visit along with evaluation by an expert in clinical biochemistry.

Past medical history, including smoking habits and anthropometrics were obtained during enrollment. Arterial blood pressure measurements, and laboratory investigations comprising of complete blood count, serum glucose and HbA1c levels, liver and kidney biochemistry, and detailed lipid profile including TC, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, serum TG, apoB, and apolipoprotein A, urate, B12 and folate, thyroid function, homocysteine, Lp-a, and oxLDL levels were obtaind at baseline and during follow-up visits at 1,3,6, 12 months and then yearly up to 10 years. Blood samples were collected after an at least a 12-hour fast; a light, low-fat meal was advised the night before sample collection. Standard biochemistry vacutainer tubes were used to collect blood samples, except for whole blood count, HbA1c and homocysteine, which were collected in ethylenediaminetetraacetic acid (EDTA) vacutainers. Serum for biochemistry analysis was centrifuged at 4000g at 4°C for 7 min and was immediately tested or stored in deep refrigeration.

Determination of TC, HDL, and TG was done by a Dade Behring analyser using commercially available enzymatic colourimetric methods (Dade Behring, Newark, USA). LDL was then calculated using Friedewald's equation[15]. Levels of circulating oxLDL were measured using a commercially available kit (Mercodia, Uppsala, Sweden). The method rely on a double antibody (4E6 and mouse monoclonal antiapoB)[16] capture ELISA, which primarily detects malondialdehyde LDL (MDA-LDL). The reference values range from 31 to 61mg/dl in our lab[17]. Apolipoprotein A, apoB, and Lp-a were measured using immunonephelometry with rabbit antisera (Dade Behring, Newark, USA) in a Dade Behring analyser.

Grading of stenosis was made by Duplex scanning according to the consensus statement of the society of radiologists in ultrasound[18] with the use of Apogee 800 plus scanner with a 7.5 MHz transducer (ATL Inc., Bothell WA, USA). Evaluation was carried out at baseline, at 12 months, and yearly thereafter. Internal (ICA) and common (CCA) carotid artery were evaluated on both sides for each patient by grayscale and color Doppler imaging. The vessels were imaged as completely as possible. Pulse wave Doppler spectral analysis and measurement of the bloodflow velocity of both vessels were additionally performed. Results were reported in a standardized format. Stenosis was defined as the presence of visible plaque in grayscale or color Doppler imaging. The degree of stenosis was calculated by the increase of peak systolic velocity. Other parameters such as the ICA/CCA peak systolic velocity ratio and the ICA end diastolic velocity were also calcutated in difficult cases. Stenosis >70% was characterized as severe and the patient was offered angioplasty. Stenosis 60-70% was characterized as substantial, 50-60% as moderate, and <50% as mild. The latter categories were managed conservatively. The value of the vessel with the greater degree of stenosis for each patient was used in the statistical analysis.

Table 1. Patients baseline characteristics and relevant comparisons between groups

Chacteristic	Total	Group 1	Group 2	P value
Males / females	71/35	34/16	37/19	0.833
Mean age in years ± SD	64.82 ± 7.26	65.66 ± 5.98	64.07 ± 8.22	0.263
Number of pts with DM (percentage)	32 (30,2%)	15 (30,0%)	17 (30,4%)	0.968
Number of pts with HTN (percentage)	91 (85,8%)	47 (94,0%)	44 (78,6%)	**0.023**
Number of smokers (percentage)	78 (73,6%)	42 (84,0%)	36 (64,3%)	**0.022**
Number of pts with CAD (percentage)	50 (47,2%)	26 (52,0%)	24 (42,9%)	0.347
Mean ± SD TC (mg/dl)	249.01 ± 24,7	254.8 ± 29.0	243.84 ± 18.94	**0.025**
Mean ± SD LDL cholesterol (mg/dl)	171.27 ± 21.92	174.76 ± 26.12	168.16 ± 16.98	0.132
Mean ± SD HDL cholesterol (mg/dl)	46.33 ± 9.24	46.08 ± 8.35	46.55 ± 10.04	0.794
Mean ± SD TG (mg/dl)	150.63 ± 29.22	154.78 ± 34.78	146.93 ± 22.87	0.179
Mean ± SD oxLDL (mU/l)	52.33 ± 10.91	62.06 ± 3.99	43.65 ± 7.09	**<0.001**
Mean ± SD homocysteine (mU/l)	15.06 ± 6.67	15.64 ± 5.55	14.55 ± 7.55	0.102*
*Mann Whitney test due to skewed data distribution				

SD=standard deviation, DM=diabetes mellitus, HTN=arterial hypertension, CAD=coronary artery disease, TC=total cholesterol, LDL=low-density lipoprotein, HDL=high-density lipoprotein, TG=triglycerides, oxLDL=oxidized low-density lipoprotein

Statistical analysis

Continuous variables were presented as mean values ± standard deviation, while qualitative variables were presented as absolute and relative frequencies. Normality tests were applied using the Shapiro-Wilk test and QQ plots were also considered. Univariate analysis was initially applied to test differences in baseline values in several patient characteristics between the two groups. Repeated measures analysis was applied to examine the changes in the patients' lipid profile during the follow up period. Correlations between skewed continuous or discrete variables were evaluated using Spearman's p-coefficient, whereas correlations of normally distributed variables were evaluated by calculating the Pearson's r-coefficient. Comparisons between normally distributed, continuous variables and categorical variables were made using the Student t-test. Analysis of categorical data was carried out with the chi square test or Fischer's exact test when appropriate. The effect of group and oxLDL on carotid stenosis was also tested through time dependent multiple Cox proportional hazard model. The results obtained were presented as Hazard Ratios (HR) and the 95% Confidence Intervals (CI). A backward elimination procedure was applied to all multivariate models (using P<5% as the threshold for removing a variable from the models). All models were adjusted for age, smoking, gender, HT, TC, BMI, homocysteine levels and DM diagnosis. Kaplan-Meier curves concerning stenosis over the study period were plotted. All reported P-values were based on two-sided tests and compared to a significance level of 5%. STATA 13.0 software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) was used for the analysis.

Results

Out of the 106 patients 71 were males and 35 females with a mean age of 64.82±7.26 years. Group 1 comprised of 50 patients and group 2 of 56. Diabetes mellitus was recorded in 32 patients (30%), 22 males (69%) and 10 females (31%). Hypertension had 91 patients (86%), 58 males (64%) and 33 females (36%). All patients had metabolic syndrome according to the national cholesterol education programme-adult treatment panel III (NCEP-ATP III) criteria[19]. Active smoking (defined as current or discontinued as far back as 5 years) was reported by 78 (74%) patients, 64 (82%) males and 14 females (18%). Of the 50 patients of group 1, 12 had transient ischemic attack, 8 had amaurosis fugax, and the remaining were asymptomatic. All patients of group 2 were asymptomatic.

The mean dose of atorvastatin at baseline was 20 mg in both groups. After 3 months the respective doses were 20 mg in 71 patients (67%) and 40 mg in 35 patients (33%). Within Group 1, 28 patients (56%) received 20 mg and 22 patients (44%) 40 mg. In Group 2, 43 patents (77%) received 20 mg and the remaining 13 patients (23%) 40 mg. This difference was not statistically significant (p=0.877). The baseline characteristics of the patients in the two groups and their differences are depicted in **Table 1**. Group 1 had significantly more proportion of smokers and patients with hypertension, as well as significantly greater values of TC and oxLDL at baseline.

Lipid profile

TC, HDL, LDL, oxLDL, TG and apoB significantly improved soon after statin initiation in comparison to baseline in both groups (**Table 2**). Specifically, a statistically significant reduction of TC was observed in both groups after just one month of atorvastatin initiation, with further reduction recorded during the 3rd-month visit. The TC levels six months post treatment did not differ significantly compared to three months and remained approximately at 155mg/dl for both groups during the whole study period. Concern-

Table 2. Measurements of basic lipid profile values during the study period

			Tchol	TGL	HDL	LDL	ox LDL	ApoB-100
F-UP	Baseline	Mean	249,01	150,63	46,33	171,27	52,33	148,73
		St. D	24,70	29,22	9,24	21,92	10,91	19,23
	M1	Mean	195,12	135,68	48,50	119,09	27,45	118,49
		St. D	23,56	25,88	8,86	20,06	6,28	23,09
	M3	Mean	172,44	129,00	49,49	97,12	15,87	103,83
		St. D	17,86	23,72	8,46	15,16	4,87	20,29
	M6	Mean	161,71	122,45	51,54	86,49	11,66	91,92
		St. D	16,58	23,34	8,11	9,04	5,21	14,81
	Y01	Mean	159,87	121,89	51,59	83,99	8,31	88,15
		St. D	13,33	22,39	8,29	9,93	2,08	14,42
	Y02	Mean	157,30	119,85	51,33	82,38	7,97	85,36
		St. D	11,86	21,98	7,74	9,24	2,04	12,97
	Y03	Mean	156,68	118,38	51,63	81,75	7,83	84,17
		St. D	11,64	22,16	7,74	9,09	2,00	10,74
	Y04	Mean	155,76	117,28	51,99	80,57	7,58	84,62
		St. D	12,39	23,02	7,37	9,02	2,09	11,44
	Y05	Mean	155,33	114,71	52,35	80,36	7,53	83,60
		St. D	12,81	23,65	7,74	8,41	2,00	12,13
	Y06	Mean	153,92	114,41	52,75	78,69	7,36	81,95
		St. D	11,82	23,73	7,51	8,32	1,92	10,99
	Y07	Mean	154,79	113,72	53,24	79,27	7,18	80,75
		St. D	12,07	25,17	7,69	7,67	1,83	10,93
	Y08	Mean	154,89	113,69	53,10	79,48	6,97	81,68
		St. D	10,64	23,90	7,20	7,38	1,84	9,93
	Y09	Mean	154,44	114,13	53,41	78,64	6,79	81,31
		St. D	11,38	23,63	7,44	7,26	1,71	11,10
	Y10	Mean	154,66	113,75	53,72	78,80	6,60	81,31
		St. D	10,56	23,27	7,33	6,72	1,62	10,30

M=month, Y=year, F-UP=follow-up, St.D=standard deviation, Tchol=total cholesterol, TGL=triglycerides, HDL=high density lipoprotein, LDL=low density lipoprotein, oxLDL=oxidized low-density lipoprotein, apoB-100=apolipoprotein B 100.

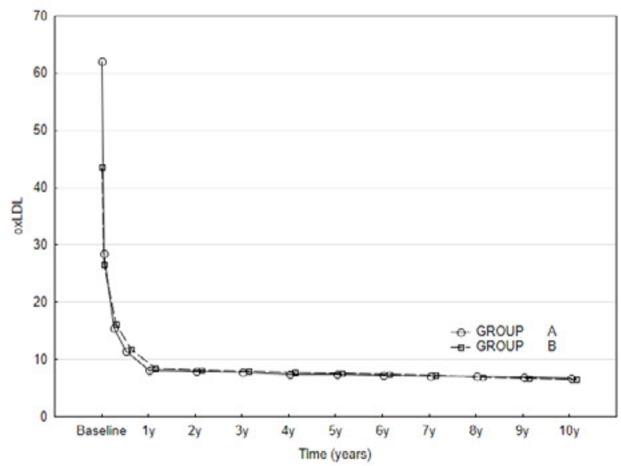

Figure 1A. oxLDL values through the 10 year follow up for groups 1 (curve A) and 2 (curve B)

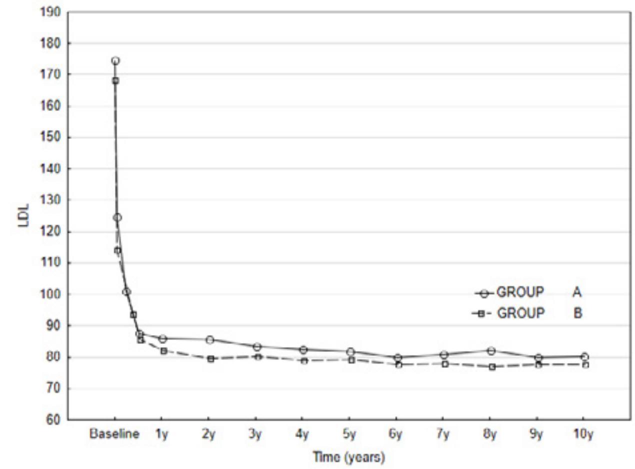

Figure 1B. LDL values through the 10 year follow up for groups 1 (curve A) and 2 (curve B)

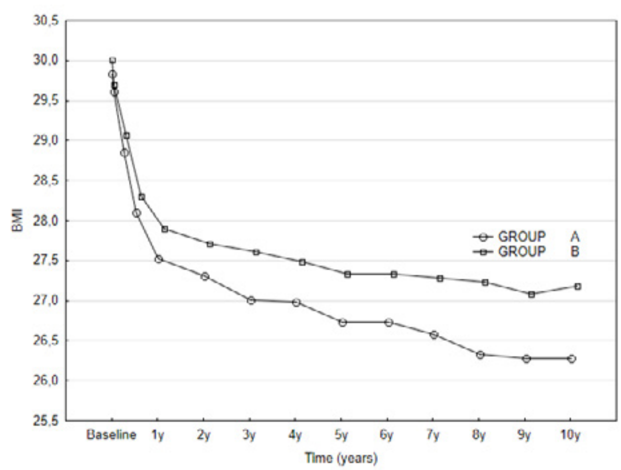

Figure 2. BMI values through the 10 year follow up for groups 1 (curve A) and 2 (curve B)

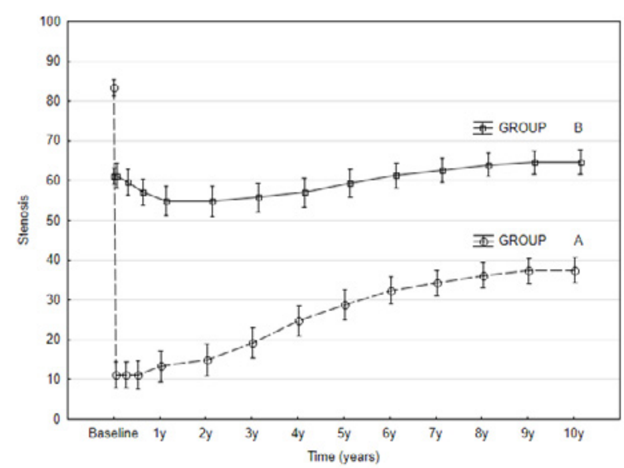

Figure 3. Stenosis values through the 10 year follow up for groups 1 (curve A) and 2 (curve B)

ing TG levels, a significant decrease was observed in both groups, reaching a nadir level after six months in group 1 and after three months in group 2. Regarding HDL values, a gradual increase was observed for both groups during the first six months, while after that timepoint no further changes were observed. There was no significant difference between group 1 and 2 regarding changes in the HDL levels at any time point. A marked reduction was observed regarding the oxLDL (**figure 1A**) as well as the LDL (**figure 1B**) levels in both groups. LDL and oxLDL values presented no statistically significant differences between group 1 and 2 at any time point except for the baseline values of oxLDL. For both parameters, a rather “flat line” was observed after the first six months (**figure 1A and B**). Specifically, mean oxLDL dropped from 52.33 +/- 10.91 mg/dl at baseline to 11.66 +/- 5.21 mg/dl at six months (p<0,001), and 8.31+/-2.08 at 12 months (p=NS). Finally regarding ApoB100, the observed changes are in parallel between the two groups, showing a marked reduction during the first six months and no further reduction for the remaining study period. The ApoB100 values of patients in group 1 were consistently higher compared to the values of group 2.

Within group 2, the subgroup of patients with mild stenosis (< 60%) had a significant reduction of oxLDL from 34.94±4.23 mg/dl at baseline to 12.12±7.53 mg/dl at 12months (p<0.001). It must be noted that a 10 unit statistically significant decrease of oxLDL levels was observed quite early - only after 3 months of atorvastatin therapy. Within group 2, the subgroup of patients with substantial stenosis (≥ 60% and < 70%) had a significant reduction of oxLDL from 44.68±1.98 mg/dl at baseline to 11.79±4.21 mg/dl at 12months ($p<0.001$). It must be noted that a 17 unit statistically significant decrease was already demonstrable 3 months after the initiation of atorvastatin therapy.

Anthropometrics

During the first year of follow-up a marked reduction of body mass index (BMI) and net body weight was noticed, followed by a less prominent decline during the second year. There was no significant change beyond this timepoint until the end of the 10-year observation period. BMI reduction was significantly greater in group 1 compared to group 2 (**figure 2**). During the first three months no significant change was noticed in reference to waist circumference and waist:hip ratio, yet a significant decrease was observed after 6 months and continued until the second year of follow-up. The measurements beyond the second year indicate a rather steady profile for both groups. There was no significant difference in the reduction of waist circumference between the two groups.

***Carotid stenosis and plaque stability*.**

In group 1 after 12 months of statin therapy, no case of restenosis was reported. At the end of the study period at 10 years 4 cases were observed. All patients in group 2 had significant stenosis at baseline (100%), which was reduced to 96.4% at 12 months and 80.4% the end of the observation period. The stenosis values and respected comparisons for the two groups are depicted in **figure 3**. Patients in group 2 who achieved LDL levels <70mg/dl during the observation period had a greater but not significant reduction of carotid stenosis compared to those with LDL levels between 70 and 100mg/dl.

Regarding plaque echogenicity, the 95% of patients (n=53) of group 2 had type III or IV plaque defined as stable by year two, while 100%

Table 3. Frequencies and percentages of echogenic plaques in group 1 (A) and group 2 (B) during the observation period and respective comparisons with p values

	GROUP								
	1				2				
	Echogenic		Echolucent		Echogenic		Echolucent		
	N	%	N	%	N	%	N	%	p-value
Baseline	9	18,0%	41	82,0%	12	21,4%	44	78,6%	0,658
1 month	50	100,0%	0	0,0%	13	23,2%	43	76,8%	<0,001
3 months	50	100,0%	0	0,0%	16	28,6%	40	71,4%	<0,001
6 months	50	100,0%	0	0,0%	29	51,8%	27	48,2%	<0,001
1 year	50	100,0%	0	0,0%	42	75,0%	14	25,0%	<0,001
2 years	50	100,0%	0	0,0%	53	94,6%	3	5,4%	0,245
3 years	50	100,0%	0	0,0%	55	98,2%	1	1,8%	1,000
4 years	50	100,0%	0	0,0%	56	100,0%	0	0,0%	-
5 years	50	100,0%	0	0,0%	56	100,0%	0	0,0%	-
6 years	50	100,0%	0	0,0%	56	100,0%	0	0,0%	-
7 years	50	100,0%	0	0,0%	56	100,0%	0	0,0%	-
8 years	50	100,0%	0	0,0%	56	100,0%	0	0,0%	-
9 years	50	100,0%	0	0,0%	56	100,0%	0	0,0%	-
10 years	50	100,0%	0	0,0%	56	100,0%	0	0,0%	-

of patients had stable plaque by year four. That means that no patient in either group had an "unstable plaque" after four years of statin therapy, while patients in group 2 had low plaque echogenicity during the first year of follow-up (**Table 3**).

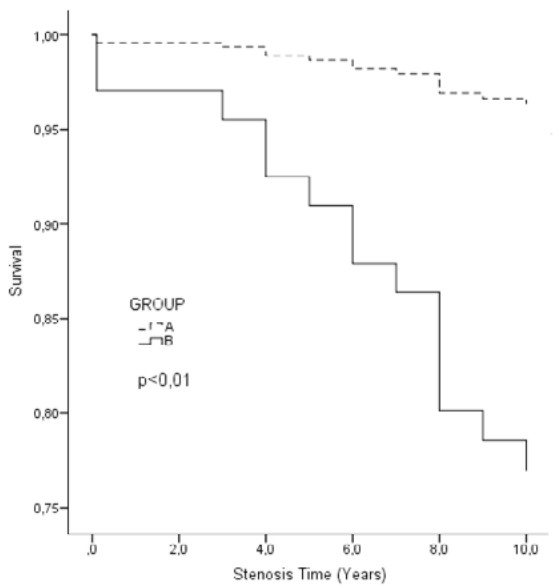

Figure 4. Cumulative stenosis rates using life table analysis 1 (curve A) and 2 (curve B)

The Cox regression analysis showed that there was a statistically significant difference between the two groups and a significant effect of the oxLDL levels only for group 2 (**figure 4 and table 4**). Specifically, the hazard of restenosis was significantly higher in group 2 where for every unit of greater baseline oxLDL value the hazard of restenosis increases by 56,7% (95% C.I.: 22,2% - 100,9%), p<0,001. The model was adjusted for the effect of age, diabetes mellitus, gender, hypertension, baseline cholesterol and baseline BMI for group 2, while for Group 1 HTN, diabetes and smoking were excluded as no convergence could be achieved. Time was not a statistically significant factor and therefore the interaction of time for the time dependent covariates (diabetes mellitus, hypertension, cholesterol, oxLDL and BMI) was in all cases and both groups, not significant.

Discussion

This study demonstrates that atorvastatin administered in individualised doses, titrated to maintain serum LDL cholesterol levels <100mg/dl, significantly improved lipid profile, decreased circulating oxLDL levels, reduced carotid artery stenosis and improves plaque stability in patients managed conservatively or prevented restenosis in patients with prior angioplasty. This effect was durable over a prolonged period , reaching ten years, thus indicating a possible survival benefit in such patients.

Oxidised LDL has been shown by multivariate analysis to represent an independent risk factor for carotid artery stenosis (**Table 3**). Specifically, oxLDL levels at baseline serve as a prognostic risk marker for future deterioration of carotid ar-

Table 4. Cox multivariate regression analysis for risk factors of restenosis

	GROUP 1				GROUP 2			
			95,0% CI for HR				95,0% CI for HR	
Baseline characteristics	p	HR	Lower	Upper	p	HR	Lower	Upper
Age	0,079	1,667	0,942	2,948	0,124	1,088	0,977	1,213
Homocysteine	0,793	0,520	0,004	68,556	0,917	1,089	0,219	5,418
GENDER	0,962	0,930	0,045	19,133	0,671	1,708	0,144	20,252
T chol	0,843	1,007	0,940	1,079	0,121	0,966	0,925	1,009
OxLDL	0,553	1,147	0,729	1,805	**0,000**	**1,567**	**1,222**	**2,009**
BMI	0,943	0,963	0,338	2,743	0,307	1,282	0,796	2,063
HTN	-	-	-	-	0,459	0,400	0,035	4,519
DIABETES	-	-	-	-	0,499	0,604	0,140	2,605
SMOKING	-	-	-	-	0,797	0,700	0,046	10,700

HTN=arterial hypertension, T chol=total cholesterol, BMI=body mass index, oxLDL=oxidized low-density lipoprotein.

tery stenosis under statin therapy. This was true for patients treated conservatively, in group 2, as the number of patients with restenosis in group 1 was rather small. Moreover, it is anticipated that patients that did not undergo invasive procedures would be at greater risk for long-term consequences and possible worsening of stenosis. Our study estimated a specific, significant risk for patients with greater oxLDL levels at baseline, showing that this target group might benefit more from statin therapy. Most importantly, the prognostic significance of oxLDL was not influenced by any other classic cardiovascular risk factor such as gender, aging, smoking, diabetes mellitus, or hypertension at any time point.

The two groups in our study did not serve the purpose of internal control but rather represented the two most common medical scenarios in carotid atherosclerotic disease. As expected, patients undergoing angioplasty (group 1) had worse atherogenic characteristics at baseline such as hypertension, smoking, and diabetes, yet the possibility for re-stenosis was alleviated with statin therapy used for secondary prophylaxis. Patients treated conservatively benefited from statin therapy as a measure of primary prophylaxis. Though such patients had a higher degree of restenosis between the 4th and 10th years of follow-up, yet the plaque was more echogenic indicating greater stability and by inference, posing a decreased overall risk for stroke.

This study aimed to investigate whether oxLDL could pose an independent risk marker of carotid artery stenosis in both types of patients, and this was shown by our results. To our knowledge, this study is among the few prospective studies with such a long observation period of ten years to investigate changes of oxLDL with statin therapy, yet among the first to report not only a clear, significant reduction of oxLDL levels following atorvastatin therapy but also, an association of the remission of oxLDL levels with the reduction of the degree of carotid stenosis. Noteworthy, this significant and long-standing reduction of oxLDL levels was achieved with everyday-life, usual doses of atorvastatin. Most of atorvastatin benefit was completed during the first six-month period. Practically no further reduction was noticed beyond this time point.

The mechanism by which statins alleviate oxLDL levels is still a matter of investigation in the literature. Moreover, a clear association of oxLDL level reduction with improvement of carotid atherosclerosis and a better overall survival benefit is not unequivocally established by large, double-blinded, randomised clinical trials. Under this perspective, the present observational cohort study with a 10-year observation period provides reasonable evidence that reducing oxLDL may independently improve carotid stenosis.

Carotid IMT is a validated measure of carotid atherosclerosis. Nevertheless, in the present study, a direct estimation of stenosis by ultrasonography was opted because it is readily available in most clinical settings and is apparently associated with clinical symptoms and signs. Besides, it is a reliable and reproducible method, and practically the one used for the pre-operative evaluation of patients eligible for endarterectomy. Carotid stenosis is a well-established surrogate marker for cardiovascular disease (CVD)[20]. Other parameters of the vessel wall status, such as the estimation of IMT and plaque morphology, although associated with CVD in the literature, require a more specific radiological evaluation and are not readily available in most real-life clinical settings. Future studies would ideally include such measurements. On the other hand, oxLDL has been recognized as a risk factor for carotid atherosclerosis in asymptomatic men[21] and has also been linked with CVD[21]. Increased oxLDL[2] and MDA-LDL levels[6] are related to plaque instability. It has also been reported that oxLDL is weakly associated with carotid IMT.[22]

Statins reduce the incidence of cardiovascular events not only due to their hypocholesterolemic properties[23], but also due to additional mechanisms of action, the so-called pleiotropic effects[12], such as the suppression of smooth muscle cell migration and proliferation[24], the reduction of monocyte adhesion to the vascular endothelium[25], the improvement of endothelial function[26], the inhibition of cell-mediated LDL oxidation[13,14], the immunomodulation of monocyte maturation and differentiation, and the modification of production of inflammatory cytokines[27]. Atorvastatin, in particular, suppresses cellular uptake of oxLDL from differentiating monocytes by reducing the expression of LOX-1 and scavenger receptors[28] and accelerates the LDL-receptor-mediated removal of the non-oxidized LDL particles[29]. It has even been reported that active atorvastatin metabolites may have more significant anti-atherosclerotic effects than other statin molecules[30]. Atorvastatin hydroxy-metabolites have a protective action against LDL oxidation[22]. The established benefit from statin therapy after acute coronary events may be attributed to the stabilization of the plaque through the removal of oxLDL from the vessel wall[31], transient binding with apoB-100 particles and clearance from the circulation.

In the STAT trial[32], antibodies against oxLDL were equally decreased with aggressive and conventional lipid-lowering therapy. This indicates that statins reduce oxLDL in a non dose-dependent manner. The results of the present study confirm this as well. It may be attributed to their pleiotropic actions rather to their hypocholesterolemic potential. A study by Orem et al. using low doses of atorvastatin demonstrated a significant reduction of autoantibodies against oxLDL levels.[23]. Similarly in our study ox-LDL levels were reduced with low atorvastatin doses. This might explain why in the conservatively treated group 2, no further improvement of stenosis was noticed in patients achieving LDL levels lower than 100mg/dl. Alternatively, this could be attributed to the small sample size and the diversity of our population, although there are indications in the literature that intensification of statin therapy does not confer additional protection and only those with LDL >125mg/dl would benefit from a more aggressive statin therapy[34].

In acute coronary events statins have a dose-related action, but this has not been the case regarding oxidative stress[35]. This might also be explained by the hypothesis that statins achieve their uttermost benefit on oxLDL after a certain time point[33], beyond which, no additional benefit might be expected. Continuation of treatment in such cases serves only the purpose of maintenance. Atorvastatin reduces small dense LDL subfractions, remnant-like particles cholesterol and oxLDL, and improve endothelial function, after just a few weeks of therapy[36, 37]. This time-related effect may possibly explain the finding of our study that during the first six months, a sharp decline of oxLDL levels was noticed, followed by a milder reduction rate thereafter, and stabilization for the next ten years.

The concomitant reduction of both oxLDL and carotid stenosis in our study by statins may be explained by the fact that those drugs influence common pathways, responsible for the production of oxLDL and initiation of atherosclerosis; alternatively, the reduction of oxidative stress with statins may have resulted in remission of stenosis, as oxidation of LDL is the driving force of atherosclerosis. This study demonstrates that the association of oxLDL with carotid artery stenosis is independent of the LDL level changes. It could be assumed that oxLDL is reduced by statins as a consequence of the reduction of LDL levels. Nevertheless, the latter would not lead to less oxLDL, unless the oxidative capacity of the plasma was not simultaneously condensed. On the other hand, statins may decrease oxLDL independently of the changes of LDL levels in the context of their pleiotropic actions. Besides, oxLDL triggers atherosclerosis by binding with different receptors than LDL. The above mean that the cutback of oxLDL might be more critical for the reversal of atherosclerosis than the drop of LDL levels.

The Mercodia oxLDL detects the MDA-modified apoB[16]. It has been proposed that oxLDL loses its predictive value for CVD when adjustment for apoB level is performed[34]. Significant reduction of Mercodia oxLDL with 10mg of atorvastatinwas demonstrated in several studies, even after adjustment for apoB levels[3, 21, 34]. In our studies the reduction of oxLDL was still significant after adjustment for apoB and LDL levels. In our study, the reduction of carotid stenosis was associated with the decrease of oxLDL levels.

Limitations of the present study were the relatively small size, the lack of a control group comprising of patients with carotid stenosis not on statin therapy, which would be unethical, the fact that researchers were not blinded to the patients' status, the lack of randomization of the dose-schedules and the use of only one method to detect oxLDL and carotid stenosis.

Conclusions

This prospective, observational study with a ten-year follow-up provides evidence of a favorable effect of usual-dose atorvastatin therapy on oxLDL, which was associated with a reduction in stenosis progression in patients with carotid atherosclerosis. Moreover, oxLDL level modifications were associated with conversion of the plaque type to a more stable form. These findings may lead to an amendment of our policy concerning the time of carotid endovascular treatment advising the patients with carotid artery disease to receive statin therapy 2-3 months pre-angioplasty, in order to avoid complications during and post-procedure. In conclusion, we postulate that oxLDL might represent a more sensitive risk marker for stenosis than LDL and apoB as shown by multivariate analysis.

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Authors' Contibution

Dr Adamantia Polydorou wrote the protocol and had the overall supervision, as the primary investigator. She discussed the protocol with professor of Anatomy in the Medical School of Athens, National and Kapodestrian University of Athens, prof. Theodore Troupis and make amendments before applying to the ethics committee. She also contributed to the data collection and entry and reviewing the paper prior to submission

Dr Konstantinos Alexopoulos and Dr. Victoria Polydorou gathered all the information from the patients' files and organized the data of the study, updated the spreadsheet, and contributed to the writing of the paper

Dr Skopelitits overviewed the data and contributed to the writing and editing of the paper, acting as the corresponding author as well

Dr Xanthoula Kougiali was responsible for the biochemistry samples collection and processing. She also contributed to the lab data entry and statistical analysis.

Dr. Nikolaos Liasis and Dr Maura Griffin were responsible for the carotid artery ultrasound evaluation of the patients

Dr. Theano Demesticha was responsible for collecting the anthropometric data of the patients and evaluation of the restenosis during the follow-up visits.

Dr. George Dimakopoulos and Dr. Maria Piagkou and Eleni Velissariou were responsible for the data corrections and statistical analysis and contributed to the editing of the paper.

Professor Dimitris Filippou, president of the Greek FDA, was responsible for the determination of the posology of atorvastatin and the evaluation of the impact on LDL, oxLDL and other laboratory parameters.

Dr Vasilios Protegerou overviewed the correct timing of the study population follow-up visits and the collection of the questionnaires, data entry and organization of the data to tables and spreadsheets. He also contributed to paper editing

All authors read and approved the final version of the manuscript

Review of sustainable Paediatric Cardiac Surgery Program based on Humanitarian Principles at Govt. Medical College, Goa

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Keywords
Congenital heart disease, India, Goa medical college (GMC), Paediatric cardiac surgical care.

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Abstract

Introduction: Paediatric cardiac surgery and paediatric cardiology Setup is an arduous task, in developing countries, like India**.** Access to advanced cardiac care is unavailable in the majority of developing countries**.** Due to high fertility rates in India, the annual estimate of CHD is approximately 150,000- 200,000 children per year**.** Of these, approximately a third to a quarter (~50,000) would need early intervention to survive the first year of life. Goa is a small state of India situated along the western coast of Indian peninsula. Goa medical college (GMC) is the only tertiary level institute, providing medical facilities in the state. There were no cardiology or cardiac surgical facilities available at GMC, prior to 2014. The cardiac surgical unit at Goa Medical College was started in April 2014. It provides cardiac surgical services free of cost to all the state's citizens. Initially, only adult cardiac surgical cases were being performed, but from September 2014, we initiated the paediatric cardiac surgical program, for which we availed the facility of a paediatric cardiac surgeon.

Materials and Methods: From 26th Sep 2014 to 11th Jan 2020, we operated on a total of 90 cases, - during 18 visits of the visiting paediatric cardiac surgeon, who operated an average of 5 cases per visit. Mean age of operated children was 3.2 years. We operated 34 cases of VSD's, 26 cases of TOF, 8 cases of Tricuspid atresia, 9 cases of ASD, 3 cases of MV repair, 1 case of ASD+PS, 5 cases of TAPVC, 3 PA banding & PDA ligation and one permanent pacemaker implantation. Patients were managed initially in a 5 bedded ICU and after extubation were shifted to a step-down ICU for further recovery.

Results: The average duration of ventilation was 36hrs and the average length of ICU stay was 5 days. Mean CPB time was 92.46 mins and mean aortic cross-clamp time was 59.5 mins. Overall mortality was 5.55%. One patient underwent a redo MV repair, as there was moderate residual MR in the post-operative period.

Conclusion: This model of cardiac surgical program has worked well for the state of Goa and has benefitted lot of people from within the state as well as neighbouring states, where easy and affordable access to cardiac surgical facilities are missing. It has produced excellent outcomes for adult cardiac surgery and has encouraged us to extend the facility to paediatric population. Gradually as our team has become self sufficient, we are able to achieve sustainable paediatric cardiac surgical model.

Introduction

Goa is a small state of India situated along the western coast of the Indian peninsula. The "Escola Medico Cirurgica da Goa" was established in 1842 during the Portuguese rule and was renamed Goa Medical College in[1].

Paediatric cardiac surgery and paediatric cardiology set-up is demanding, in India[4]. Access to advanced cardiac care is unavailable in majority of developing countries[5]. Due to high fertility rates in India, the annual estimate approximately 150,000- 200,000 children are born with CHD in India every year[6, 10]. Of these, approximately a third to a quarter (~50,000) would need early intervention to survive the first year of life[7, 10].

Goa medical college (GMC) is the only tertiary-level institute, providing medical facilities in the state. There were no facilities for cardiology or cardiac surgery available at GMC, prior to 2014.The department of cardiac sciences was created by the government of Goa in February 2014. All the services here are provided, absolutely free of cost for the people of the state. The govt. of Goa, appointed cardiologists and cardiac surgeons not on regular govt. employee's terms, but as professional consultants, on contract with the govt, at a higher remuneration.

The cardiac surgical unit was started by a team of 2 cardiac surgeons, one anaesthesiologist and 2 clinical perfusionists. Initially only adult cardiac surgical cases were being performed, but from September 2014, we initiated the paediatric cardiac surgical program, for which we availed the facility of a visiting paediatric cardiac surgeon.

Department of cardiology was 18th Feb 2014. The cardiac surgery unit initially started performing adult cardiac surgeries like CABG, valve replacements, adult congenital heart surgeries, thoracic and vascular cases. Our annual caseload is about 500 pump cases (350 CABG's, 120 Valve replacements and repairs and 30 congenital heart surgery cases) along with 200 vascular and 50 thoracic cases.

Paediatric cardiac surgery program was started in September 2014. We started calling a visiting paediatric cardiac surgery consultant, - who used

Figure 1. Picture of Escola Medico Cirurgica Da Goa, established under Portuguese in 1942, at Marquinez palace, Panaji[2]

to visit GMC, - once every 3 months, mainly over the weekends, for a total duration of 3 to 5 days.

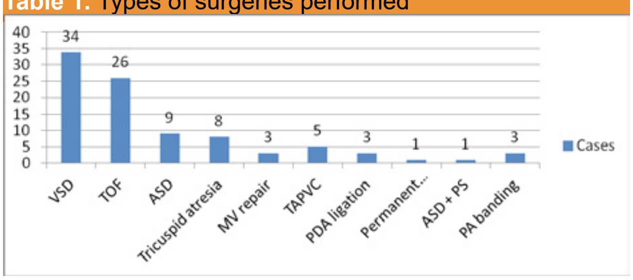
All the children with congenital heart disease were carefully screened, - pre-operatively by our in-house paediatric cardiologist and the prospective cases to be selected for the surgery were discussed in detail, - with the visiting surgeon prior to finalizing the operation list. In some cases where the 2D-echo data was inadequate, catheterisation studies and angiogram were done and shared with the visiting surgeon. He performed 4 to 6 open-heart surgeries during each of his visits. All the post-operative care was provided by the home team, with telephonic consultation with the visiting consultant in case of any doubts or difficulties.

Materials and Methods

From 26th Sep 2014 to 20th Jan 2020, we operated 90 cases. During this time the consultant paediatric cardiac surgeon, - visited us 18 times. We operated an average of 5 cases per visit. The mean age of operated children was 3.2 years.

Results

Table 1. Types of surgeries performed



All operated patients were initially managed in a 5 bedded ICU. Postoperative 2D echocardiograms were performed on all the children by our in-house paediatric cardiologist. After extubation, the children were shifted to a step-down ICU for further recovery.

Table 2. Operative details summary

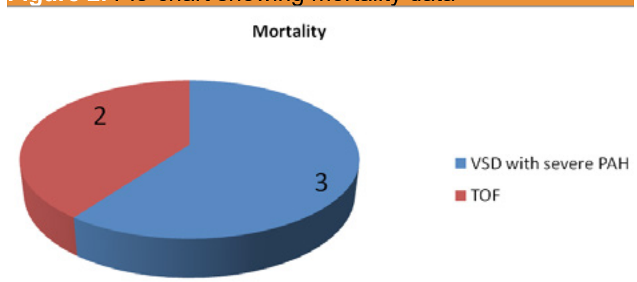
Parameter	Outcome
Average duration of ventilation	36 hrs
Average ICU stay	5 days
Mean CPB time	92.46 mins
Mean ACC time	59.5 mins
Overall mortality	5.55%

Mortality

We had a total of 5 deaths. Two patients with TOF, developed severe RV dysfunction and low cardiac output in the postoperative period. One patient of VSD, - developed tension pneumothorax, - with mediastinal shift and hemodynamic compromise. Two patients of VSD with severe PAH developed pulmonary hypertensive crisis; with a low cardiac output state.

These children were low birth weight; with severe malnourishment. These mortalities occurred during the budding stages of our paediatric cardiac surgical program. Our institute does not have inhaled nitric oxide facilities. Our post-operative cardiac ICU is being managed by the anaesthesiologists, who are more used to routinely see adult cardiac surgical patients.

Figure 2. Pie-chart showing mortality data



Morbidity

Neurological deficits were seen in 3 patients. One patient post TAPVC repair had seizures in the post-operative period and two patients following VSD repair have neurological deficits, which are gradually improving with physiotherapy. All of these patients are following up with physiotherapy at the paediatric neuro-rehabilitation centre at GMC.

One patient of mitral valve repair had to undergo a redo MV repair, as there was significant (moderate) residual MR in the post-operative trans-thoracic 2D-echocardiogram. We do not have paediatric TEE facilities.

Discussion

The sustainability of a cardiac surgical program depends on 3 factors:

1. Adequate number of patients,
2. Uninterrupted funding and
3. A capable surgical team.

An adequate number of patients

At Goa medical college, we do not have a dearth of patients.

We not only provide services to the entire state of Goa, but also cater to the adjacent states of southern Maharashtra and northern Karnataka, from where numerous people who come to the institute are below the poverty line and do not have access to avail cardiac surgical facilities in view of prohibitive costs of the procedures. We have a waiting list for our elective cases, running for over 2 weeks.

Uninterrupted funding

Regarding the availability of funds, the govt. of Goa has been kind enough to support the cardiac department right from its inception. It has been sponsoring the program wholeheartedly with no limitation of funding.

Local cardiac surgical team

We have a regular adult cardiac surgical program, running successfully at GMC for the last 7 years. A cost-effective method for skill acquisition is to engage a cardiac team from a good cardiac centre to work with the local team continuously until skill transfer is achieved[8]. We require the assistance of a visiting paediatric cardiac surgeon only for performing surgeries for complex congenital heart defects. Initially we used to call a visiting perfusionist as well, for a period of up to one year. Gradually our in-house perfusionist has become well trained to handle all types of congenital heart surgeries, including babies less than 5 kgs of weight.

Our team has also grown during this period. We have appointed one more junior consultant cardiac surgeon, two consultant cardiac anaesthesiologists, six new cardiologists, three more clinical perfusionists and more nursing staff in the operation theatre and ICU. All the team members with the support staffs work round the clock to provide comprehensive care and support in the peri-operative period.

Figure 3. Map of India showing the location of the western state of Goa and its relationship with the adjacent states[3]

The pediatric cardiac surgical emergencies which were duct-dependant cyanotic congenital heart lesions were managed by duct stenting by our cardiologists. Other complex congenital defects like obstructed TAPVCs, TGA, Defects requiring a conduit or homograft for reconstruction were referred to higher centres outside the state. From February 2014 to January 2022, we have referred 37 cases to a higher cardiac centre, outside the state. This paediatric cardiac surgical program has enabled the post graduate resident doctors from the departments of General surgery, Paediatrics and Anaesthesiology to get exposed to various surgical options available for congenital heart diseases and to get trained in the peri-operative management of babies which are operated for congenital heart problems.

As there were no cardiac surgical facilities before 2014, the department of paediatrics used to refer all such patients to metropolitan cities of other states like Bangalore or Mumbai. One-third of the children suffering from congenital heart disease within the state used to go to other states to get operated. However a large majority, - belonging to a poor socio-economic status never travelled, due to financial and logistic constraints. This model of cardiac surgical program has worked well for the state of Goa and has benefitted a lot of people from within the state as well as neighbouring states.

Our cardiac surgical team is capable of taking ICU care and handling post-operative complications. Our surgical team has been doing adult surgeries and only needed some assistance in handling small babies. There are different specialities & super-specialty services available at GMC, - for cross consultation and providing backup. Our cardiac anesthesia team was comfortable in handling small babies' right from the beginning and have been competently taking care of these cases during the intra-operative and post-operative period.

Conclusion

Gradually, our local surgical team has become trained in performing various types of paediatric cardiac surgical procedures and we have been performing them regularly.

Sustainability cannot be achieved if a team is not locally self-sufficient and remains completely dependent on visiting (cardiac surgical, anaesthesia and perfusion) teams at all times. Gradually as our team has become self-sufficient, we are able to achieve a sustainable paediatric cardiac surgical model.

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Years of Cardiac Surgery in Africa The experience of La Chaîne de l'Espoir A Global Concept

Sylvain Chauvaud and Chaîne de l'Espoir Group[1]

[1] Gérard Babatasi; Olivier Baron; Najeebullah Bina; Daniel Sidi; Thierry Langanay; Paul Neville; Erwan Flecher; Gilles Dreyfus; Olivier Raisky E .Cheysson, and A.Deloche.

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La Chaîne de l'Espoir is a French NGO (non-governmental organization) founded in 1988. It aims to strengthen the health systems in order to give everyone, especially children of developing countries, the same chances of survival as in developed countries. The NGO does prevention and screening from an early age and provides care and surgery (especially cardiac) to meet the most urgent needs of children and their mothers, training, and transfer of skills to local teams, and construction and equipment of hospital facilities adapted to local needs.

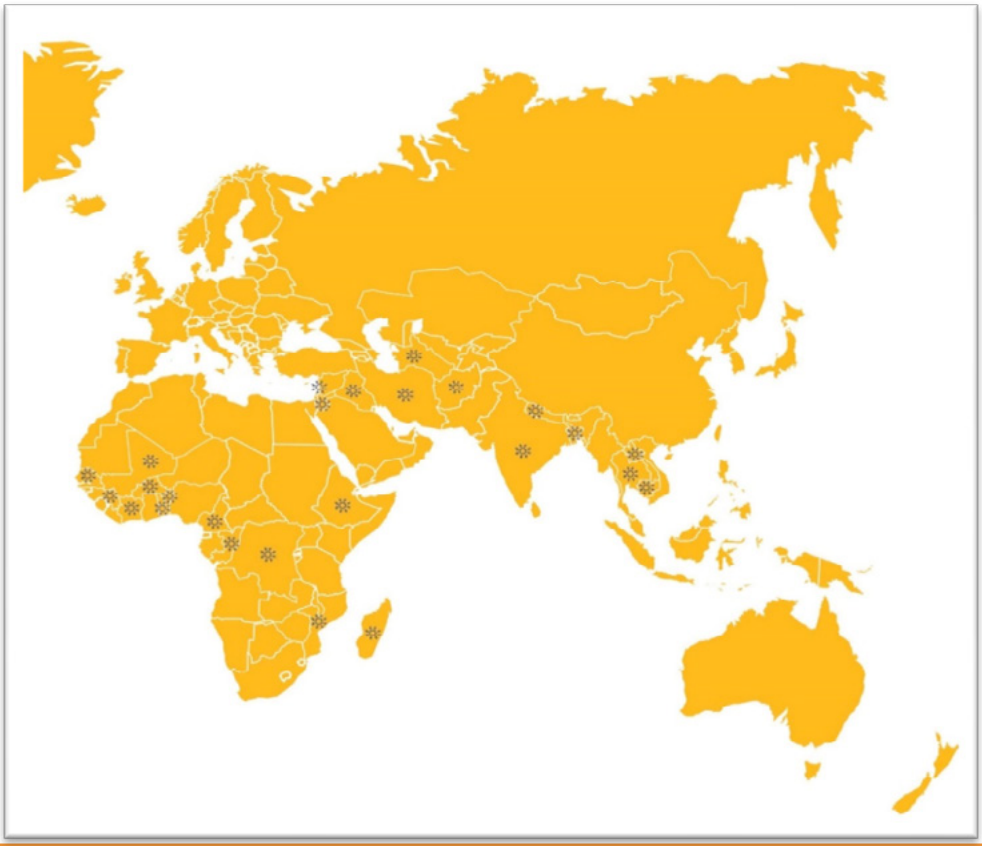
La Chaîne de l'Espoir is present on the African continent through partnerships with Benin, Burkina Faso, Cameroon, Chad, Congo Brazzaville, Ivory Coast, Guinea-Conakry, Madagascar, Mauritania, Mali, Mozambique, Senegal and Togo.

Among these countries, two have medical centers of reference where cardiac surgery is performed: Mali, with the André Festoc Center in Bamako, and Senegal, with the Cuomo Pediatric Cardiology Center of Dakar.

Transfer of children to France

Transfers of children to France began in 1989. To date, 5,000 children have been transferred. The process includes a local selection, a request for visas allowing the transfer, a residency with volunteer families, follow-up care and rehabilitation, an echo check-up and treatment, and a return home.

These transfers are expensive without any relaying of medical training for foreign doctors. This is the reason why the NGO reaches for the construction and management of local hospitals associated with training.



Countries of intervention of La Chaîne de l'Espoir in 2021.

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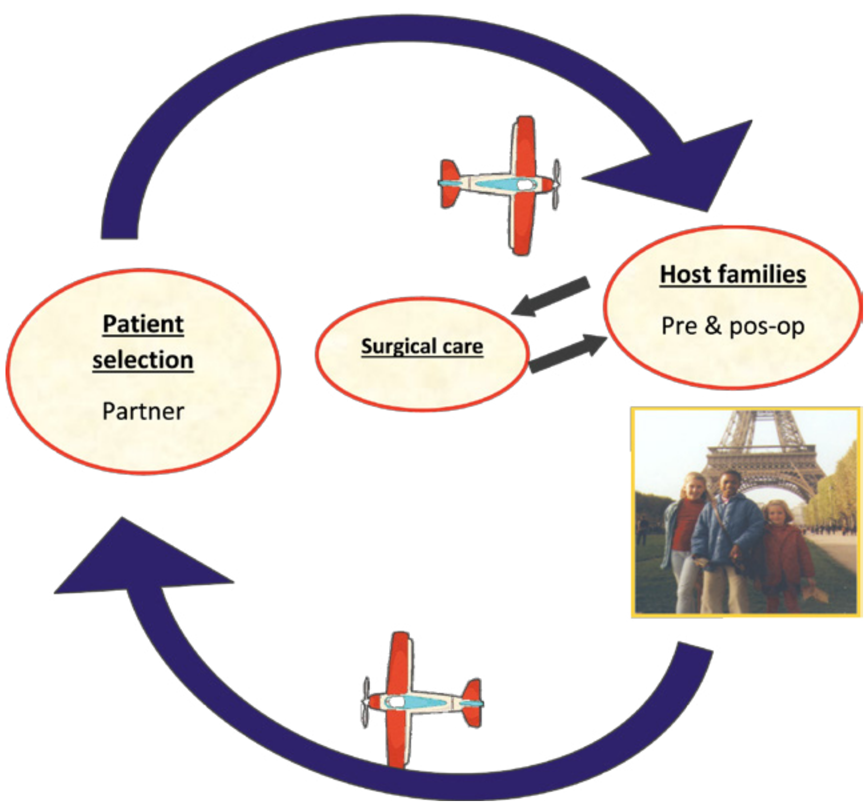

The hospitals where La Chaîne de l'Espoir is a major partner

Istitut du Coeur de Maputo (Heart Institute of Mapuoto) - Mozambique

La Chaîne de l'Espoir is at the origin of the Heart Institute of Maputo project in Mozambique and is the consortium's president.

Partnerships include La Chaîne de l'Espoir UK and Portugal, Amigos de Coracao (Mozambique), Heart for All (Switzerland), and the Red Cross Children's Hospital.

The specialties of this center are cardiology, diagnostics, and ophthalmology as well as cardiac and general surgery.

From 1998 to 2001, 4 annual grants from the French Ministry of Foreign Affairs were conceded.

From 2002 to 2019, 11 cardiologists and 4 surgeons, 2 anesthetists and paramedical staff were trained.

In the self-supporting Heart Institute, 3 children are operated on each week as well as 170 adults and children each year. On average, 25 children undergo surgical procedure during each international mission.

The construction and equipment budget reached $4,8 million, including $22, million for equipment.

The support budget reached $72,000 in 2018.

Centre Cardio-Pédiatrique Cuomo (Pediatric Cardiology Center) -Dakar, Senegal

La Chaîne de l'Espoir is the leader of the Cuomo Pediatric Cardiology Center of Dakar project and provides training support and management of the center. The NGO is a member of the steering committee. Partnerships include the Cuomo Foundation, the FANN Hospital and the Senegalese government.

This center is totally autonomous from the medical point of view. Its specialty is pediatric cardiac surgery.

607 surgeries have been conducted in the center since 2017. Since then, the hospital has become a regional training center for doctors and paramedical staff from West Africa. The allocated budget amounts to $6 million for construction and equipment and $500,000 for the construction of the Children's Pavilion. The 5-year support that was granted is equivalent to $2 million.

André Festoc Pediatric Surgery Unit at the *Hopital Mère-Enfant du Luxembourg* (Mother-Child Hospital Luxembourg) - Bamako, Mali

La Chaîne de l'Espoir is the operating partner and delegated owner for the construction and implementation of the *André Festoc Pediatric Surgery Unit at the Luxembourg Mother-Child Hospital in the Bamako project*. Partnerships include the Luxembourg Mother-Child Hospital, *Fondation pour l'Enfance*, the Pierre Fabre Foundation and the Mulliez Institute and the Lefoulon-Delalande Foundation. The specialty of the center is pediatric cardiac surgery.

34 medical personnel members were trained from 2017 to 2019 in Vietnam in Centre Médical International (Ho Chi Minh).

259 heart surgeries were conducted in the hospital between 2018 and 2019 during international expert missions.

The construction and equipment budget amounted to $3,4 million. The budget allocated by La Chaîne de l'Espoir for this project reached $770,000.


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Six-year-old becomes first in Mali to have open heart surgery

By AFP

PUBLISHED: 22:07 BST, 10 September 2018 | UPDATED: 22:08 BST, 10 September 2018

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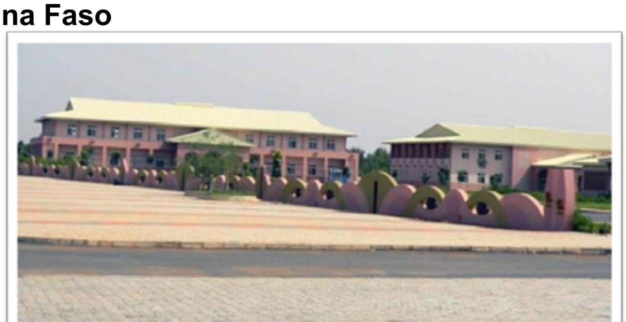
Tengandogo Hospital - Ouagadougou, Burkina Faso



The CHU Tengandogo in Ouagadougou, Burkina Faso, was built and equipped by the Chinese government. The first open-heart surgery was conducted in 2021 by Pr. Gérard Babatasi, and others were carried out during several missions by the Pr. Gabriel Ciss from Bamako in the frame of intra-African cooperation. Today, the missions need to be focused on pediatric cardiac surgery.

Institut du Coeur d'Abidjan (Heart Institute of Abidjan) - Abidjan, Ivory Coast

The missions need to be focused on pediatric cardiology. There is also a need for a new project for pediatric cardiology in HME of Bingerville.

Soavinandrina Hospital - Tananarive, Madagascar

This project is currently in progress since 2021. La Chaîne de l'Espoir has a role in the renovation of the Military Hospital and in the construction of an operating theatre for cardiac surgery.

The training of 2 surgeons, 2 anesthetists, 2 nurse anesthetists and 14 intensive care nurses is planned.

The yearly training program includes 20 surgical and 12 medical and paramedical missions. Training in Senegal is scheduled for 2022.

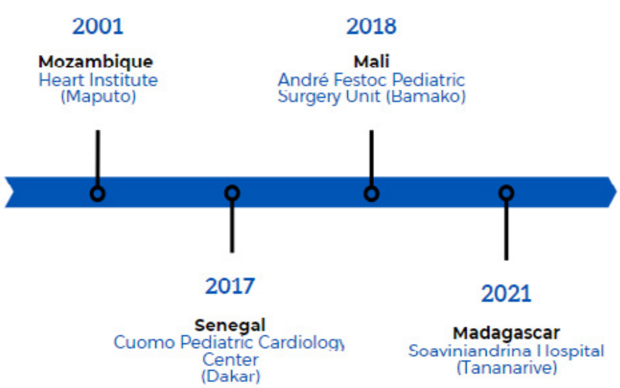
100 closed heart procedures were conducted in 2021.

The global budget for this project amounts to €1,5 million.

Centre National de Cardiologie (National center of cardiology) - Nouakchott, Mauritania

The Nouakchott authorities asked for the initiation of this project. Pr. Olivier Raisky conducted an exploratory mission in 2020. The first pediatric open-heart surgery was performed in April 2022.

Hospital buildings: Infrastructures to strengthen health systems



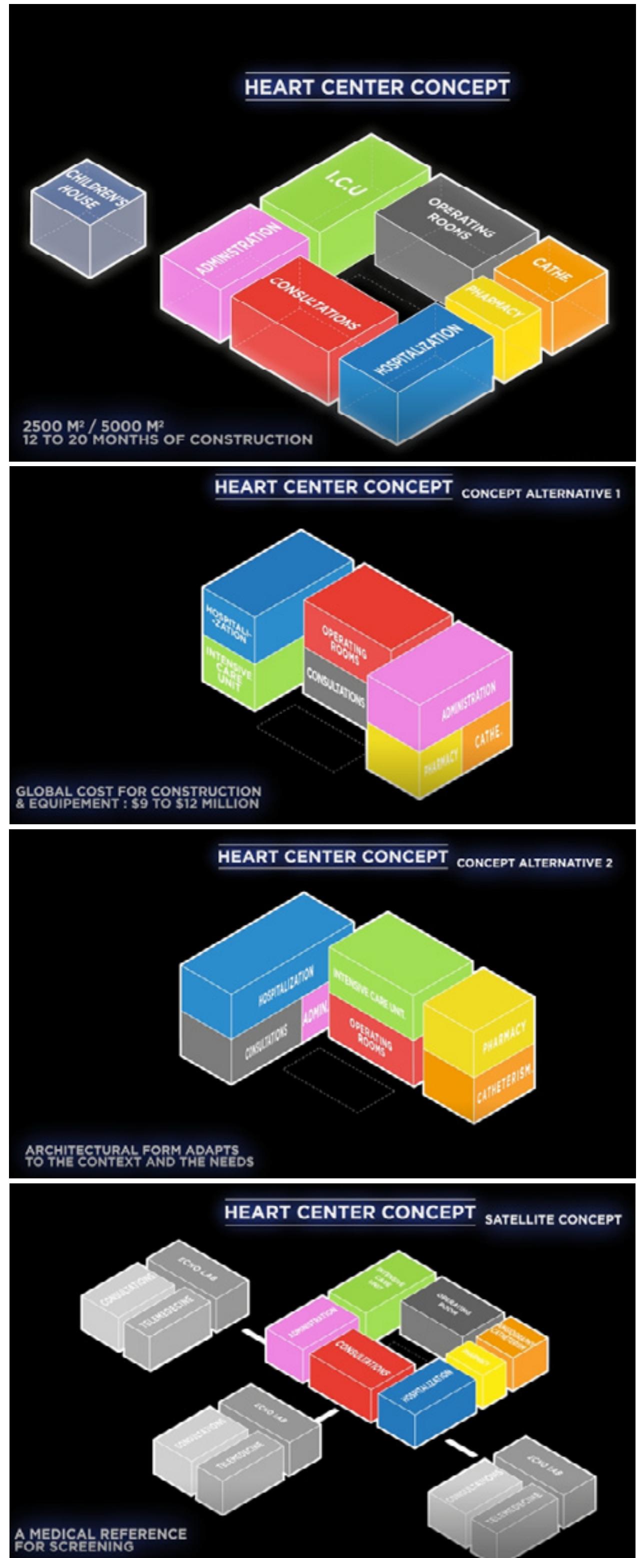
Hospitals built by La Chaîne de l'Espoir

Infrastructure and Medical Equipment

La Chaîne de l'Espoir is involved in several projects of construction, equipment, and rehabilitation of hospitals. Mozambique, Senegal, and Mali have benefited from this help.

Each year, 17 tons of medical equipment (adapted to pathologies and specific local needs, repair facilities, local maintenance services, and others) are sent to foreign hospitals.

Here below is a diagram of the Heart Center Concept of La Chaîne de l'Espoir and its different alternatives.



Elsa Negre
The different types of hospital are chosen according to the local situation.

The Echoes Program

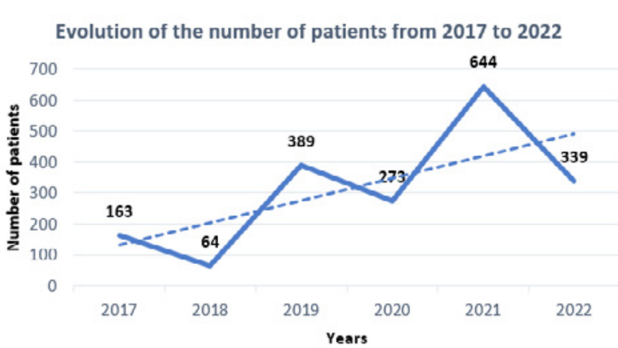
Echoes is a tele-ultrasound platform allowing diagnosis through real-time sessions with foreign doctors and La Chaîne de l'Espoir's specialists. It enables the training in pediatric cardiac ultrasound of the NGO's network doctors.

The platform supports the development of cardiac surgery programs by strengthening the capacity of local health care teams and giving a preview of patients' pathologies to facilitate the surgical missions.

It also assists the NGO's partner centers by providing training and giving a second opinion on complex cases.

Once the children's medical records are evaluated, the specialists of La Chaîne de l'Espoir decide whether a transfer to France is needed (or to other partner countries). The NGO assures a following-up of the operated patients.

644 children were examined through Echoes sessions in 2021, representing an increase of 236 % compared to the previous year.



Echoes live conference between Paris and Pnom Penh. Any country in the world could be connected with an expert when an Internet connection is correct

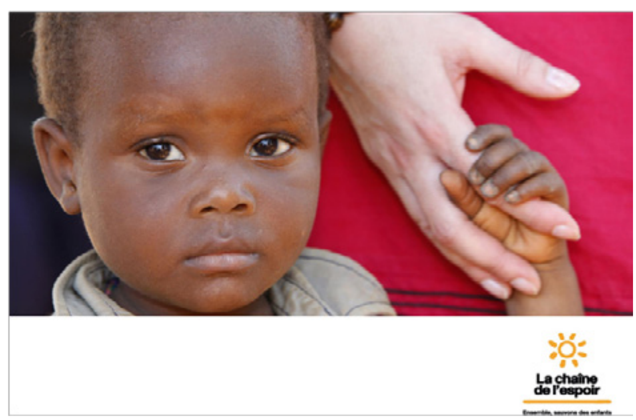
Summary

Pediatric cardiac surgery is challenging in low-income countries such as in Africa. La Chaîne de l'Espoir is a french NGO devoted to the health care of poor and sick children.

This article presents the actions La Chaîne de l'Espoir. It introduces, in particular, the transfer to France system of sick children from developing countries for surgical care, the growing tele-expertise program in cardiac ultrasound, as well as the main stages of the activity in Africa since the creation of the NGO involving seven centers allocated in different countries of the continent.

Conclusion

La Chaîne de l'Espoir is devoted to children's care and provides educational programs for medical and para-medical local teams. Hospital building and management are parts of our concern.



Cardiac Care in Belize: Building a Local, Sustainable Program from "Square One"

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Since the writing of this paper, sadly Dr. Francis Robicsek passed away on April 3rd, 2020. A world renowned cardiothoracic and vascular surgeon, as well as a devoted humanitarian, his foresight and wisdom made these and many other clinical and benevolent programs possible and successful.

Conflict of Interest: none declared.

The manuscript was accepted for presentation at the Global Humanitarian Forum biannual meeting, hosted virtually from Athens, Greece, November 11-13, 2021

"Give a man a fish and you feed him for a day. Teach a man to fish and you feed him for a lifetime." [1]

Cardiology and cardiac surgery care and facilities are often limited, or non-existent in many regions worldwide. Prior to 2012, this was the case in Belize, formerly British Honduras.

Belize, the only English-speaking country in Central America, has a population of approximately 430,000. The gross per capita income is the equivalent of $11,900 or less with one-third of the population living below the poverty level and many living in poor or indigent conditions. The prevalence of cardiovascular disease is high, second only to malnutrition and metabolic diseases. In 2020, cardiovascular disease and COVID 19 tied for leading causes of death. The country is extremely poor and unable to upgrade its health facilities with operating funds focused to combat conditions such as malaria, dengue, malnutrition, parasite, and HIV.[2, 3]

There are 4 health regions, but Karl Heusner Memorial Hospital Authority (KHMHA), situated in Belize City, Belize, is the only tertiary care hospital in the country. While attempting to provide care to the citizens of Belize, there was a significant shortcoming; the lack of a program for treating cardiovascular diseases. Before 2012, cardiac care for the general population was limited to an electrocardiograph.

Francis Robicsek, MD PhD and Heineman Medical Outreach, Inc. (now Heineman-Robicsek Foundation, Inc. (HRF)) historically had pursued a variety of local and international humanitarian projects, including international medical outreach centered in Central America in the 1970s. Such philanthropy and international outreach led to co-founding the subcontinent's first and only dedicated heart institute, Unidad de Cirugía Cardiovascular de Guatemala (UNICAR), in Guatemala City, Guatemala, which thrived under the leadership of Dr. Raúl Cruz Molina.[4]

Dr. Robicsek had a similar vision for Belize. Working with local leaders including Sir Barry Bowen and the Ministry of Health, our team set out on another journey to develop a sustainable cardiovascular medicine and surgery program in Belize.

Understanding that the creation of sustainable healthcare in medically underserved countries is a multifaceted process, HRF was committed to partnering with local leaders, a local surgeon, Dr. Adrian Coye, who had recently completed his cardiac surgery fellowship in the United Kingdom, and KHMHA to create such a model. HRF operates under the belief that the success of such ventures, rests upon strong and reliable partnerships through which fully functional units are created, setting local teams up for success from the beginning. Through HRF’s collaborations with Atrium Health, a healthcare system of 40 hospitals and more than 1,400 care locations, as well as Atrium’s Sanger Heart & Vascular Institute (SHVI), in Charlotte, North Carolina, we were able to donate new and refurbished medical equipment, as well as supplies. Local institutions and governmental agencies are expected to provide the facility space and desire to move forward in a sustainable manner.

After ensuring appropriate facility space and commitment, the journey began in 2011 through the donation of a cardiac catheterization laboratory, ECHO sonography equipment (ECHO), and operating room equipment for cardiac surgery, to KHMHA. Simultaneous efforts were ongoing to establish an ECHO network in Central America with access to reading oversight at SHVI.

Through the financial support of Heineman-Robicsek Foundation, Inc., Edwards Lifesciences Foundation, and Heineman Foundation of New York, teams coordinated by HRF were sent to Belize to oversee and/or perform cardiac ECHO’s, cardiac catheterizations (cardiac caths), and ultimately cardiac surgical procedures. The concept was to enlist, educate, and facilitate progressive development of local medical expertise, rather than to go and perform the procedures without the involvement of the local medical personnel.

The first cardiac caths were performed in 2011. After performing a number of procedures, efforts began toward establishing a cardiac surgery program with the first open heart surgeries following in July 2012. Teams from SHVI worked along-side Dr. Coye and local healthcare personnel. Such teams included a supporting cardiac surgeon, perfusionist, OR nursing, and anesthesia/critical care specialists.

With incremental growth, HRF has donated more echocardiographic stations, operating rooms, and intensive care unit equipment, fully outfitting an ICU and cardiac OR. Education and training have been provided by HRF for ECHO and interventional cardiology, cardiac catheterization technology, nursing - both scrub and critical care. Local cardiologist, hospitalists and critical care specialists have chosen to go for advanced training.[5]

Free public screening events began in 2015 and continue annually in rural underserved areas of the country.

The journey has not been without hurdles; however, despite natural disasters wreaking havoc on the hospital structure, and a subsequent global pandemic, the journey continues to gain momentum. Currently, there is a robust 5-year commitment timeline with KHMHA to achieve an independent, sustainable program. Two key components of the commitment timeline are the training of a KHMHA provider under an accredited extracorporeal program and hiring a specialized cardiologist in echocardiography, both of which have been fulfilled. This type of collaborative commitment is the first step in achieving sustainability. Success will be reliant upon multiple factors including the continued dedication and hard work of our Belizean colleagues, KHMHA, and governmental commitment despite the country’s ongoing financial difficulties. A longstanding belief of Dr. Robicsek is that it is most important to be present in a supporting role, allowing local colleagues to develop the necessary skill sets and to do the procedures. Our role is to provide assistance and support, as well as to ensure that the results are excellent thus building local confidence and infrastructure. This is significantly different from visiting brigades where the work is done entirely by the visitors who after a limited number of visits, leave very little behind except for ongoing need.

HRF, through Dr. Robicsek’s vision, has shown success with a similar program at UNICAR in Guatemala City, Guatemala 45 years ago, which today is the only facility in Central America dedicated to adult and pediatric cardiac care. Based on that experience, we are confident of future success in Belize. Figure 1

Figure (and Video) legends

1. Heineman-Robicsek Foundation video: https://youtu.be/gVW-CkXiSQ-g

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Rural Cardiac Screening: Leveraging Technology from a Previously Established Echocardiographic Network

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As reported by the Pan American Health Organization, cardiovascular diseases (CVD) are the leading cause of death globally, impacting approximately 1.8 million deaths annually in the Americas.[1] Latin America and the Caribbean have the highest socioeconomic disparities in the Americas, which is a contributing factor, as well as high blood pressure, high blood glucose, high cholesterol, obesity, tobacco, and alcohol abuse. CVD is a non-communicable disease that is highly preventable and treatable in the industrialized world, yet it is the leading cause of death for essentially one-third of the region's mortality, particularly those living in remote areas.[2]

The International Medical Outreach Program (IMO), a collaborative partnership between Atrium Health and Heineman-Robicsek Foundation, Inc. (HRF), both located in Charlotte, North Carolina, began addressing these alarming statistics in Guatemala and Belize, first by laying a solid foundation in Guatemala.

According to World Bank, it is estimated that in Guatemala 47 percent of the total population of 17 million live in poverty.[3] Approximately 35% of the country's population lacks access to basic health care services, particularly in rural communities, and cardiovascular disease is the leading cause of death among non-communicable diseases.[4] This has been the outlook for decades.

During a trip to Guatemala in the early 1970s, Dr. Francis Robicsek, cardiothoracic surgeon and at that time Chief of the Department of Thoracic and Cardiovascular Surgery at Carolinas Medical Center, known today as Atrium Health Carolinas Medical Center, met with then-President Carlos Manuel Arana Osorio. Seeing the shortcoming of cardiovascular care in Guatemala, in 1972 the Guatemalan government supported the training of a cardiac team at Carolinas Medical Center. It began with training a young general surgeon, Dr. Raúl Cruz Molina, under the tutelage of Dr. Robicsek. The team completed the training in two years through the support of a team from the Sanger Clinic, known today as Atrium Health Sanger Heart & Vascular Institute

(SHVI). In 1974 the first cardiac procedures were performed at the Roosevelt Hospital in Guatemala City.

Seventeen years later, under the leadership of Dr. Cruz, and with the vision, guidance, and support of Dr. Robicsek, the success of the program brought about the establishment of Unidad de Cirugía Cardiovascular de Guatemala (UNICAR) in Guatemala City. Located on the campus of the Roosevelt Hospital, today UNICAR operates robust adult and pediatric cardiology and cardiac surgery programs with volumes and outcomes close to those in the United States. The institution not only treats the people of Guatemala, but also from the neighboring countries of Honduras, Belize, El Salvador, Nicaragua, and some Caribbean countries.[5]

UNICAR has made numerous advancements over the decades, however, it recognized the disconnect between the institution and reaching those living in rural communities.

Leadership from UNICAR and IMO met with the Guatemalan Ministry of Health in 2010 to discuss the possibility of establishing a cardiac echo network in the rural public hospitals. There were no cardiac echo sonographers in the country, and the cardiologists performed and interpreted the scans, causing a tremendous backlog of patients in need. IMO proposed training echo sonographers. The Ministry of Health fully supported the concept and suggested several hospitals to initiate the program, with UNICAR being the nucleus. In 2011, UNICAR sent a radiology technician for intensive training in cardiac echo sonography. The education and training were conducted for three months in Charlotte at the Sanger Heart and Vascular Institute (SHVI), followed by an additional 3-months apprenticeship at UNICAR in Guatemala City. Within 6-months, scanning began identifying cardiac anomalies, thus leading to subsequent medical treatment and surgical interventions. This solidified the idea and the feasibility to establish a cardiac echo network within Guatemala.[6]

IMO sought and was awarded grants from Heineman-Robicsek Foundation, Inc., Edwards Lifesciences Foundation, and Heineman Foundation of New York,- to cover the cost of education, training, and equipment.

Over the course of 5-years, nurses trained in echo sonography analogously to the previous training program. Consequently, the original trainee eventually became the trainer with oversight by UNICAR and SHVI Cardiologists. At the conclusion of each sonographer training, the IMO program donated a cardiac echo machine, computer, and other equipment to establish the new ECHO station. Each sonographer performs the scans, the images are sent to the computer and then electronically transferred to UNICAR for interpretation, and backup support is provided by SHVI. Diagnosis and treatment options are relayed to the primary care physician at the rural public hospital.

Ten cardiac echo sonographers have been trained, and stations have been established at rural public hospitals throughout Guatemala. Known as the Nan Van Every Cardiology Diagnostic Network (Nan Van Every CDN), there are a total of sixteen diagnostic stations throughout Central America and the Caribbean.

Simultaneously while IMO was working toward expanding the cardiology reach in Guatemala, the initial stages of a cardiac program in Belize was underway. There are over 400,000 multi-ethnic people living in Belize, and according to the Statistical Institute of Belize, 52% of the population lives in poverty. Cardiovascular disease is the leading cause of death among non-communicable diseases.[7]

In 2009, IMO assessed the cardiology needs in Belize and found that the country was about half a century behind in cardiovascular care. There was a need for diagnostic and interventional cardiology, as well as a cardiothoracic surgical program.

Through the support of Heineman-Robicsek Foundation, Inc., Edwards Lifesciences Foundation, and Heineman Foundation of New York, IMO began to address the cardiovascular care shortcomings in Belize.

In 2011 IMO began working with Karl Heusner Memorial Hospital Authority (KHMHA) in Belize City, the only tertiary care facility in Belize, and

Dr. Adrian Coye, the only cardiothoracic surgeon in the country. Medical equipment and supplies to establish the cardiac program were donated to KHMHA. Among the medical equipment donations were two cardiac echo stations that were established in Belize City and San Ignacio. Additionally, volunteer teams from SHVI perform diagnostic and interventional cardiac catheterizations, and supported Dr. Coye with cardiac surgeries.

While UNICAR was fully sustainable, the echo network was performing well, and the cardiac program in Belize was gaining traction, both UNICAR and KHMHA believed that more could be done to reach the most vulnerable in the rural areas.

Leveraging the Nan Van Every CDN, in 2015 IMO initiated the first free public cardiac screening events ever held in Belize and Guatemala. The screenings are modeled after SHVI's Heart of a Champion that is held annually in Charlotte, North Carolina. The scope and aim of the Guatemalan and Belizean programs are to provide a pathway for reaching disenfranchised individuals with unknown risk factors associated with cardiovascular diseases, as well as identifying potential and confirmed heart conditions.

In Guatemala, the screenings are held at the rural public hospital or nearby public clinics where a cardiac echo station resides. Similarly, in Belize the screenings are held at rural public hospitals or clinics throughout the country.

Prior to the screenings, community healthcare providers at the rural public hospitals and clinics attend lectures on cardiovascular and structural heart diseases and associated contributing factors. There is a separate meeting to discuss logistics for the events and identification of healthcare personnel who will assist with the screenings. The events are also supported by volunteers from SHVI, Carolinas College of Health Sciences and pre-medical and public health students from U.S. based universities.

Stations are set up for the comprehensive screenings: (1) demographic, family and individual health history is gathered; (2) vital signs are taken, including height, weight, temperature, SpO2 (oxygen saturation), blood pressure and glucose testing; (3) participants are seen by a primary care physician who reviews the preliminary information; (4) participants are sent for electrocardiogram; (5) participants are sent for cardiac echo; (6) participants are seen by a cardiologist who reviews all collected data, examines the patient and explains the results from tests performed; (7) participants and any accompanying family members and friends are educated on the risk factors, signs, and symptoms, as well as healthy eating habits, smoking cessation, and more to encourage a healthy lifestyle.

Participants in Guatemala with a suspected heart issue are referred to the local public hospital where a cardiac echo station is located for a more comprehensive evaluation. The completed tests are digitally forwarded via the Nan Van Every CDN for interpretation by cardiologists at UNICAR. In Belize, participants are sent to KHMHA in Belize City. Findings are discussed with the local primary care physician, after which appropriate action is determined.

Public cardiac screening events bring heart disease to the forefront in communities where there is little to no previous access and clinicians are educated to identify heart problems. What began as an echo network to provide cardiac screenings, diagnosis, and treatment to the most vulnerable population, has grown beyond individual echocardiographic stations. The network, combined with public screenings, have yielded over 38,000 patients screened, diagnosed, and/or treated since 2011. This has led to a full breadth of cardiovascular diagnoses including hypertension, coronary artery disease, congenital heart disease, and structural heart disease. Rheumatic heart disease constitutes a significant portion of structural heart diseases resulting as a long-term consequence of acute rheumatic fever which continues to be a problem among low and middle-income countries. Ten percent of those screened over the 5-year period were found to have significant cardiovascular disease.

The success of Unidad de Cirugía Cardiovascular de Guatemala (UNICAR) in Guatemala City, and the cardiology and cardiac surgical programs at Karl Heusner Memorial Hospital Authority in Belize, and the Nan Van Every Cardiology Diagnostic Network, are cornerstones to scaling expansion, providing access for individuals who have little, if any recourse to seek cardiac care, and is the basis for knowledge about cardiac diseases, signs, symptoms, and prevention. Such efforts will allow potential access for medical and surgical interventions, hopefully offering a potential reduction in mortality and morbidity from cardiovascular diseases. Leveraging local public clinics, hospitals, and the Nan Van Every CDN as adjuncts to provide free public screenings has brought about awareness, education, and the capacity to capture even more undiagnosed and untreated patients, particularly the most vulnerable.[Figure 1, 2]

Figure legends

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