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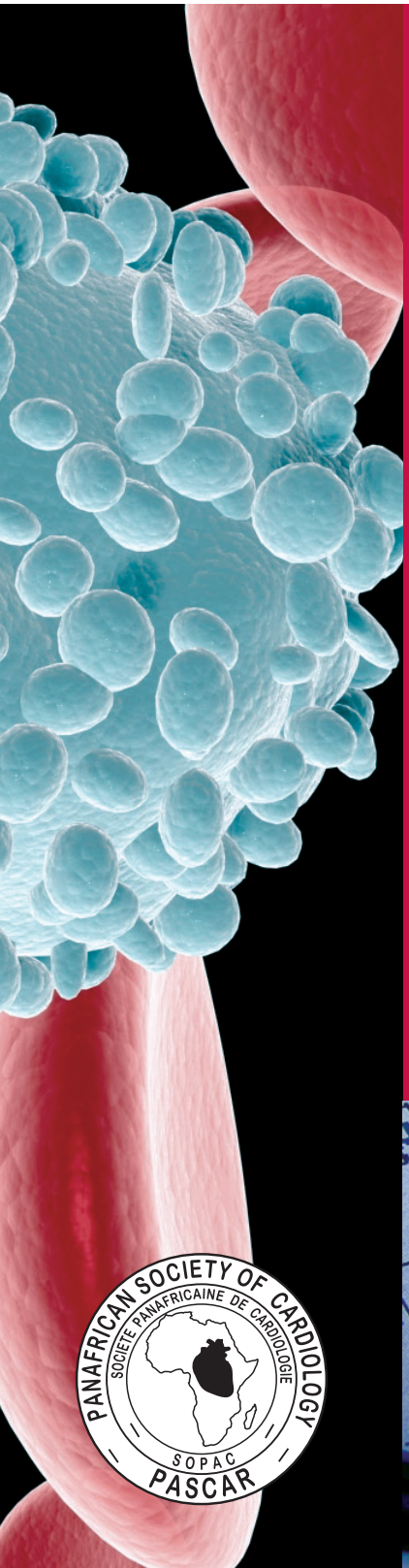

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FINANCIAL & PRODUCTION CO-ORDINATOR
ELSABÉ BURMEISTER
Tel: 021 976 8129
Fax: 086 664 4202
Cell: 082 775 6808
e-mail: elsabe@clinicscardive.com

PRODUCTION EDITOR
SHAUNA GERMISHUIZEN
Tel: 021 785 7178
Cell: 083 460 8535
e-mail: shauna@clinicscardive.com

CONTENT MANAGER
MICHAEL MEADON (Design Connection)
Tel: 021 976 8129
Fax: 0866 557 149
e-mail: michael@clinicscardive.com

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Postal address: PO Box 1013, Durbanville, RSA, 7551

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Editorial

The prevalence of congenital heart disease: we need to work towards getting more data

John Lawrenson

In 2020, 80% of children with congenital heart disease will survive into adulthood if the abnormality is recognised early and the child is offered appropriate surgery or intervention. Due to many competing health needs, there are many barriers to obtaining effective treatment in many parts of the world. One of the barriers is poor recognition of disease. It is therefore essential that the contribution of congenital heart disease to the burden of disease in a given area is well documented.

In this issue (page 257), Mazhani and colleagues describe the patients seen with congenital heart disease at the major referring hospital in Botswana over a two-year period, starting in January 2010.[1] By using a second, shorter time period in 2014 as a comparator, the authors estimated that the prevalence of congenital heart disease in Botswana is between 2.8 and 4.95 per 1 000 live births.

Determining the incidence and prevalence of congenital heart disease offers the epidemiologist a unique set of challenges. The diagnosis of 'a gross structural abnormality of the heart or intrathoracic great vessels'[2] is not only dependent on the tools used to define the abnormality but also on mode of presentation. In most instances, the best tool to describe the occurrence of new cases of children with congenital heart disease is actually the prevalence of congenital heart disease in children from birth to one year of age rather than the incidence at birth.[3]

The authors of the most recent publication of the Global Burden of Disease collective on congenital heart disease[4] estimate that the global birth prevalence of congenital heart disease is 18/1 000 live births; the prevalence in southern sub-Saharan Africa is around 20/1 000 live births.

A systematic review including 260 publications published in 2019[5] concluded that the global birth prevalence of congenital heart disease was 9.410/1 000 live births at the end of 2017. The authors of this article and those of a systematic review from 2010[6] pointed out that data from Africa are poor.

The difference between the global burden of disease data and the systematic review is probably related to the methodology used by the global burden of disease group where multiple tools, including sophisticated mathematical modelling, are used to make up for the lack of 'conventional' data.[4]

Paediatric Cardiology Service of the Western Cape; Department of Paediatrics and Child Health, Stellenbosch University; Red Cross War Memorial Childrens' and Tygerberg Hospitals, Cape Town, South Africa
John Lawrenson, MB BCh, FCP (SA), MMed (Int),
john.lawrenson@uct.ac.za

Why is it important to obtain accurate data on congenital heart disease in Africa?

Julien Hoffman, the leading epidemiologist who died in June 2020, published a 'thought experiment' in this journal in 2013,[7] where he pointed out that if a figure of 8/1 000 is applied to the younger and more fertile population of Africa, about 335 000 children with congenital heart disease would be born every year in Africa out of a total of 1.3 million children worldwide.

The infant and under-five mortality data of a country could generally be considered to be effective markers for the social determinants of health of that community. As socio-economic conditions improve, fewer children will die from infectious diseases.[4] In many countries in Europe, for example, congenital heart disease is the leading cause of under-one-year mortality after deaths resulting from premature birth.[4]

As socio-economic conditions improve in our part of the world, more children with congenital heart disease should be recognised. Currently it is possible that many children with severe (yet potentially treatable) congenital heart disease die and their deaths are ascribed to septicaemia or respiratory disease. As access to cardiac surgery improves in a country, the value of early diagnosis of treatable disease becomes obvious. In addition, survivors with untreated congenital heart disease become adults who are chronically ill.[8]

Why are good data so hard to obtain?

As a result of improvements in echocardiography, the recognition of congenital heart disease has improved, and the prevalence figures have tripled since the 1950s.[6] The majority of children with congenital heart disease (> 65%) do not have other phenotypic abnormalities.[9] Determining the presence of congenital heart disease at birth in all children would therefore depend on routine, high-quality foetal ultrasound examination or post-natal echocardiography in all children, not only children with obvious genetic abnormalities.

The best estimate of the birth prevalence of congenital heart disease in a given community would require the performance of a prospective study involving many thousands of participants. About a third of children (3–4/1 000 live births) with congenital heart disease have severe disease and will most likely die from the condition in the first year of life if left untreated. Therefore, small prevalence studies (such as the study of Mahzani *et al*. in this issue)[1] with a median population age of 1.3 years are likely to miss critically ill patients who have died. In addition, as noted by the authors, children referred for evaluation in this study were symptomatic; children with large atrial septal defects for example, may not have been seen.

Is the prevalence of congenital heart disease in Africa less than elsewhere?

The increasing prevalence of congenital heart since the 1950s is ascribed to better recognition of less-severe disease. Worldwide, data are consistent, and it would be surprising if the prevalence of a congenital condition is truly half that of the rest of the world. As indicated above, the global burden of disease data would suggest that data from Africa are equivalent to the rest of the world. More recent studies, some of which are spin-offs from screening studies for rheumatic heart disease, would suggest that this is the case. Ekure *et al*., for example, documented a prevalence of 9.410/1 000 in school-going children in Nigeria,[10] with a median age of 11 years.

How can better data be obtained?

Prospective patient registries (as suggested by Mahzani *et al*.) may offer a good solution. In a small country such as Botswana with one major referral hospital, it may be easier to link the data in a registry to birth data and get a better idea of prevalence. The performance of prospective prevalence studies in newborns (ideally as regional research projects) would be the best way of showing the community of paediatricians that children with congenital heart disease are not rare.

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Cocoa may improve walking in people with peripheral artery disease: small study

In a small study of 44 peripheral artery disease patients over age 60 years, those who drank a beverage containing flavanol-rich cocoa three times a day for six months were able to walk up to 42.6 metres further in a six-minute walking test, compared to those who drank the same number and type of beverages without cocoa. Those who drank the flavanol-rich cocoa also had improved blood flow to their calves and some improved muscle function compared to the placebo group.

Peripheral artery disease or PAD, a narrowing of the arteries that reduces blood flow from the heart to the legs, affects over 8.5 million people 40 years of age and older in the USA. The most common symptoms are pain, tightness, cramping, weakness or other discomfort in leg muscles while walking.

'Few therapies are available for improving walking performance in people with PAD,' said lead study author Dr Mary McDermott, the Jeremiah Stamler professor of medicine and preventive medicine at the Feinberg School of Medicine at Northwestern University in Chicago. 'In addition to reduced blood flow to the legs, people with peripheral artery disease have been shown to have damaged mitochondria in their calf muscles, perhaps caused by the reduced blood flow. Mitochondria are known as the powerhouse of the cell, converting food to energy. Previous research has shown that better mitochondrial health and activity are associated with better walking performance and improving the health of damaged mitochondria could lead to walking improvements.'

Researchers hypothesised that epicatechin, a major flavanol component of cocoa, may increase mitochondrial activity and muscle health in the calves of patients with lower-extremity PAD, potentially improving patient walking ability. Epicatechins and flavanols also have the potential to improve blood flow.

Study participants were randomly assigned to drink milk or water mixed with the contents of a powder packet containing flavanol-rich cocoa (15 g of cocoa and 75 mg of epicatechin daily) or a placebo powder packet without cocoa or epicatechin, three times daily over six months. Walking performance was measured at the beginning of the study and at six months, with a six-minute walking measured test twice: 2.5 and 24 hours after drinking the beverage.

continued on page 235 …

Cardiovascular Topics

A new inflammatory marker: elevated eosinophil-to-lymphocyte ratio associated with presence and severity of isolated coronary artery ectasia

Mücahid Yilmaz, Hidayet Kayançiçek, Hasan Korkmaz, Nevzat Gözel, Mehmet Nail Bilen, Özlem Seçen, Pinar Öner, Ökkeş Uku, Suat Demirkiran, Yusuf Çekici, Orkun Eroğlu, Kurtoğlu Ertuğrul

Abstract

Objectives: The pathophysiology of isolated coronary artery ectasia (CAE) involves atherosclerosis and inflammation. Eosinophils and lymphocytes have been found to play a significant role in inflammation, atherosclerosis and endothelial dysfunction. Many studies have explored the relationship between isolated CAE and systemic inflammation. However, there are no data regarding the relationship between eosinophil-to-lymphocyte ratio (ELR) and isolated CAE. Therefore, this study analysed the relationship between ELR and isolated CAE.

Methods: All patients who underwent coronary angiography between January 2009 and June 2018 were investigated retrospectively. Of 16 240 patients, 232 patients with isolated CAE (141 males) and 247 age- and gender-matched control subjects (130 males) with normal coronary angiography (NCA) were enrolled in this study. Baseline demographic and laboratory data were obtained from the hospital database. The severity of isolated CAE was determined according to the Markis classification, vessel count and diffuseness of ectasia.

Results: Patients with angiographic isolated CAE had significantly elevated white blood cell (WBC) and eosinophil counts and ELR values compared to patients with NCA [8.11 ± 1.75 vs 7.49 ± 1.80 × 10^9 cells/l, $p < 0.0001$; 0.22 (0.13–0.32) vs 0.19 (0.12–0.28) × 10^9 cells/l, $p = 0.02$; 0.11 (0.06–0.17) vs 0.08 (0.05–0.12), $p < 0.0001$. The ELR value for Markis I was significantly higher than for Markis IV ($p = 0.04$), and three-vessel isolated CAE was significantly higher than one-vessel isolated CAE ($p = 0.04$). Additionally, the ELR value for diffuse ectasia (Markis class I, II and III) was significantly higher compared to focal (Markis class IV) ectasia ($p = 0.02$). In receiver operating characteristics (ROC) analyses, it was determined that an ELR value > 0.099, measured in isolated CAE patients at application, had a predictive specificity of 60.3% and a sensitivity of 56.5% (area under the curve: 0.604, 95% confidence interval: 0.553–0.655, $p < 0.0001$).

Conclusion: Patients with isolated CAE had higher blood eosinophil counts and ELR. Furthermore, the ELR was significantly correlated with severity of isolated CAE. These findings demonstrate that ELR may have a significant role in the aetiopathogenesis of isolated CAE.

Department of Cardiology, Elazığ Medical Park Hospital and Department of Cardiology, Istinye University, Elazığ, Turkey
Hidayet Kayançiçek, MD
Suat Demirkıran, MD

Department of Cardiology, Fırat University School of Medicine, Elazığ, Turkey
Hasan Korkmaz, MD

Department of Internal Medicine, Fırat University School of Medicine, Elazığ, Turkey
Nevzat Gözel, MD

Department of Cardiology, Elazığ Education and Research Hospital, Elazığ, Turkey
Mücahid Yilmaz, MD, mucahid.yilmaz@hotmail.com
Mehmet Nail Bilen, MD
Özlem Seçen, MD
Ökkeş Uku, MD
Yusuf Çekici, MD

Department of Microbiology, Elazığ Education and Research Hospital, Elazığ, Turkey
Pinar Öner, MD

Department of Ear, Nose and Throat, Elazığ Education and Research Hospital, Elazığ, Turkey
Orkun Eroğlu, MD

Department of Cardiology, Malatya Education and Research Hospital, Malatya, Turkey
Kurtoğlu Ertuğrul, MD

Keywords: eosinophil count, eosinophil-to-lymphocyte ratio, isolated coronary artery ectasia, inflammation

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Coronary artery ectasia (CAE) is a congenital or acquired coronary anomaly. CAE is described as the local or wide extension of a partial or entire epicedial coronary artery that is 1.5 times larger than the diameter of the adjacent

normal coronary artery.[1-5] CAE aetiology has been attributed to atherosclerosis (50% of cases), congenital malformations (20–30% of cases) and inflammatory or connective tissue disease (10–20% of cases).[6] CAE is considered a unique form of atherosclerotic cardiovascular disease. Various studies have indicated that CAE is characterised by a denser vascular inflammation than occlusive coronary artery disease.[7,8]

Some publications have reported that CAE causes coronary slow flow in the coronary arteries, resulting in thrombosis. CAE has also been suggested to cause clinical symptoms of ischaemic heart disease and myocardial infarction without occlusive coronary artery disease.[9] The ischaemic mechanism in patients with CAE has not been fully clarified, as the basic cause of ischaemia and angina is considered to be microvascular perfusion impairment. The slow or turbulent flow during vasodilation is believed to cause thrombosis in the ectatic segment or embolus formation in the distal coronary artery, resulting in ischaemia.[3] Güleç *et al*. indicated that epicardial and microvascular perfusion is destroyed in ectasia patients. The same study noted that the thrombolysis in myocardial infarction square number could be used to predict microvascular perfusion impairment when ectatic and non-ectatic arteries were compared.[10]

Eosinophil and lymphocyte cells are associated with an immune response and inflammation. A low number of lymphocyte cells is considered one of the main reasons for progression of cardiovascular disease.[11,12] Eosinophil elevation and low lymphocyte levels reflect systemic inflammation and physiological stress.[13-15] Therefore the eosinophil-to-lymphocyte ratio (ELR) is an indicator of systemic inflammation.[16,17]

Eosinophils have a significant status in endothelial dysfunction, inflammation, vasoconstriction and thrombosis.[18,19] Eosinophils stimulate platelet activation and aggregation and contribute to thrombus formation by inhibiting thrombomodulin.[20] Some publications have revealed that vascular anomalies, such as aneurysms, may be associated with hypereosinophilic syndrome.[21,22]

Can eosinophils (with their strong vasoactive and procoagulant effects) and the ELR (which is a good indicator of systemic inflammation) be associated with isolated CAE and its microvascular perfusion impairment? Although there is a small study examining the relationship between blood eosinophil concentration and CAE, no large studies that could indicate a correlation between blood eosinophil level and ELR, and CAE severity were found in the literature.[13] This study aimed to determine whether there was an association between plasma eosinophil level, ELR and the existence and severity of CAE.

Methods

Angiographic records of 16 240 Turkish patients who had coronary angiography between January 2009 and June 2018 in the Elazığ Education and Research Hospital were retrospectively investigated for the presence of isolated CAE. The study included 232 subjects with isolated CAE and 247 age- and gender-matched subjects who had normal coronary anatomy (NCA). The routine clinical and laboratory tests (complete blood count, total biochemistry values and demographic data) of the subjects were obtained from their files (Fig. 1).

The study was conducted according to the Helsinki principles, and ethical approval was obtained from the TC Firat University ethics committee. The ethics committee did not require informed written consent forms as the data are anonymous.

Coronary angiographies were performed with Siemens Axiom Artis FC diagnostic equipment using the Judkins technique (Siemens Healthcare GmbH, Forchheim, Germany).[23] Nitroglycerin was not used during the coronary angiographies.

Coronary angiography records were gained from the left and right anterior oblique cranial, anterior–posterior (AP) cranial, right anterior oblique, caudal and horizontal positions. Isohexol 350 mg/ml (Amersham Health Co, Cork, Ireland) was used for opacifity when performing the coronary angiogram; 6 ml was administered into the coronary arteries at each position. The angiography was recorded digitally with a frame rate of 25 frames/ms. The coronary artery diameters were determined by computerised quantitative angiography. These evaluations were gained by analysing the digital inputs obtained from the coronary angiographies.

Scientific quantification coronary analysis software (Siemens Healthcare Gmbh, Forcheim, Germany) was used for these procedures. The computations were obtained at the proximal, mid and distal segments of the coronary arteries to define the artery segment as ectatic. The largest diameter of the segments was taken into account.

CAE was defined as 1.5 times or more enlargement of the coronary artery compared to the adjacent coronary artery. Isolated CAE was defined as regional or widespread expansion without significant coronary artery stenosis. Angiographic stenosis of more than 50% of the coronary artery was considered as significant occlusion. Patients without significant coronary artery stenosis who had ectatic segments were included in the isolated CAE group. The characteristics of CAE were categorised as diffuse or discrete ectasia to classify the severity of CAE. Fusiform dilatations of the coronary arteries were defined as diffuse ectasia, and localised/focal vesicular or spheroidal dilatation of the coronary arteries was defined as discrete ectasia[6] (Figs 2–5).

Classification by Markis *et al*. was used to determine the distribution of CAE. This classification depends on the diffuseness of ectasia. Accordingly, patients who have isolated CAE were classified into four groups. Diffuse ectasia in two or three vessels was defined as type I, diffuse ectasia in one vessel and focal ectasia in another vessel was defined as type II, diffuse ectasia in only one vessel was defined as type III and focal ectasia was defined as type IV.[4]

The coronary angiographies were evaluated by two angiography experts who specialise in coronary angiography and had no knowledge about the history of the patients.

Study exclusion criteria: subjects with acute coronary syndrome at study entrance, significant coronary artery stenosis (angiographic stenosis > 50%) or isolated coronary slow flow, anaemia (Htc < 30%), cardiac failure, thyroid dysfunction, malignancy, chronic renal deficiency [glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2], chronic liver failure, chronic obstructive pulmonary disease and/or bronchial asthma, or were found to have used immunosuppressive therapy or steroids, or subjects who had a body mass index of > 30 kg/m^2 were excluded. Subjects who had a recent past of an acute infection and/or high body temperature > 37.2°C or an inflammatory or allergic disease were also excluded from the analysis.

Subjects who had taken antihypertensive medication and

Fig. 1. Flow-chart diagram of subject inclusion.

had systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg were defined as hypertensive. Diabetes mellitus was defined as having a fasting blood glucose level > 126 mg/dl (6.99 mmol/l) or current use of a diet or drug to lower blood glucose level. Hyperlipidaemia was defined as having total serum cholesterol > 200 mg/dl (5.18 mmol/l), low-density

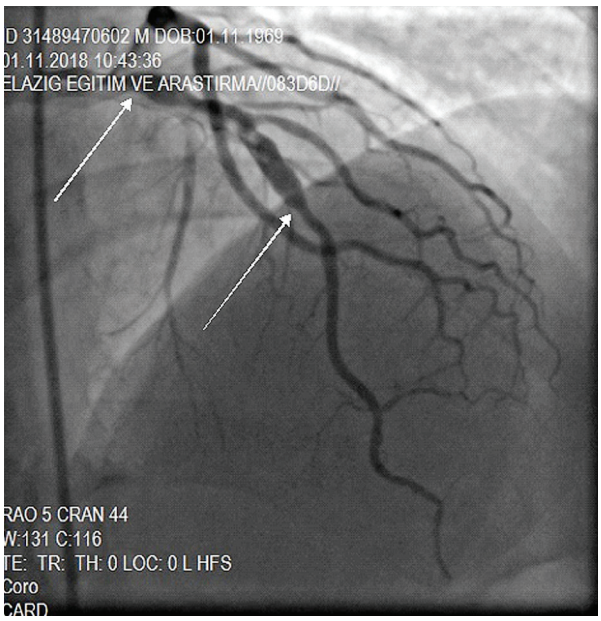

Fig. 2. Demonstration of a fusiform ectasia in the left anterior descending artery in the region between the white arrows.

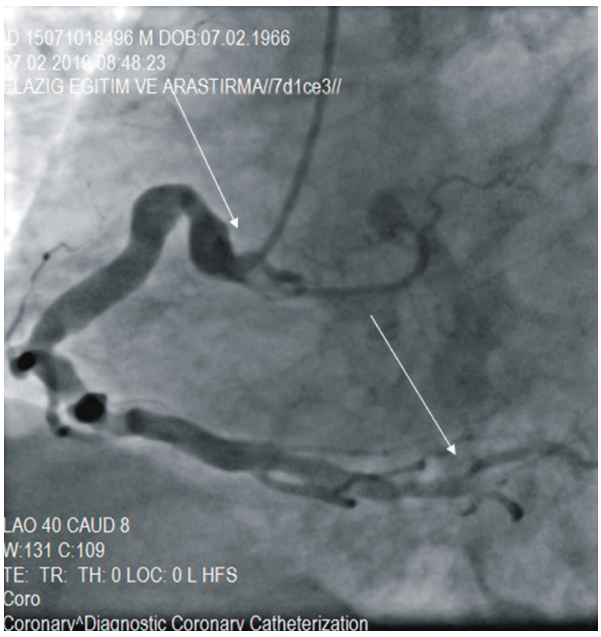

Fig. 4. Demonstration of a fusiform ectasia in the right coronary artery in the region between the white arrows.

lipoprotein cholesterol > 130 mg/dl (3.37 mmol/l), triglycerides > 150 mg/dl (1.69 mmol/l) or the use of a lipid-lowering drug.

Statistical analysis

The results were statistically evaluated with SPSS 16.0 (SPSS Inc, Chicago, IL, USA) analysis program for Windows. The distribution of the results was determined with the Kolmogorov–Smirnov test. Continuous variables are shown as means with standard deviations or medians in the 25th–75th percentiles. Categorical variables are represented as numbers with percentages. Continuous data were analysed with the Student's *t*-test for normally distributed variables and the Mann–Whitney *U*-test was used for non-normally distributed variables. Aside from white blood cells (WBC) and calcium, all continuous

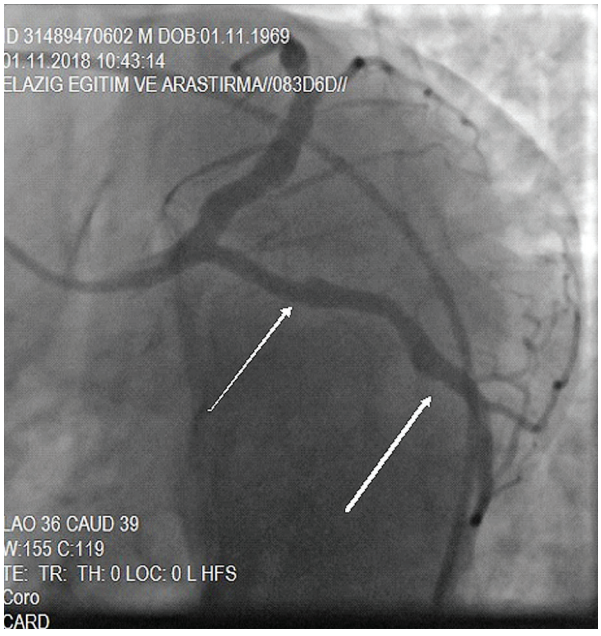

Fig. 3. Demonstration of a fusiform ectasia in the circumflex artery in the region between the white arrows.

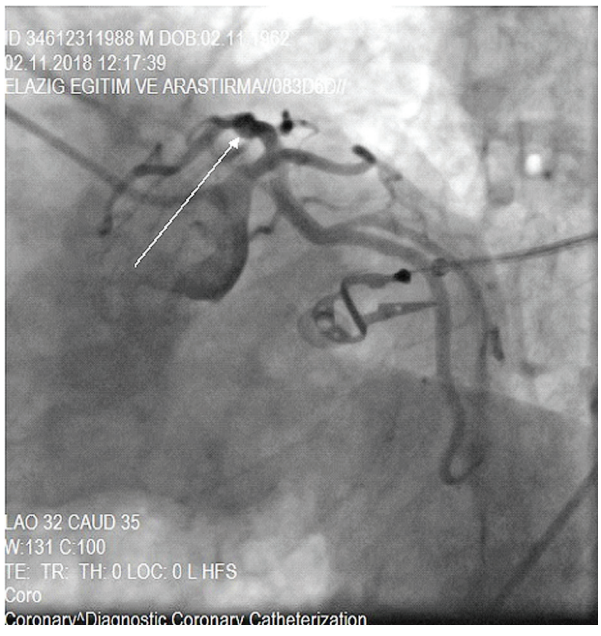

Fig. 5. Demonstration of a saccular ectasia in the left anterior descending artery, shown with a white arrow.

Table 1. Inter-group comparison of demographic and laboratory data

Parameters	*Isolated CAE (232)*	*NCA (247)*	*p-value*
Gender, *n* (male/ female)	141/91	130/117	0.07
Hypertension, *n* (%)	72/232 (31.0)	64/247 (25.9)	0.21
Hyperlipidaemia, *n* (%)	82/232 (35.3)	71/247 (28.7)	0.12
Diabetes mellitus, *n* (%)	50/232 (21.6)	49/247 (19.8)	0.64
Smoking, *n* (%)	79/232 (34.1)	76/247 (30.8)	0.44
Age (year)	56.0 (53.0–60.0)	55.0 (52.0–59.0)	0.15
Platelets ($\times 10^9$ cells/l)	257.0 (223.0–296.75)	250.0 (209.0–292.0)	0.10
Glucose (mg/dl)	100.0 (89.25–110.30)	99.0 (90.0–109.0)	0.25
(mmol/l)	5.55 (4.95–6.12)	5.49 (5.0–6.05)	
Triglycerides (mg/dl)	133.5 (100.25–190.25)	131.7 (95.0–152.0)	0.09
(mmol/l)	1.51 (1.13–2.15)	1.49 (1.07–1.72)	
LDL-C (mg/dl)	115.0 (92.0–134.25)	112.0 (88.0–125.0)	0.06
(mmol/l)	2.98 (2.38–3.48)	2.90 (2.28–3.24)	
Total cholesterol (mg/dl)	186.0 (160.0–213.5)	185.2 (161.0–203.0)	0.65
(mmol/l)	4.82 (4.14–5.53)	4.80 (4.17–5.26)	
HDL-C (mg/dl)	42.0 (36.0–49.0)	47.0 (40.9–55.2)	< 0.0001
(mmol/l)	1.09 (0.93–1.27)	1.22 (1.06–1.43)	
Eosinophils ($\times 10^9$ cells/l)	0.22 (0.13–0.32)	0.19 (0.12–0.28)	0.02
Lymphocytes ($\times 10^9$ cells/l)	2.05 (1.62–2.54)	2.18 (1.80–2.90)	0.002
ELR	0.11 (0.06–0.17)	0.08 (0.05–0.12)	< 0.0001
Haemoglobin (g/dl)	14.4 (13.6–15.1)	14.1 (13.5–15.0)	0.09
Haematocrit (%)	43.1 (41.0–45.5)	42.0 (41.0–45.0)	0.07
White blood cells ($\times 10^9$ cells/l)	8.11 ± 1.75	7.49 ± 1.80	< 0.0001#
Urea (mg/dl)	30.0 (25.0–36.0)	29.2 (23.7–35.0)	0.10
Creatinine (mg/dl)	0.67 (0.54–0.78)	0.66 (0.55–0.77)	0.50
Sodium (mmol/l)	140.0 (138.0–142.0)	140.0 (138.0–142.0)	0.36
Potassium (meq/l)	4.3 (4.0–4.6)	4.3 (4.1–4.6)	0.40
Calcium (mg/dl)	9.21 ± 0.49	9.27 ± 0.47	0.23#

CAE: coronary artery ectasia; NCA: normal coronary arteries; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ELR: eosinophil-to-lymphocyte ratio.
#Normality of the distribution was evaluated by the Kolmogorov–Smirnov test, and the Mann–Whitney *U*-test was applied to compare for continous variables except for white blood cells and calcium.

variables were not distributed normally, and the Mann–Whitney *U*-test was used to compare these variables. Categorical data were analysed using the chi-squared test. The Bonferroni test was used to validate one-way ANOVA analysis for comparison between groups (among Markis I, II, III and IV and among one-, two- and three-vessel disease). The receiver operating characteristics (ROC) test was used to estimate the sensitivity and specificity of ELR and its optimal cut-off value. Correlation analyses were fulfilled using Spearman's correlation test; $p < 0.05$ was considered to indicate statistical significance.

Results

The records of 16 240 patients who underwent coronary angiography were retrospectively screened, of whom 232 patients with isolated CAE (141 males) and 247 age- and gender-matched subjects with NCA (130 males) were detected. It was observed that WBC and eosinophil counts and ELR for the isolated CAE group were significantly higher than in the NCA group 8.11 ± 1.75 vs 7.49 ± 1.80 × 10^9 cells/l, $p < 0.0001$; 0.22 (0.13–0.32) vs 0.19 (0.12–0.28) × 10^9 cells/l, $p = 0.02$; 0.11 (0.06–0.17) vs 0.08 (0.05–0.12) $p < 0.0001$, respectively (Table 1, Fig. 6). However, high-density lipoprotein cholesterol (HDL-C) level and lymphocyte count for the NCA group were significantly higher than in the isolated CAE group [47.0 (40.9–55.2) vs 42.0 (36.0–49.0) mg/dl = 1.22 (1.06–1.43) vs 1.09 (0.93–1.27) mmol/l, $p < 0.0001$; 2.18 (1.80–2.90) vs 2.05 (1.62–2.54) × 10^9 cells/l, $p = 0.002$, respectively) (Table 1).

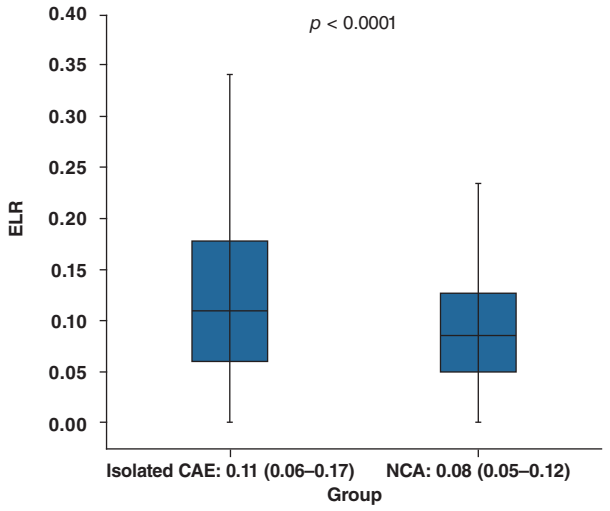

Fig. 6. Comparison of ELR between isolated CAE and NCA.

Eosinophil and lymphocyte counts were not significantly different among patients with one-, two- and three-vessel isolated CAE (Table 2). Likewise, the eosinophil and lymphocyte counts were not significantly different among Markis types I, II, III and IV (Table 3). However, the ELR for three-vessel isolated CAE was significantly higher than for one-vessel isolated CAE ($p = 0.04$) (Table 2). Furthermore, the ELR for Markis I was significantly higher than for Markis IV ($p = 0.04$) (Table 3, Fig. 7).There were no statistically significant differences between focal (Markis type IV) and diffuse ectasia (Markis type I, II and III) in terms of eosinophil count ($p = 0.54$) (Table 4). In contrast, the ELR for diffuse ectasia (Markis type I, II and III) was significantly higher compared to focal (Markis type IV) ectasia, and the lymphocyte count for diffuse ectasia (Markis types I, II and III) was significantly lower than for focal (Markis type IV) ectasia ($p = 0.02$; $p = 0.001$, respectively) (Table 4).

Table 2. Eosinophil and lymphocyte counts and ELR values according to vessel count

Vessels	*Noun*	*Eosinophil count ($\times 10^9$ cells/l)*	*Lymphocyte count ($\times 10^9$ cells/l)*	*ELR value*
One vessel	135	0.22 ± 0.12	2.23 ± 0.81	0.11 ± 0.07
Two vessels	42	0.26 ± 0.14	2.05 ± 0.59	0.14 ± 0.10
Three vessels	55	0.24 ± 0.12	1.96 ± 0.79	0.14 ± 0.09

All *p*-values for eosinophil and lymphocyte counts > 0.5.
p-value for ELR (between one and three vessels): 0.04.

Table 3. Eosinophil and lymphocyte counts and ELR values according to the Markis classification

Markis classification	*Noun (%)*	*Eosinophil count ($\times 10^9$ cells/l)*	*Lymphocyte count ($\times 10^9$ cells/l)*	*ELR value*
Type I	51 (21.98)	0.25 ± 0.12	1.93 ± 0.79	0.15 ± 0.10
Type II	38 (16.38)	0.24 ± 0.12	1.98 ± 0.60	0.14 ± 0.09
Type III	41 (17.67)	0.21 ± 0.13	2.15 ± 0.94	0.11 ± 0.07
Type IV	102 (43.96)	0.23 ± 0.13	2.29 ± 0.73	0.11 ± 0.08

All *p*-values for eosinophil and lymphocyte counts > 0.5.
p-value for ELR (between Markis type I and IV): 0.04.

Table 4. Comparison of ELR values, and eosinophil and lymphocyte counts between focal (Markis type IV) and diffuse ectasia (Markis type I, II, III)

Counts	*Focal ectasia (n = 102)*	*Diffuse ectasia (n = 130)*	p-*value*
Eosinophil count (× 10^9 cells/l)	0.20 (0.12–0.32)	0.22 (0.14–0.33)	0.54
Lymphocyte count (× 10^9 cells/l)	2.21 (1.81–2.67)	1.93 (1.55–2.36)	0.001
ELR	0.10 (0.05–0.15)	0.12 (0.06–0.18)	0.02

Table 5. Spearman's correlation analysis between vessel count, extension of isolated CAE and Markis classification, and eosinophil and lymphocyte counts and ELR value.

	Eosinophil count		*Lymphocyte count*		*ELR value*	
	r	p	r	p	r	p
Vessel count	0.107	0.103	–0.127	0.052	0.185	0.005
Extension of isolated CAE (as diffuse)	0.040	0.544	–0.211	0.001	0.145	0.027
Markis classification	–0.066	0.314	0.211	0.001	–0.182	0.005

No significant correlations were observed between eosinophil count and any Markis classification ($p = 0.314$, $r = –0.066$) or between eosinophil count and diffuse ectasia ($p = 0.544$, $r = 0.040$) (Table 5). Likewise, there was no correlation between eosinophil count and vessel count ($p = 0.103$, $r = 0.107$) (Table 5). However, the ELR significantly correlated with the Markis classification and diffuse ectasia and vessel count ($p = 0.005$, $r = –0.182$; $p = 0.027$, $r = 0.145$; $p = 0.005$, $r = 0.185$, respectively), and the lymphocyte count significantly correlated with the Markis classification and diffuse ectasia ($p = 0.001$, $r = 0.211$; $p = 0.001$, $r = –0.211$, respectively) (Table 5).

ROC curve analysis revealed that the specificity of an ELR > 0.099 (measured before coronary angiography) in predicting isolated CAE was 60.3%, and the sensitivity was 56.5% [area under the curve (AUC): 0.604, 95% CI: 0.553, 0.655; $p < 0.0001$) (Fig. 8). No differences were observed between the two groups with regard to other analysed laboratory data (Table 1).

Discussion

The analysis revealed that ELR, and eosinophil and WBC counts were significantly higher in the isolated CAE group compared to the NCA group. However, HDL-C levels and lymphocyte counts were significantly lower for the isolated CAE group than for the NCA group (Table 1). In addition, the study revealed no relationship between eosinophil count and number of ectatic vessels, the diffuseness of the ectatic segment and Markis classification. However, it was found that ELR values were significantly related to the stated classifications.

Coronary artery ectasia may be acquired or congenital.[24-28] The associated diseases reported in its aetiology are 50% atherosclerosis, 20–30% congenital diseases and 10–20% inflammatory or connective tissue diseases.[6] The association between inflammation and CAE has been revealed using well-recognised inflammatory markers such as WBC, neutrophil and monocyte counts, and interleukin-6, matrix metalloproteinase, tumour necrosis factor-α and C-reactive protein (CRP) levels.[29,30]

The ischaemic mechanism in patients with CAE has not been fully understood. However, it is accepted that the leading cause of ischaemia and angina is impaired microvascular perfusion. Slow or turbulent flow in dilated vessels has been reported to cause ischaemia by causing thrombosis in the ectatic segment and embolism in the distal coronary artery.[3] Eosinophils are loaded with many granule-associated molecules that cause vascular thrombosis and endothelial damage. Major basic protein and eosinophil peroxidase, as the most well-known of these granules, are also platelet agonists and play an important role in thrombus formation.[20] Eosinophils may additionally cause thrombosis by secreting tissue factor and stimulating platelets and leukocytes, in addition to secreting major basic protein and eosinophil peroxidase.[20,31]

These three proteins (tissue factor, basic protein and eosinophil peroxidase) contribute considerably to thrombus formation by stimulating thrombocytes and inhibiting thrombomodulin.

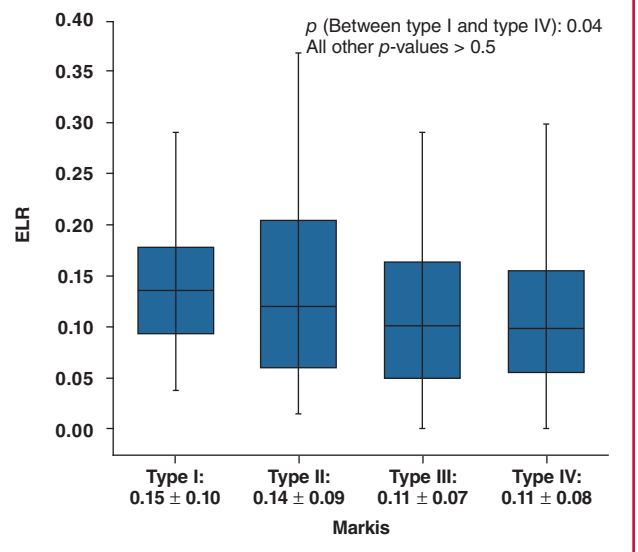

Fig. 7. Comparison of ELR among Markis type I, II, III and IV.

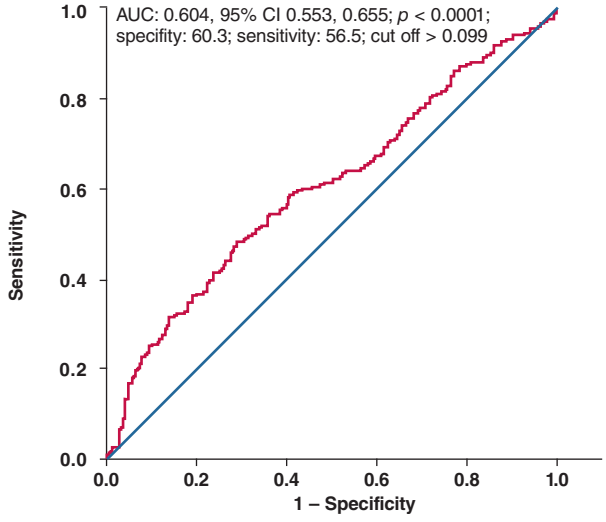

Fig. 8. ELR ROC analysis between isolated CAE and NCA. AUC: area under the curve; CI: confidence interval; ELR: eosinophil-to-lymphocyte ratio; ROC: receiver operating characteristics.

It has been reported that eosinophils and their granule-associated molecules have been isolated from necrotic and thrombotic lesions, and these structures were extracted from small arterial walls, especially after acute ischaemic damage to the endocardium. These findings suggest that eosinophils may cause inflammation, thrombosis and embolus-induced vascular damage.[32-34]

It has been reported that eosinophils are related to arterial tortuosity, thrombosis, cardiac syndrome X, dilatation and aneurysm in patients with hypereosinophilic syndromes.[35,36] Cytotoxic secretions secreted from eosinophils have been suggested to cause direct medial destruction leading to aneurysmal formation or spontaneous intimal dissection and sudden cardiac death.[37] This suggests that eosinophil secretion may be one of the causes of vascular injury, therefore eosinophils may affect the cardiovascular system via an inflammatory mechanism.

Lymphocytes are related to the immune response and systemic inflammation. Stress-induced low lymphocyte levels (lymphopaenia) have been found to be associated with inflammatory conditions and adverse cardiovascular events.[11,12] Low lymphocyte counts might result from increased cortisol levels that induce apoptosis specifically in lymphocytes but also increase the total WBC count.[38] Eosinophil elevation and low lymphocyte levels reflect systemic inflammation and physiological stress and contribute to the development of cardiovascular disease.[13-15,20]

A strong correlation was found between CAE and low HDL-C levels, and this study suggests that low HDL-C levels could lead to isolated CAE.[39] Several studies have previously reported that HDL-C levels decrease in the presence of systemic inflammation, and systemic and vascular inflammation impair the structure of HDL-C and disrupt its function, reducing its protective effect on the vascular endothelium.[40-43]

In this study, we observed that HDL-C levels were lower in the isolated CAE group than in the NCA group (Table 1). This finding may be reflective of the systemic and vascular inflammation consistent with previous studies. Moreover, the low HDL-C levels observed in the isolated CAE group may be considered one of the mechanisms responsible for endothelial dysfunction and vascular destruction. Nevertheless, larger studies that focus only on this issue are necessary to draw more concrete conclusions.

Increased WBC count, WBC sub-type and sub-type ratios have been accepted as important inflammatory markers in forecasting cardiovascular outcomes.[11,44] Elevated eosinophil count and ELR values and decreased lymphocyte levels are associated with systemic inflammation and atherosclerosis.[13,16,17,45,46] In some studies, the relationship between some haematological parameters actively functioning in inflammation, such as neutrophils, lymphocytes, monocytes and eosinophils, and parameters such as the monocyte-to-HDL-C ratio (MHR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) and their relationship with coronary artery ectasia has been revealed.[13,14,47-49] However, as far as we know, the relationship between CAE and ELR has not previously been studied.

Based on the role of inflammation in the aetiopathogenesis of isolated CAE and in light of the study results, we hypothesised that ELR may be associated with isolated CAE. The present study revealed an increased eosinophil count and a decreased lymphocyte count in isolated CAE patients compared to subjects with NCA (Table 1). However, we did not observe a significant association between eosinophil count and Markis classification, diffuse ectasia or vessel count (Tables 2–5). Likewise, we did not observe a significant difference between lymphocyte count and Markis classification or vessel count (Tables 2–5). However, the study showed that ELR was significantly associated with these parameters (Tables 2-5). In addition, correlation analyses revealed a significant association between lymphocyte count and Markis classification, diffuse ectasia and vessel count (Table 5).

This indicates that the eosinophil count was higher in isolated CAE compared to NCA but was not correlated with the severity of CAE. However, lymphocyte count and ELR value not only increased in isolated CAE patients but also were significantly correlated with the severity of isolated CAE. The data obtained in this study suggest that an analysis of only lymphocyte and eosinophil levels may not provide reliable results, whereas the use of ELR as a systemic inflammatory marker may be more reliable. Although the sensitivity and specificity of ELR for predicting isolated CAE were low in the ROC analysis, all correlation analyses in other areas found that ELR indicated the presence and severity of isolated CAE.

Since the study was designed retrospectively, data on acute or chronic diseases that may affect ELR were obtained in accordance with patient statements. Some patients may not have been aware of inflammatory diseases such as allergic rhinitis, conjunctivitis or atopic dermatitis, or they may not have declared these diseases. Because advanced equipment such as intravascular ultrasound could not be used in this study, the coronary arteries of the subjects examined could not be confirmed to be completely normal. These factors may explain the results of the ROC analysis.

Limitations

Although there may be an atherosclerotic plaque over large segments, the related vessel can be observed as normal angiographically.[50,51] In this study, it was not possible to confirm that the coronary arteries were completely normal because a device such as intravascular ultrasound could not be used. Second, as the study was retrospective, inflammatory markers such as CRP could not be investigated or compared to ELR.

Conclusions

The results of this study may contribute to the aetiopathogenesis of isolated CAE. As a new, simple, effortless and cost-effective inflammatory marker, ELR may be able to forecast isolated CAE in daily clinical practice. Increased ELR may explain the vascular destruction, endothelial dysfunction, thrombosis and distal microvascular embolisation seen in isolated CAE patients.

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Participants were also given a treadmill walking test and had the blood flow to their legs measured using magnetic resonance imaging. Participants who consented had a calf muscle biopsy to evaluate muscle health.

The cocoa used in the study is commonly available, natural, unsweetened cocoa powder, which is rich in the flavanol epicatechin, found in larger quantities in dark chocolate (> 85% cacao) than in milk chocolate. Regular chocolate would not be expected to have the same effect.

Researchers found that the patients who consumed cocoa showed significant improvement, walking an average of almost 43 m further in the six-minute walking test compared to their baseline results during the test performed at 2.5 hours after the final study beverage. Researchers also found increased mitochondrial activity, increased capillary density, and other improvements to muscle health in those who consumed the cocoa.

Patients who drank the placebo beverage had a decline of 24.2 m in their walking distance at 2.5 hours after the final study beverage, compared to their baseline results. This is consistent with other studies, in which people with PAD without treatment have declines in their six-minute walk distance over time.

Cocoa appeared to have no effect on treadmill walking performance. However, McDermott said the treadmill walking and the six-mile walking test are distinct measures of walking endurance and do not respond identically to the same therapy. The improvement in six-minute walking distance better reflects the type of walking required in daily life and therefore these results are a more relevant outcome for patients with PAD.

'While we expected the improvements in walking, we were particularly pleased to see that cocoa treatment was also associated with increased capillary density, limb perfusion, mitochondrial activity, and an additional measure of overall skeletal muscle health,' McDermott said. 'If our results are confirmed in a larger trial, these findings suggest that cocoa, a relatively inexpensive, safe and accessible product, could potentially produce significant improvements in calf muscle health, blood flow and walking performance for PAD patients.'

Limits to this pilot study include: a small sample size; an imbalance between the two study groups in the number of participants of each gender, race and in body mass index; and a lack of data for overall dietary consumption.

'Patients with PAD have difficulty walking that is as bad as people with advanced heart failure. Leg muscles don't get enough blood supply in PAD, leading to injury and in this study, cocoa appeared to be protecting the muscle and improving metabolism,' said Dr Naomi Hamburg, chair of the American Heart Association's Peripheral Vascular Disease Council and author of an editorial on the study that also appears in this issue. 'We know that exercise therapy helps people with PAD walk farther, and this early study suggests that cocoa may turn out to be a new way to treat people with PAD. We will need larger studies to confirm whether cocoa is an effective treatment for PAD, but maybe, someday, if the research supports it, we may be able to write a prescription for chocolate for our patients with PAD.'

Source: Medical Brief 2020

Echocardiographic abnormalities in children and adolescents living with human immunodeficiency virus on highly active antiretroviral treatment

Tewolde Wubayehu, Workeabeba Abebe, Endale Tefera

Abstract

Background: The availability and use of highly active antiretroviral treatment (HAART) has turned human immunodeficiency virus (HIV) into a chronic disease, allowing patients to live much longer.

Objectives: To report asymptomatic cardiac abnormalities in children and adolescents based on both conventional and tissue Doppler imaging (TDI) echocardiography.

Methods: One hundred and fifty-one patients on HAART were recruited. Demographic and clinical variables were collected through patient interviews and medical record reviews. Conventional echocardiography and TDI were performed on each patient.

Results: Mean age was 13.0 ± 3.2 (4.0–19.0) years. Eighty-three patients (55%) were female. Age at diagnosis of HIV infection was 5.7 ± 3.3 years. Age at initiation of HAART was 7.34 ± 3.54 years, while duration of HAART was 59 ± 39.1 months. On conventional echocardiography, three cases of left ventricular (LV) systolic dysfunction, two of pulmonary hypertension and one of minimal pericardial effusion were identified. Calculation of myocardial mass index (MMI) revealed that 16 patients had abnormal values. Twenty-seven (17.9%) patients had evidence of LV diastolic dysfunction and 18 (11.9%) had right ventricular (RV) diastolic dysfunction. Nineteen (12.6%) patients had tricuspid annular systolic velocity of < 9.5 cm/s, indicating asymptomatic RV systolic dysfunction.

Conclusion: While few patients had abnormalities such as reduced LV ejection fraction, pulmonary hypertension and minimal pericardial effusion detectable on conventional echocardiography, a larger proportion of patients had subtle abnormalities such as increased MMI, LV diastolic dysfunction on TDI, RV dysfunction and abnormal myocardial performance index. Such patients may need routine screening and cardiac follow up.

Department of Paediatrics and Child Health, Aksum University, Aksum, Ethiopia
Tewolde Wubayehu, MD

Department of Paediatrics and Child Health, Division of Infectious Diseases, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia
Workeabeba Abebe, MD

Department of Paediatrics and Adolescent Health, Division of Cardiology, Faculty of Medicine, University of Botswana, Gaborone, Botswana
Endale Tefera, MD, endalet2008@gmail.com

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Close to 90% of children infected with human immunodeficiency virus (HIV) live in sub-Saharan Africa.[1] Most of these children are believed to have acquired the infection via mother-to-child transmission. The availability and use of highly active antiretroviral treatment (HAART) has turned HIV into a chronic disease, allowing patients to live much longer.[2]

Cardiac abnormalities are frequent in HIV-infected children, most of whom remain asymptomatic.[3,4] Subclinical cardiac abnormalities in HIV-infected children are common, persistent and often progressive.[5-8] Various mechanisms may lead to cardiac involvement in HIV including direct cytopathic effect of the HI virus, HIV-related opportunistic infections and effects of HAART on the heart.[9] Myocarditis, dilated cardiomyopathy, inappropriate left ventricular (LV) hypertrophy/increased LV mass, impaired LV diastolic function, pericarditis and pulmonary hypertension are just some of the many forms of cardiac pathologies that HIV patients may present with.[4-8,10-13] It is also believed that the use of HAART has played a role in transforming HIV-associated heart disease from symptomatic to mild and asymptomatic conditions.[14]

Studies from sub-Saharan Africa have also reported significant incidence of cardiac involvement in HIV-infected children in both the pre-HAART and HAART era.[2,3,13-16] Of the estimated 738 976 patients living with HIV in Ethiopia, about 178 500 were believed to be children under 15 years of age. Although antiretroviral treatment (ART) has been provided free of charge in Ethiopia since 2005, ART coverage for children under 15 years of age remains one of the lowest in the world, being at 23.5% of treatment-eligible children.[17] This study reports asymptomatic cardiac abnormalities that may exist in children and adolescents, based on both conventional and tissue Doppler imaging (TDI) echocardiography.

Methods

This was a cross-sectional study of children and adolescents living with HIV who were on HAART and being followed at the Paediatric Infectious Disease Clinic of the Addis Ababa University Hospital (Tikur Anbessa Specialised Hospital), the largest referral

and teaching hospital in the country. The study was conducted between June and October 2015 on a consecutive sample of patients. The institutional review board approved the study.

Sample size was calculated based on the single population proportion formula and it was then corrected for a finite population: $n = Z^2 \times P(1–P)/d^2$ and adjusted sample size (n) = $(N \times n)/(N + n)$, where Z is the value from the standard normal distribution corresponding to the desired confidence level (Z = 1.96 for 95% confidence interval), P is the expected true population proportion (P = 26.6%), taken from another study reporting prevalence of echocardiographic abnormalities,[18] d is the desired precision (0.05), and N is the finite population estimated to be 300 at the time of data collection. The adjusted final sample size was 151.

Socio-demographic data were collected on a questionnaire through interviewer-administered direct interview of the parent/guardian, and whenever appropriate, interview of the patient, after written consent/assent was obtained from each patient and/or legal guardian. Clinical as well as relevant laboratory data were extracted from patient records. Patients were excluded from the study if they declined to consent or if there was established congenital or rheumatic heart disease.

For echocardiographic examinations, SonoScape SSI-800 ultrasound equipment (SonoScape Medical Corporation, Shenzhen, China) was used to scan all the patients. An experienced paediatric cardiologist performed the echocardiographic examinations in all patients. Standard subcostal, apical four-chamber, parasternal long- and short-axis as well as suprasternal view examinations were performed to exclude congenital cardiac lesions and rheumatic valvular heart disease. LV systolic function was estimated from the parasternal long-axis view with the M-mode cursor placed approximately at the level of the mitral valve leaflet tips (roughly at the level of the papillary muscles). End-diastolic and -systolic indices were recorded.

Diagnosis of pulmonary hypertension was based on tricuspid regurgitation velocity of > 3.4 m/s (pressure gradient between the right ventricle and right atrium of > 50 mmHg).[19] This has also been reflected in the 2018 guideline protocol from the British Society of Echocardiography.[20] Similarly, estimated right ventricular (RV)/pulmonary artery systolic pressure refers to the sum of the tricuspid regurgitation gradient and estimated right atrial pressure (roughly assumed to be 5–10 mmHg). Pericardial effusion was graded as minimal if it was seen only in the systolic phase, mild if it was < 10 mm, moderate if it was 10–20 mm, and severe if it was > 20 mm in the longest diameter.[21]

Myocardial mass was calculated from the left ventricular end-diastolic indices and indexed to body surface area using a myocardial mass and myocardial mass index (MMI) calculator.[22] Normal values and classification of severity of increased myocardial mass were according to the recommendations of the American Society of Echocardiography of 2015 and 2005.[23,24]

Transmitral diastolic flow velocities were measured in the apical four-chamber view with the pulsed-wave Doppler sample volume placed at the tip of the mitral and tricuspid valve leaflets. Myocardial tissue velocities as well as isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT) and ejection time (ET) were measured in the apical four-chamber view with the pulsed-wave Doppler sample volume placed at the lateral mitral annulus, septal side of the mitral annulus and lateral tricuspid annulus. Standard classification of cardiac pathologies was used.

Statistical analysis

Data were entered into the Statistical Package for Social Sciences (SPSS) version 24 for Mac (IBM Corporation, New York, USA) and analysed. Descriptive statistics are displayed as mean ± standard deviation (range). Categorical variables are displayed as frequencies and percentages. The chi-squared test, non-parametric tests and binary logistic regression method were used to analyse correlations between patient factors and observed cardiac pathologies.

Results

One hundred and fifty-one consecutive patients underwent echocardiographic examination. Age of the patients was 13.0 ± 3.2 (4.0–19.0) years and 83 (55%) were female. Age at diagnosis of HIV-infection was 5.7 ± 3.3 years (six weeks – 13 years). Age at initiation of HAART was 7.34 ± 3.54 years (four months – 15 years), while duration of HAART was 59 ± 39.1 (1–126) months. Baseline socio-demographic, clinical and important laboratory variables are displayed in Table 1. About 17.8% of the patients had moderate-to-severe malnutrition based on body mass index (BMI) for age.

Regarding echocardiographic findings, three patients were found to have LV systolic dysfunction as defined by LV ejection fraction of < 56% by M-mode measurement.[25] The LV ejection fraction of the three patients was between 50 and 52%. One patient had minimal pericardial effusion. Two other patients were found to have pulmonary hypertension as evidenced by tricuspid regurgitation jet velocity > 3.4 m/s or RV-to-right atrial pressure gradient of > 50 mmHg) with mildly dilated right side chambers. The estimated RV/pulmonary artery systolic pressure in both patients was between 60 and 70 mmHg. None of these patients reported having cardiac symptoms.

Including the above three patients with LV systolic dysfunction, 16 patients were noted to have abnormal LV mass index (gm/m^2) compared to the cut-off points for normal values given by the American Society of Echocardiography (43–95 g/m^2 for females and 49–115 g/m^2 for males) using the linear technique.[23] Of the 16 patients with abnormal MMI, six had mildly abnormal (96–108 g/m^2 for females and 116–131 g/m^2 for males), six had moderately abnormal (109–121 g/m^2 for females and 132–148 g/m^2 for males) and four had severely abnormal (≥ 122 g/m^2 for females and ≥ 149 g/m^2 for males) MMI.[24] Three of the four patients with severely abnormal MMI were also the ones who had LV systolic dysfunction on M-mode echocardiography.

With regard to Doppler and TDI indices, mean transmitral flow velocity, E/A ratio, was 1.81 ± 0.45 (1.02–2.93). Septal mitral annulus, E/E′, was 6.40 ± 1.30 (0.95–9.87) whereas lateral mitral annulus, E/E′, was 5.9 ± 1.1 (2.2–8.9). Twenty-seven (17.9%) patients had evidence of LV diastolic dysfunction (higher E/E′ values compared to age-adjusted normal values).[26] Tricuspid lateral annular Et/E′t was 3.1 ± 1.0 (1.42–6.15). Eighteen (11.9%) of the patients had abnormal Et/E′t values, indicating the presence of RV diastolic dysfunction. Nineteen (12.6%) had tricuspid annular systolic velocity of < 9.5 cm/s, indicating asymptomatic RV systolic dysfunction.

Calculated myocardial performance index (MPI) for the lateral mitral annulus, septal mitral annulus and lateral tricuspid annulus was 0.60 ± 0.14 (0.30–0.95), 0.58 ± 0.12 (0.31–0.95) and 0.53 ± 0.20 (0.09–0.96), respectively. Details of

Table 1. Demographic and clinical characteristics of 151 HIV-infected children on HAART

Characteristics	*Values*
Age (years), mean ± SD (range)	13.0 ± 3.2 (4.0–19.0)
Gender, *n* (%)	
Female	83 (55.0)
Male	68 (45.0)
Weight (kg), mean ± SD (range)	35.5 ± 11.3 (12.0–65.0)
Height (cm), mean ± SD (range)	142.8 ± 15.9 (92.0–177.0)
WHO clinical stage at initiation of HAART, *n* (%)	
I	13 (8.6)
II	42 (27.8)
III	68 (45.1)
IV	28 (18.5)
Parental status, *n* (%)	
Both alive	45 (29.8)
Single orphan	59 (39.1)
Double orphan	47 (31.1)
Maternal education, *n* (%) (alive only, *n* = 62)	
Primary or less	29 (46.8)
Secondary	29 (46.8)
Higher	4 (6.4)
Paternal education, *n* (%) (alive only, *n* = 61)	
Primary or less	16 (26.2)
Secondary	29 (47.5)
Higher	16 (26.2)
Age at diagnosis (years), mean ± SD (range) *n* = 119	5.7 ± 3.3 (0.12–13)
Age at disclosure (years), (mean ± SD (range), *n* = 96	11.6 ± 2.4 (3–18)
Lowest CD_4 count ever recorded, mean ± SD (range)	328.8 ± 225.8 (3–1210)
Latest CD_4 count, mean ± SD (range)	706.0 ± 389.3 (3–3034)
Age at initiation of HAART (years)	7.34 ± 3.54 (0.33–15.75)
HAART duration (months)	59 ± 39.1 (1–126)
Cotrimoxazole prophylactic therapy duration (months), *n* = 148	55.9 ± 30.7 (2–120)

WHO, World Health Organisation; HAART, highly active antiretroviral treatment.

Table 2. Conventional echocardiography and TDI indices from 151 HIV-infected children and adolescents on HAART

Echocardiographic indices	*Mean ± SD (range) (n = 151)*
Heart rate (beats/min)	86 ± 16 (56–125)
LV end-diastolic diameter (cm)	4.0 ± 0.5 (3.0–5.5)
Interventricular septal thickness in diastole (cm)	0.73 ± 0.15 (0.50–1.20)
LV posterior wall thickness in diastole (cm)	0.73 ± 0.16 (0.50–1.30)
Myocardial mass, indexed for body surface area (gm/m^2)	73.0 ± 25.8 (43–188)
LV ejection fraction (%)	66.2 ± 6.0 (50–79)
LV fibre-shortening fraction (%)	36.0 ± 4.7 (25–45)
Mitral valve inflow velocity (cm/s)	
E	83.3 ± 16.4 (36–123)
A	47.7 ± 10.8 (27–86)
E/A	1.81 ± 0.45 (1.02–2.93)
TDI lateral mitral annulus tissue velocities (cm/s)	
E′ lateral MVA	17.3 ± 3.1 (7.9–25.0)
A′ lateral MVA	7.1 ± 1.9 (2.0–12.5)
S′ lateral MVA	6.8 ± 1.5 (3.2–11.7)
IVRT (ms)	63.6 ± 12.8 (30–70)
IVCT (ms)	80.6 ± 18.6 (40–130)
E/E′ lateral MVA	5.9 ± 1.1 (2.2–8.9)
MPI lateral MVA	0.60 ± 0.14 (0.30–0.95)
TDI septal mitral annulus tissue velocities (cm/s)	
E′ septal MVA	13.3 ± 4.5 (8.5–63)
A′ septal MVA	6.7 ± 1.8 (2.3–11.3)
S′ septal MVA	6.1 ± 0.9 (4.0–8.9)
IVRT (ms)	68.1 ± 13.3 (40.0–70.0)
IVCT (ms)	74.4 ± 16.6 (40.0–58.0)
E/E′ septal MVA	6.40 ± 1.30 (0.95–9.87)
MPI-septal MVA	0.58 ± 0.12 (0.31–0.95)
Tricuspid valve inflow peak velocities (cm/s)	
Et	47.5 ± 12.7 (24.0–85.0)
At	27.5 ± 9.1 (13.9–56.0)
Et/At	1.8 ± 0.6 (1.42–3.15)
TDI lateral tricuspid annulus tissue velocities (cm/s)	
E′t	15.7 ± 3.3 (8.9–29)
A′t	9.5 ± 2.5 (2.0–20.0)
S′t	12.3 ± 2.5 (7.4–20.0)
IVRT	54.1 ± 35.2 (43–98)
IVCT	66.6 ± 21.4 (40–130)
Et/E′t	3.1 ± 1.0 (1.42–6.15)
RV MPI	0.53 ± 0.20 (.09–0.96)

LV, left ventricular, RV, right ventricular; TDI, tissue Doppler imaging; MVA, mitral valve annulus IVRT, isovolumic relaxation time; IVCT, isovolumic contraction time; MPI, myocardial performance index.

the echocardiographic indices are shown in Table 2. Correlation between different patient factors and cardiac involvement is shown in Table 3.

Discussion

This study shows the spectrum of echocardiographic abnormalities in our sample of patients living with HIV and taking HAART, although none of these patients had clinically apparent cardiac symptoms. This has been demonstrated in other similar studies.[3,4,14]

In this study, conventional echocardiographic examination picked up only six straightforward abnormalities (three cases of LV systolic dysfunction, two of pulmonary arterial hypertension and one of minimal pericardial effusion), which would have made the prevalence of cardiac abnormalities in this cohort only about 4%. However, calculation of the MMI from the LV M-mode indices (LV end-diastolic diameter, interventricular septal thickness in diastole, and posterior wall thickness in diastole), and height and weight of each patient showed that 16 patients actually had abnormal MMI ranging from mild to severe.

Considering that 17.8% of our patients had moderate-to-severe malnutrition and knowing the effect of malnutrition on cardiac muscle (atrophy), it is possible that our calculation of MMI may actually underestimate the proportion of patients with abnormal myocardial mass. However, it can also be argued that the values are still valid reflections as long as they are indexed for body surface area. There were additional indices, such as measures of cardiac strain and strain rate, which we did not measure due to logistic problems. Other investigators have demonstrated that these indices were also commonly impaired.[27]

All the study patients were on HAART and had good adherence to treatment, except a few patients who interrupted the treatment for some time in their course due to perceived or confirmed drug side effects. The reported effect of HAART on incidence of cardiovascular abnormalities in HIV patients is mixed. Some studies have reported that HAART is cardioprotective,[28-30] and in some cases, resolution of conditions such as dilated cardiomyopathy have been reported.[31] But on the other hand, exposure to HAART is actually one of the mechanisms of

Table 3. Factors associated with cardiac abnormalities in 151 HIV-infected children and adolescents on HAART

Variables tested for association	*Abnormal echo findings*	p-*value*
Age at time of study (years)		
≤ 12	22/57	0.728
> 12	33/94	
Gender		
Female	28/83	0.498
Male	27/68	
Body mass index *Z*-scores		
< –2	11/26	0.511
≥ –2	44/124	
Initial WHO clinical stage		
I and II	15/55	0.082
III and IV	40/96	
Lowest CD4 count		
< 200	39/97	0.220
≥ 200	16/54	
Age at initiation of HAART (years)		
< 9	11/80	0.490
10–13	14/59	
14–19	2/12	
Duration of HAART (months)		
< 24	11/29	0.894
≥ 24	45/121	
Previous treatment for opportunistic infections (per WHO definition)		
Yes	33/78	0.131
No	22/73	

WHO, World Health Organisation; HAART, highly active antiretroviral treatment; LV, left ventricular.

involvement of the heart in HIV-infected patients.[9] However, it appears that HAART converted symptomatic cardiac disease to mild or asymptomatic disease in one study,[14] significantly improving patient survival and quality of life. Our study was not powered to draw any conclusions as to the effect of HAART on incidence of cardiac involvement, since we did not compare patients on ART with those who were not.

We also performed TDI studies on both the LV and RV (Table 2). TDI has been shown to unmask subtle abnormalities that were not detected by conventional echocardiography.[32,33] Some important abnormalities were observed in our patients. A significant proportion of patients who had normal findings on conventional echocardiography had shown abnormal MPI, LV diastolic dysfunction and RV systolic and diastolic dysfunction on TDI. MPI, which involves load, heart rate and ventricular geometry, and is an independent measure of systolic and diastolic ventricular function, was also abnormal for both ventricles in our group of patients compared to critical cut-off points and *Z*-scores set by multiple investigators in the past,[23,34-37] indicating the presence of subclinical LV and RV dysfunction. MPI includes both diastolic and systolic time intervals and is a sensitive marker of ventricular systolic and diastolic function, even when it is unrecognisable by conventional echocardiography.

Our study attempted to show an association between patient clinical factors such as age, gender, BMI, World Health Organisation clinical stage, previous treatment for opportunistic infections, CD4 count, age at initiation of HAART, duration of HAART and having a specific type of cardiac involvement such as increased LV mass index, LV diastolic dysfunction, or RV systolic/diastolic dysfunction. We did not find a statistically significant association. We then considered an association between such patient factors and having any of the cardiac abnormalities combined (Table 3). Although there was a tendency towards an association, none of these reached a statistically significant level. Previous work by different authors has also reported inconsistent associations between such factors and cardiac involvement in children living with HIV.[4,13,16,38]

Our study has important limitations. First, interpretation of TDI findings was based on previously set reference values and *Z*-scores. However, this has its own drawbacks and the more appropriate way would have been to take a control group of healthy children and adolescents matched for age and gender. Second, there were other important and relevant echocardiographic indices that we did not measure due to logistical issues.

Conclusion

Our sample of children and adolescents living with HIV had subclinical cardiac abnormalities detected on conventional echocardiography as well as TDI. While few patients had abnormalities detectable on conventional echocardiography, such as reduced LV ejection fraction, pulmonary hypertension and pericarditis, a larger proportion of patients had subtle abnormalities, such as increased MMI, LV diastolic dysfunction, RV dysfunction and abnormal MPI. However, to make better sense of the TDI indices, it would probably have been better to compare with a group of healthy children, drawn from a similar socio-demographic background. Our study did not show a strong association between specific patient factors and echocardiographic abnormalities in this sample of patients.

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Effect of heroin on right ventricular cardiac performance

Murat Selcuk, Ersin Yildirim, Faysal Saylik, Ozgur Deniz, Ferit Onur Mutluer

Abstract

Objective: The aim of this study was to investigate the effects of heroin addiction, which is an important social and health problem, on right cardiac function.

Methods: A total of 85 individuals were included in the study. The study group comprised 45 patients smoking heroin and the control group was 40 healthy individuals with no drug addiction. Patients injecting heroin were excluded. Echocardiographic evaluation of patients using heroin was performed and compared with those in the control group.

Results: The right ventricle and pulmonary artery diameters in the heroin group were found to be higher compared to the control group. The myocardial performance index (MPI) was higher and more abnormal in the heroin group (0.48 ± 0.22 vs 0.39 ± 0.11, $p < 0.05$) whereas isovolumic acceleration (IVA) of the right ventricle was significantly lower in the heroin group (2.92 ± 0.69 vs 3.4 ± 0.68 m/s^2, $p < 0.01$). No significant difference was observed between the groups with regard to the right ventricular ejection fraction (RVEF) (59.6 ± 2.5 vs 60.6 ± 2.3%, $p = 0.08$), tricuspid annular plain systolic excursion (TAPSE) (24.1 ± 4.2 vs 24.5 ± 2.4 mm, $p = 0.7$), tissue Doppler imaging S wave (TDI-S) (13.7 ± 2.1 vs 13.8 ± 2.1 cm/s, $p = 0.86$) and right ventricular fractional area change (RVFAC) (42.7 ± 8.3 vs 43.9 ± 3.5%, $p = 0.4$). Multivariate and univariate regression analyses revealed independent correlation between the pulmonary artery diameter and RVIVA, and heroin addiction.

Conclusion: Heroin addiction negatively affected right ventricular function and more attention should be paid to the cardiac function of these patients.

Keywords: heroin, right ventricular function, myocardial performance index

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Department of Cardiology, Van Education and Research Hospital, University of Health Sciences, Van, Turkey
Murat Selcuk, MD,
Faysal Saylik, MD
Ferit Onur Mutluer, MD

Department of Cardiology, Istanbul Umraniye Education and Research Hospital, University of Health Sciences, Istanbul, Turkey
Ersin Yildirim, MD, ersinyil44@gmail.com

Department of Psychiatry, Van Education and Research Hospital, University of Health Sciences, Van, Turkey
Ozgur Deniz, MD

Heroin addiction is one of the most destructive and expensive public health problems. Heroin, which is a central nervous system depressant (diacetylmorphine), is a semi-synthetic opiate. Mortality rate among heroin users varies between 1 and 3%, and the most effective treatment method for heroin addiction is opioid replacement therapy.[1,2] Heroin is commonly smoked, snorted and injected intravenously.

A common negative effect of heroin addiction is respiratory depression, which may lead to death, especially following intravenous (IV) injection. Additionally, heroin-related pulmonary oedema has been reported in previous studies.[3] IV use of the drug is difficult to evaluate since the injection is generally performed together with other chemical substances named adulterants.[4]

Heroin addiction is a serious social health problem. We evaluated patients who smoked heroin and aimed to investigate its effect on right heart function since not much is known about the cardiac effect of heroin addiction.

Methods

Informed consent was obtained from all patients and they signed a consent form to participate in the study. The Van Education and Research Hospital ethics committee approved the study.

A total of 85 individuals were included in the study. The study group comprised 45 patients smoking heroin and undergoing therapy in the Alcohol and Drug Addiction Treatment and Training Centre of the Van Training and Research Hospital between 2014 and 2016. The control group consisted of 40 healthy individuals with no drug addiction other than smoking cigarettes.

Subjects who used heroin via the IV route, alcoholics, those with coronary artery disease, cardiac failure, cardiac valve disorders, known arrhythmias, hypertension, congenital cardiac diseases, diabetes, hepatic or renal failure, chronic obstructive pulmonary disease, endocrine diseases, metabolic or electrolyte disorders, acute or chronic infections or those on medications due to any type of disease, were excluded from the study.

The clinical and demographic characteristics of the patients, and status and duration of heroin addiction were obtained from the patients and patient files in the hospital. Body mass index, defined as body mass divided by the square of the height, was determined. Electrocardiography (ECG) records of the patients were obtained via the Schiller Cardiovit AT-102 plus using the standard 12 derivation (10 mm/mV calibration and 25 mm/s sliding rate). Complete blood counts and biochemical tests were performed using a Beckman Coulter LH-750 and Beckman Coulter L × 20, respectively, and the results of each patient were recorded.

Echocardiographic evaluations of the patients were performed at the time of admission to our hospital while the patients were still under the influence of heroin. All participants underwent two-dimensional (2D) and Doppler echocardiographic evaluation (VIVID 3, General Electric, USA). 2D echocardiographic

studies were performed in the left lateral decubitus position with the conventional views (parasternal long- and short-axis, apical four-chamber views). Right ventricular ejection fraction (RVEF) from 2D methods was calculated as: (end-diastolic volume – end-systolic volume)/end-diastolic volume.

Right ventricular M-mode, tissue Doppler records, isovolumic acceleration (IVA) and myocardial performance index (MPI) measurements were performed for right ventricular systolic and diastolic function indicators. Peak myocardial speed during isovolumic contraction was defined as isovolumetric contraction velocity (IVV) (m/sec) and time elapsed to reach peak speed was defined as acceleration time (AT). IVA was calculated with the following formula: IVA = IVV/AT.

Right ventricular MPI was calculated as the ratio between the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ejection time (ET): MPI = (ICT + IRT)/ET. Right ventricular fractional area change (RVFAC) was assessed in the four-chamber view and calculated as: RVFAC = [RV end-diastolic area – RV end-systolic area]/RV end-diastolic area × 100%. Pulsed tissue Doppler imaging (TDI) was performed to measure systolic and diastolic myocardial velocities at the basal level of the RV free wall. Peak myocardial IVV, peak myocardial systolic velocity (Sm), peak early and late diastolic velocities (Em and Am), ICT, IRT and ET were measured.

We used M-mode scanning to measure tricuspid annular plane systolic excursion (TAPSE) in the apical four-chamber view with the cursor placed at the free wall side of the tricuspid annulus to assess RV longitudinal function. TAPSE was measured as the distance between the peak and trough of the M-mode tracing curve, and at least three consecutive beats were averaged. All Doppler measurements were performed at the end of the expiration in order not to affect flow parameters with respiration and to be more consistent.

Averages of measurements were used for comparison. Measurements were generally consistent and this provided more stable results. Inter-observer agreement was evaluated by calculating the Pearson's correlation coefficient ($r = 0.93$).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc, Chicago, IL) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium) programs. Compliance of the data to the normal distribution was tested using the Kolmogorov–Smirnov test. Normally distributed numeric variables are expressed as mean ± standard deviation and non-normally distributed variables are expressed as medians. Categorical variables are expressed as numbers and percentages.

For comparisons between the heroin and control groups, the Student's *t*-test was used for parametric variables and the Mann–Whitney *U*-test for non-parametric variables. The chi-squared and Fisher's exact chi-squared tests were carried out for comparison of categorical variables. Single-variate logistic regression analysis was performed in order to determine the effects of potential prognostic factors on right ventricular function. Significant risk factors were included in the multivariate logistic regression and independent predictors were determined. A *p*-value of < 0.05 was accepted as statistically significant.

Results

In the heroin group, the mean duration of heroin use was 4.6 years. The mean red cell distribution width (RDW) in the heroin group was observed to be significantly higher compared to the control group (15 ± 1.6 vs 13.4 ± 1.1%, $p < 0.01$). No significant differences were found in other demographic and laboratory characteristics between the groups (Table 1).

Comparison of the echocardiographic characteristics between the groups revealed statistically larger right ventricular basal (39.4 ± 4.7 vs 35.6 ± 4.3 mm, $p < 0.01$), mid (37.2 ± 4.7 vs 31.8 ± 3.6 mm, $p < 0.01$) and apicobasal (60.8 ± 7.2 vs 53.6 ± 11.1 mm, $p = 0.01$) diameters and pulmonary artery diameter (22.4 ± 2.5 vs 20 ± 2.5 mm, $p < 0.01$) in the heroin group compared to the control group. Tricuspid pulsed wave E (PW E) (62.9 ± 14.8 vs 52.6 ± 12 cm/s, $p = 0.01$) and tissue Doppler e wave (17.2 ± 4.5 vs 14.3 ± 3 cm/s, $p = 0.01$) values in the heroin group were observed to be statistically higher compared to the control group. The MPI value was higher and abnormal in the heroin group (0.48 ± 0.22 vs 0.39 ± 0.11, $p < 0.05$), whereas the right IVA was observed to be significantly reduced in the heroin group (2.92 ± 0.69 vs 3.4 ± 0.68 m/s^2, $p < 0.01$). No significant differences were observed between the groups with regard to RVEF (59.6 ± 2.5 vs 60.6 ± 2.3%, $p = 0.08$), TAPSE (24.1 ± 4.2 vs 24.5 ± 2.4 mm, $p = 0.7$), TDI-S (13.7 ± 2.1 vs 13.8 ± 2.1 cm/s, $p = 0.86$) and RVFAC (42.7 ± 8.3 vs 43.9 ± 3.5%, $p = 0.4$) values (Table 2).

An independent correlation was observed between the RVIVA and heroin use in univariate [0.36 (0.18–0.72), $p < 0.01$] and multivariate [0.42 (0.19–0.88), $p = 0.02$] regression analyses. Furthermore, an independent correlation was detected between the pulmonary artery diameter and heroin use in univariate [1.49 (1.19–1.85), $p < 0.01$] and multivariate [1.43 (1.14–1.81), $p < 0.05$] regression analyses (Table 3).

Discussion

Addiction to heroin-like drugs is currently an important health problem however knowledge on the cardiac effects of heroin addiction is limited. To our knowledge, the present study is the first in the literature on the subject.

Table 1. Baseline characteristics and laboratory findings of the groups

Variables	*Heroin (+)* (n = *45*)	*Heroin (–)* (n = *40*)	p-*value*
Age (years), mean (SD)	29.6 ± 9.6	30.1 ± 8.1	0.81
Gender (female), *n* (%)	2 (4.4)	6 (15)	0.09
Diabetes mellitus, *n* (%)	0	0	–
Hypertension, *n* (%)	0	0	–
Coronary artery disease, *n* (%)	0	0	–
BMI, kg/m^2	26.5 ± 2.7	27.5 ± 2.7	0.11
WBC (× 10^3 cells/µl)	8.1 ± 1.7	7.9 ± 1.5	0.61
Haemoglobin (g/dl)	16.2 ± 0.9	15.7 ± 1	0.02
RDW (%)	15 ± 1.6	13.4 ± 1.1	< 0.01
Creatinine (mg/dl)	0.84 ± 0.13	0.82 ± 0.1	0.31
Platelet count (× 10^3 cells/µl)	283.6 ± 80.5	279.6 ± 79.4	0.82
Sodium (mmol/dl; SD)	140.5 ± 3.4	140.8 ± 3.2	0.62
Potasium (mmol/dl; SD)	4.3 ± 0.38	4.32 ± 0.33	0.73
Calcium (mg/dl; SD)	9.2 ± 0.5	9.3 ± 0.4	0.84

$p < 0.05$ is statistically significant. Continues variables are reported as mean ± SD or median (IQR). Categorical variables are reported as *n* (%).
BMI: body mass ındex, WBC: white blood cells, RDW: red cell distribution width.

Table 2. Echocardiographic features of the groups

Variables	*Heroin (+)*	*Heroin (–)*	p-*value*
RVEF (%)	59.6 ± 2.5	60.6 ± 2.3	0.08
Intraventricular septum (mm)	8.7 ± 1.3	8.6 ± 0.9	0.79
Right atrium area (mm^2)	16.2 ± 2.9	14.9 ± 2.6	0.04
RV basal diameter (mm)	39.4 ± 4.7	35.6 ± 4.3	< 0.01
RV mid diameter (mm)	37.2 ± 4.7	31.8 ± 3.6	< 0.01
RV apicobasal (mm)	60.8 ± 7.2	53.6 ± 11.1	0.01
Pulmonary artery diameter (mm)	22.4 ± 2.5	20 ± 2.5	< 0.01
RV wall thickness (mm)	4.7 ± 1.1	4.6 ± 1	0.81
RVFAC (%)	42.7 ± 8.3	43.9 ± 3.5	0.44
TAPSE (mm)	24.1 ± 4.2	24.5 ± 2.4	0.71
Pulsed Doppler MPI	0.48 ± 0.22	0.39 ± 0.11	0.02
Tricuspid PW E (cm/s)	62.9 ± 14.8	52.6 ± 12	0.01
Tricuspid PW A (cm/s)	44.1 ± 11.4	40.7 ± 8.2	0.12
Tissue Doppler S wave (cm/s)	13.7 ± 2.1	13.8 ± 2.1	0.86
Tissue Doppler e wave (cm/s)	17.2 ± 4.5	14.3 ± 3	0.01
Tissue Doppler a wave (cm/s)	12.6 ± 3.1	13.1 ± 3.1	0.50
RVIVA (m/s^2)	2.92 ± 0.69	3.4 ± 0.68	< 0.01

$p < 0.05$ statistically significant. Continuous variables are reported as mean ± SD or median (IQR). Categorical variables are reported as *n* (%).
RVEF: right ventricular ejection fraction, TAPSE: tricuspid annular plane systolic excursion, RVFAC: right ventricular fractional area change, MPI: myocardial performance index, RVIVA: right ventricular isovolumic acceleration, PW: pulsed wave.

The effect of heroin use on cardiac function has been investigated in several studies previously. It was demonstrated in the study by Pons Llado *et al.* on patients using IV heroin that heroin use had no effect on left ventricular systolic or diastolic function, but significantly increased the rate of mitral and tricuspid valve abnormalities.[5] In another study, it was demonstrated that synthetic cannabinoids negatively affected left ventricular function, whereas heroin did not.[6] However, these studies do not provide any information on the effect of heroin addiction on right ventricular function.

Although heroin use does not seem to have any effect on left ventricular function, according to the results of these studies, others have demonstrated atrial and myocardial irregularities by histopathological sampling.[7] Orlando *et al*. reported a subclinical reduction in the ejection fraction of the left ventricle in 20 heroin addicts.[8] In another case report, cardiogenic shock was reported in a young heroin addict, which was related to severe depression of left ventricular contractility. However, the authors attributed this to another cause, right ventricular failure.[9] All these conflicting results suggest the need for further studies.

The cardiac effects of heroin are not limited to myotoxic effects. It was reported in the study by Pavlidis *et al.* that myocardial infarction was observed rarely, but the mechanism is unknown. Increased cardiac weight, which is observed as a result of increased thickness of the cardiac walls, could be a factor and therefore should be investigated.[10]

Table 3. Multiple logistic regression analysis to detect independent factors related to heroin-using group

Variables	*Univariate OR,95% CI*	p-*value*	*Multivariate OR,95% CI*	p-*value*
RVIVA (m/s^2)	0.36 (0.18–0.72)	< 0.01	0.42 (0.19–0.88)	0.02
Pulsed Doppler MPI	16.4 (1.12–239.27)	0.04	9.45 (0.51–172.1)	0.13
Pulmonary artery diameter (mm)	1.49 (1.19–1.85)	< 0.01	1.43 (1.14–1.81)	< 0.05

MPI: myocardial performance index, RVIVA: right ventricular isovolumic acceleration.

In another case of heroin-related cardiac crisis, the authors attributed it to heroin-related cardiotoxic effects and vasospasm.[11] Furthermore, in studies investigating the mechanism of heroin-related arrhythmias and subsequent sudden death, it was demonstrated that heroin use did not only lead to myocardial infiltration, but also to fibromuscular dysplasia in the sinus and atrioventricular nodes, in the transmission pathways and to fat infiltration. They concluded that this may be the cause of arrhythmia-related sudden death in heroin addicts.[12,13]

Another important heroin-related problem is pulmonary oedema, which was demonstrated as one of the most frequent causes of heroin-related death. There are many studies in the literature on the subject,[3,14,15] however, the mechanism could not be clearly defined. Although the direct pulmonary effects have been primarily considered, depression in cardiac contractility has been suggested as a possible mechanism.

In order to better understand the mechanism of pulmonary oedema, which is an important problem in heroin addicts, the cardiac effects of heroin should be defined. However, when heroin is used via the IV route, it is administered together with additional chemical substances named adulterants (acetaminophen, caffeine, diphenhydramine, methorphan, alprazolam, quetiapine, chloroquine, diltiazem, cocaine, procaine, lidocaine, quinine/quinidine, phenacetine and thiamine), and the potential cardiac effects of these substances complicate evaluation of the cardiac effects of heroin.[16] Therefore in order to investigate the cardiac effects of heroin only, we excluded patients using heroin via the IV route.

This study demonstrated that heroin use significantly increased right ventricle and pulmonary artery diameters, and negatively affected the MPI and RVIVA. Assessing right ventricular performance is not easy and is underestimated in many studies. Generally, evaluation of more than one parameter is recommended.[17] Being a pilot study on the subject, our study is important, since it shows impairment in multiple parameters. However, it is notable that values such as TDI-S and TAPSE were unaffected. Further studies with larger sample sizes, using new techniques such as three-dimensional and strain echocardiography are needed to better define the subject.

Our study had some limitations; these were the single-centre design and lack of examinations such as three-dimensional and strain echocardiography during cardiac function investigations. Also this was a retrospective, observational study therefore it does not provide conclusive results in this regard.

Conclusion

Heroin addiction, which is an important public health problem, negatively affects right ventricular function and more attention should be paid to the cardiac function of these patients. Since present knowledge on the effect of heroin use on cardiac function is limited, this study is important for its contribution to the literature. However, further studies with a larger sample size are needed for clearer results.

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Simple cardiac blood test before surgery can predict adverse outcomes

A common cardiac blood test done before surgery can predict who will experience adverse outcomes after most types of surgery, says an international study led by Canadian researchers.

Globally, of the 200 million adults who undergo major surgery, 18% will experience serious cardiac and vascular complications including death within 30 days following their intervention, such as hip and knee replacements, bowel resections and abdominal aortic aneurysm repair.

'Any type of surgery has the potential to cause damage to heart tissue, through blood clot formation, long periods of inflammation, or bleeding,' said study lead, Dr PJ Deveraux, professor of medicine, cardiologist at Hamilton Health Sciences (HHS) and scientific lead for peri-operative research at McMaster University and HHS' Population Health Research Institute (PHRI).

The VISION study looked at whether levels of a cardiac blood test, NT-proBNP, measured before surgery can predict cardiac and vascular complications. Higher levels of NT-proBNP, which can be caused by various anomalies in the cardiac muscle, such as stress, inflammation or overstretch, can help identify which patients are at greatest risk of cardiac complications after surgery.

The study included 10 402 patients aged 45 years or older having non-cardiac surgery with overnight stay from 16 hospitals in nine countries. 'As a result of these findings, doctors can predict who is at greater risk of heart attacks and other negative vascular events after surgery,' said Devereaux.

This phase of the VISION study builds upon six years of research studies to understand pre- and post-operative factors that lead to cardiac complications. 'This simple blood test can be done quickly and easily as part of a patient's pre-operative evaluation, can help patients better understand their risk of post-operative complications and make informed decisions about their surgery,' said first author of the publication, Dr Emmanuelle Duceppe, internist and researcher at the Centre Hospitalier de l'Universite de Montreal (CHUM), PhD candidate in clinical epidemiology at McMaster University, and associate researcher at PHRI. 'This blood test is 20 times cheaper than more time-consuming tests such as cardiac stress tests and diagnostic imaging.'

Results of this simple blood test may inform the type of surgery the patient will undergo, such as laparoscopic or open surgery, the type of anaesthesia used during surgery and who will require more intense monitoring post-operatively. Blood test results can also reduce the need for pre-surgical medical consultations for patients who show no risk for cardiac complications.

'Heart injury after non-cardiac surgery is emerging as an important health issue requiring attention. Using CIHR funding, the research group led by PHRI and Devereaux has clarified the association between an elevation of a common biomarker and the risk of per-operative morbidity and mortality,' said Dr Brian H Rowe, scientific director, Institute of Circulatory and Respiratory Health, Canadian Institutes for Health Research.

Source: Medical Brief 2020

The therapeutic management of South African dyslipidaemic patients at very high cardiovascular risk (CARDIO TRACK): a cross-sectional study

Dirk Jacobus Blom, Naresh Ranjith, Pankaj Joshi, Poobalan Naidoo, Alet van Tonder, Moji Ganiyat Musa, Shaifali Joshi, Rory Leisegang, Julien Shane Trokis, Hemant Makan, Frederick Johan Raal

Abstract

Background: Dyslipidaemia is a major modifiable risk factor for atherosclerotic cardiovascular disease. At the time the study was conducted, guidelines recommended a low-density lipoprotein cholesterol (LDL-C) target of less than 1.8 mmol/l and a reduction of at least 50% if the baseline LDL-C was between 1.8 and 3.5 mmol/l in patients with either very high cardiovascular risk or established atherosclerosis. In South Africa, there is a paucity of data on attainment of LDL-C goal in patients with very high cardiovascular risk who are on maximum tolerated statin with or without ezetimibe.

Objective: The aim was to assess the percentage of very high cardiovascular risk South African patients with dyslipidaemia not reaching an LDL-C goal of less than 1.8 mmol/l, despite maximum tolerated statin with or without ezetimibe.

Methods: This was a multi-centre, observational, cross-sectional study conducted at 15 private healthcare sector sites and one public sector site. Adults (> 18 years) with very high cardiovascular risk of familial hypercholesterolaemia receiving stable, maximum-tolerated statin therapy for at least four weeks prior to their latest lipid profile were enrolled into the study, and electronic case report forms were completed after written informed consent was provided. LDL-C goal attainment was modelled, first assuming an increase in the statin dose to the registered maximum, followed by the addition of ezetimibe or a PCSK9-inhibitor.

Results: In total, 507 patients were screened, of whom 492 were eligible for study participation. One patient was excluded from the analysis because of a missing LDL-C value. Most participants were male (male 329, 67%; female 162, 33%). Most patients were either obese (223, 46.0%) or overweight (176, 36.3%). Hypertension and diabetes mellitus were frequent co-morbidities and were found in 381 (77.6%) and 316 (64.4%) patients, respectively. Eighty (16.3%) patients reported current smoking. Only 68 (13.8%) patients were taking ezetimibe in addition to a statin. Reasons for not using ezetimibe included no requirement for ezetimibe in the opinion of the treating physician (229, 48.7%), cost (149, 31.7%), physician's choice (39, 8.3%), or other (53, 11.3%). Only 161 (32.8%) of the patients attained their goal LDL-C level. In our modelling analysis, increasing the statin dose to the registered maximum and adding ezetimibe brought an additional 34.5% of patients to goal, while adding a PCSK9-inhibitor, irrespective of any other changes to lipid-lowering therapy brought over 90% of not-at-goal patients to goal.

Conclusion: Most study participants were not at LDL-C goal despite maximum-tolerated statin, highlighting the need for treatment intensification in this high-risk population. Although intensifying treatment by adding a PCSK9-inhibitor brought more patients to goal, the initial addition of ezetimibe would be more reasonable, given the cost of PCSK9-inhibitors.

Division of Lipidology and Hatter Institute for Cardiovascular Research in Africa, Department of Medicine, University of Cape Town, Cape Town, South Africa
Dirk Jacobus Blom, PhD, dirk.blom@uct.ac.za

Cardiovascular Research Centre, Durban, South Africa
Naresh Ranjith, MD

Diabetes Care and Clinical Trials Centre, Pretoria, South Africa
Pankaj Joshi, MD
Shaifali Joshi, MD

Medical Affairs, Sanofi, Midrand, South Africa; Department of Health Informatics, School of Health Professions, Rutgers, State University of New Jersey, NJ, USA
Poobalan Naidoo, MD

Medical Affairs, Sanofi, Midrand, South Africa
Alet Van Tonder, MD
Moji Ganiyat Musa, MD

Department of Pharmaceutical Biosciences, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden; Family Clinical Research Unit (FAM-CRU), University of Stellenbosch, Tygerberg Hospital, Tygerberg, South Africa
Rory Leisegang, MD

Diabetes Research and Clinical Care, Kraaifontein, Cape Town, South Africa
Julien Shane Trokis, MD

Centre for Diabetes, Lenasia, South Africa
Hemant Makan, MD

Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa
Frederick Johan Raal, PhD

Keywords: cardiovascular risk, dyslipidaemia, LDL cholesterol, statins, ezetimibe, PCSK9-inhibitor

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Globally, cardiovascular disease is the leading cause of morbidity and mortality.[1] Historically, communicable disease has dominated the disease profile in Africa. However, non-communicable diseases in general, and cardiovascular disease specifically, is increasing in Africa because of increasing urbanisation and lifestyle changes.[2-5]

Dyslipidaemia is a major modifiable risk factor for atherosclerotic cardiovascular disease.[6,7] Management of dyslipidaemia in South Africa is sub-optimal in many cases. The most common problems are inaccurate risk stratification and inappropriate prescription of low-intensity statin therapy.[8-10] Frequent reasons for low-intensity statin use include restricted access to high-intensity statins, therapeutic inertia and fear of statin-associated muscular symptoms.

In South Africa most patients attending public sector clinics have access to low- and moderate-intensity statins (simvastatin 10–40 mg) only and require referral to tertiary-level hospitals for higher-dose statins. Prescription of ezetimibe is generally limited to specialist lipid clinics. Private sector patients often face formulary restrictions as well. Ezetimibe is often not reimbursed or attracts co-payments on many plans. At the time this research was undertaken, monoclonal antibodies to PCSK9 were not commercially available in South Africa.

Observational studies in South African cohorts such as CEPHEUS SA,[8] DYSIS[9] and ICLPS[10] were not adequately powered to determine the percentage of very high-risk study subjects who were not at low-density lipoprotein cholesterol (LDL-C) goal (1.8 mmol/l) despite maximum-tolerated statin, with or without ezetimibe. Because of the challenges of treating familial hypercholesterolaemia (FH), we included patients with FH in this study, even though younger patients with FH often have lower absolute cardiovascular risk in the short term (10 years) than patients with established atherosclerotic cardiovascular disease or diabetes mellitus.

CARDIO TRACK was a South African, multi-centre, non-interventional, cross-sectional study of predominantly private healthcare sector sites (15 sites) and a single public sector site. A description of the study protocol has been published.[11]

The primary objective was to assess the percentage of very high cardiovascular risk patients on maximum-tolerated statin, with or without ezetimibe, not reaching the LDL-C goal of < 1.8 mmol/l, as defined by the 2016 European Society of Cardiology (ECS)/European Atherosclerosis Society (EAS) guideline for the management of dyslipidaemia[12] and the South African lipid guidelines.[13] The LDL-C goal of < 1.8 mmol/l in the ESC/EAS guideline was derived following analysis of multiple outcome and vascular imaging studies, indicating that lower on-treatment LDL-C is associated with better outcomes.[12]

Secondary objectives included an analysis of patients with LDL-C > 5 mmol/l, to identify and characterise patients most at need of additional therapy due to their very high LDL-C level, despite receiving aggressive therapy. Additionally, we determined the percentage of patients not at target who were not receiving ezetimibe and explored reasons why ezetimibe, which is a simple and safe intervention, was not prescribed to these patients. In a further analysis we evaluated patients who failed to reach target despite receiving maximal-tolerated statin and ezetimibe, as such patients would be considered candidates for addition of PCSK9 inhibitors.

To identify factors associated with good lipid control, we characterised patients at goal, stratified by achieved LDL-C level (LDL-C < 1.8–1.0 mmol/l; LDL-C < 1.0 mmol/l). Finally, we modelled the impact of various interventions on LDL-C goal attainment using four sequential models, which are described below.

Methods

The study was conducted in accordance with the principles laid down by the 18th World Medical Assembly Declaration of Helsinki and all subsequent amendments, and the guidelines for good epidemiology practice. The study was approved by Pharma Ethics and the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town. The study was funded by Sanofi and Regeneron. The study was designed by the first and last authors in conjunction with PN, who was employed by Sanofi at the time of the study. The authors analysed and interpreted the data.

Adult patients aged > 18 years with very high cardiovascular risk or FH, receiving stable maximum-tolerated statin therapy for at least four weeks prior to their latest lipid profile, were eligible for inclusion. Very high-risk patients were defined as those with previous acute coronary syndrome (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina), coronary revascularisation (percutaneous coronary intervention, coronary artery bypass graft surgery, or other arterial revascularisation procedures), stroke or transient ischaemic attack, peripheral arterial disease (history of either intervention, surgery, amputation or symptoms with low ankle–brachial index < 0.9), calculated risk estimation ≥ 10% for 10-year risk of fatal cardiovascular disease, diabetes mellitus with target-organ damage such as proteinuria, and diabetes mellitus with another major cardiovascular risk factor such as smoking or hypertension. We also included patients with definitive familial hypercholesterolaemia according to the Dutch Lipid Clinic Network criteria.[13]

Maximum-tolerated statin was defined as either the highest licensed dose of a statin or the highest dose that a patient could tolerate. For patients not at LDL-C goal and not receiving the highest licensed dose of atorvastatin or rosuvastatin, the reason why the dose was not increased to the highest licensed dose or why a more potent statin was not prescribed needed to be documented. Acceptable reasons for a patient taking a lower statin dose included adverse events on higher doses or concomitant medications that may necessitate lower statin doses, such as verapamil, colchicine, amiodarone, digoxin, ticagrelor and sacubitril/valsartan. Patients who were not at target, and who were not receiving maximal doses of either atorvastatin or rosuvastatin with no medically valid reason for the failure to titrate were not eligible for this study. Maximum-intensified lipid-lowering therapy was defined as a high-intensity statin, either atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily, co-prescribed with ezetimibe 10 mg daily.

Sites were selected based on their potential to include the required number of patients following completion of a feasibility questionnaire. Investigators were required to consecutively include all eligible subjects who consented to participation. Data were collected at a single visit. No laboratory testing was done specifically for this study and lipid values were extracted from clinical records. Lipid profiles taken up to 12 months prior to the

Table 1. Physician characteristics

Characteristics	*Number (%)*	*Duration of practice (years), median (IQR)*	*Patient total (n = 492), n (%)*
General practitioner	7 (43.8)	29 (18–36)	229 (46.5)
Cardiologist	4 (25.0)	11 (7–19)	111 (22.6)
Specialist physician	4 (25.0)	23 (20–29)	122 (24.8)
Endocrinologist	1 (6.2)	16	30 (6.1)
Practice setting			
Private office	10 (62.5)		330 (67.1)
Private hospital	5 (31.2)		99 (20.1)
Public hospital	1 (6.3)		63 (12.8)

visit could be utilised, as long as the statin dose had been stable for four weeks prior to the blood draw.

Statistical analysis

All statistical analyses were performed using STATA version 15.1, (STATA Corporation, College Station, TX USA). Body mass index [BMI (kg/m^2)] was used to classify patients as underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (> 30.0 kg/m^2). Waist circumference (cm) was used to classify patients using a cut-off value of > 102 cm for men and > 88 cm for women. The same criteria were used for all patients irrespective of ethnicity.

Descriptive statistics were used to characterise the study population and continuous data were summarised by mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical data were summarised as number and proportion.

For the purpose of comparing dose equivalence across different statins, the following algorithm was used: rosuvastatin dose amount was unchanged, atorvastatin dose amount was divided by two, simvastatin dose amount was divided by four, and pravastatin dose amount was divided by 16. Patients who were on ezetimibe had their calculated dose equivalent multiplied by a factor of eight (two to the power of three) as adding ezetimibe to a statin usually lowers LDL-C level by a further 18%, or three dose doublings, with each doubling lowering LDL-C level by an additional 6%. For instance, doubling a 10-mg dose of rosuvastatin three times (10→20→40→80) is equivalent to rosuvastatin 80 mg. Rosuvastatin 10 mg daily plus ezetimibe 10 mg daily is approximately equivalent to rosuvastatin 80 mg daily.[12]

Table 2. Baseline characteristics

Variables	*All patients (n = 491)*	*Females (n = 162; 33%)*	*Males (n = 329; 67%)*
Age (years), mean ± SD	61.6 ± 11.0 *n* = 491	63.0 ± 10.9 *n* = 162	60.9 ± 11.1 *n* = 329
Weight (kg), mean ± SD	85.8 ± 18.2 *n* = 485*	79.2 ± 17.9 *n* = 162	89.2 ± 17.5 *n* = 323*
Height (cm), mean ± SD	168.8 ± 10.5 *n* = 486*	159.4 ± 7.9 *n* = 162	173.6 ± 8.2 *n* = 324*
BMI (kg/m^2), mean ± SD	30.1 ± 6.0 *n* = 485*	31.3 ± 7.5 *n* = 162	29.5 ± 5.0 *n* = 323*
Waist (cm), mean ± SD	102.8 ± 13.9 *n* = 478*	99.4 ± 14.6 *n* = 160*	104.5 ± 13.3 *n* = 318*
Hip (cm), mean ± SD	105.1 ± 12.1 *n* = 459*	108.2 ± 13.5 *n* = 158*	103.4 ± 11.0 *n* = 301*
Systolic blood pressure (mmHg, mean ± SD)	131 ± 15.1 *n* = 484*	132 ± 15.1 *n* = 161*	131 ± 15.1 *n* = 323*
Diastolic blood pressure (mmHg), mean ± SD	77 ± 9.4 *n* = 484*	76 ± 9.7 *n* = 161*	78 ± 9.1 *n* = 323*
Caucasian, *n* (%)	190 (38.7)	47 (29.0)	143 (43.5)
Asian, *n* (%)	139 (28.3)	36 (22.2)	103 (31.3)
Black, *n* (%)	92 (18.7)	39 (24.1)	53 (16.1)
Mixed, *n* (%)	70 (14.3)	40 (24.7)	30 (9.1)
Underweight, *n* (%)[1]	1 (0.2)	1 (0.6)	0 (0)
Normal, *n* (%)[2]	85 (17.5)	28 (17.3)	57 (17.7)
Overweight, *n* (%)[3]	176 (36.3)	47 (29.0)	129 (39.9)
Obese, *n* (%)[4]	223 (46.0)	86 (53.1)	137 (42.4)
Above cut-off for waist circumference, *n* (%)	316 (64.4)	133 (82.1)	183 (55.6)

[1]< 18.5 kg/m^2, [2]18.5–24.9 kg/m^2, [3]25.0–29.9 kg/m^2, [4]> 30.0 kg/m^2, *missing data for some patients.

Results

Most investigators were specialists (56.3%), with an equal distribution of cardiologists and specialist physicians, each speciality accounting for approximately 25% of investigators. The practice setting was predominantly private office based (62.5%), followed by private hospital based (31.2%) (Table 1).

The study was conducted between 15 November 2016 and 13 April 2017. Of the 517 patients screened, 492 were eligible to participate. One patient was subsequently excluded from the analysis as the patient had erroneously been enrolled despite having no documented LDL-C value.

Patient demographics and characteristics, cardiovascular risk factors and baseline laboratory values are displayed in Tables 2 and 3. Family history of premature atherosclerotic cardiovascular events is shown in Table 4. The mean (SD) age of the patient cohort was 61.6 (11.0) years with a mean (SD) BMI of 30.1 (6.0) kg/m^2. A total of 229 patients (46.0%) were obese. The most common cardiovascular disease reported was previous acute coronary syndrome (38.9%). A significant

Table 3. Cardiovascular risk factors and baseline laboratory values

Variables	*Values*
Cardiovascular risk factors (*n* = 491)	
Hypertension, *n* (%)	381 (77.6)
Diabetes mellitus, *n* (%)	316 (64.4)
Proteinuria, *n* (%)	71 (14.5)
Total cholesterol > 8 mmol/l, *n* (%)	67 (13.7)
Diabetic retinopathy, *n* (%)	23 (4.7)
Smoking, *n* (%)	
Current	80 (16.3)
Past	127 (25.9)
Non-smoker	284 (57.8)
Severe chronic kidney disease stage IV/V, *n* (%)	6 (1.2)
Alcohol abuse, *n* (%)[#]	11 (2.2)
FH, *n* (%)	101 (20.6)
Laboratory values	
Total cholesterol (mmol/l), median (IQR)	4.1 (3.4–5.1)
LDL-C (mmol/l), median (IQR)	2.2 (1.6–3.1)
Triglycerides (mmol/l) (473*), median (IQR)	1.6 (1.1–2.4)
HDL-C (mmol/l) (465*), median (IQR)	1.1 (0.9–1.3)
Serum glucose (mmol/l) (304*), median (IQR)	7.1 (5.7–9.8)
HbA_{1c} (%) (316*), median (IQR)	7.3 (6.3–8.7)
Serum creatinine (µmol/l) (396*), median (IQR)	82 (70–980
GFR (ml/min) (356*), median (IQR)	77 (60–89)

*Missing data for some patients, [#]based on clinician evaluation.
FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, glycated haemoglobin; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol.

Table 4. Family history of premature cardiovascular events (n = 491)

Family history	*Number (%)*
Coronary artery disease	133 (27.1)
Cerebrovascular disease	36 (7.3)
Peripheral artery disease	3 (0.6)

Table 5. Ezetimibe use in the study population

Combination of ezetimibe and statin (n = *68*)	*mg*	*Number (%)*	
Atorvastatin (n = 32)	10	2 (2.9)	
	20	1 (1.5)	
	40	2 (2.9)	
	80	27 (39.7)	
Rosuvastatin (n = 25)	10	1 (1.5)	
	20	4 (5.9)	
	40	20 (29.4)	
Simvastatin (n = 10)	20	5 (7.3)	
	40	5 (7.3)	
Pravastatin (n = 1)	10	1 (1.5)	
Maximum treatment group (n = *53*)	*mg*	*Number (%)*	*Reached LDL-C goal,* n *(%)*
Ezetimibe + atorvastatin	40	2 (3.8)	1 (50.0)
	80	27 (50.9)	2 (7.4)
Ezetimibe + rosuvastatin	20	4 (7.5)	1 (25.0)
	40	20 (37.7)	4 (20.0)

Table 6. Patient characteristics stratified by LDL-C < 1.8 mmol/l (goal) and > 5 mmol/l

Patient characteristics	*LDL-C goal (< 1.8 mmol/l)* (n = *161*)	*LDL-C > 5 mmol/l* (n = *16*)
Gender, *n* (%)		
Male	118 (73.2)	7 (43.7)
Female	43 (26.7)	9 (56.3)
Age mean (years), mean ± SD	62.9 ± 10.5	53.9 ± 10.9
Ethnicity, *n* (%)		
Black	34 (100.00)	0 (0.0)
Caucasian	48 (87.3)	7 (12.7)
Asian	72 (97.3)	2 (2.7)
Mixed	7 (50.0)	7 (50.0)
Duration of dyslipidaemia (years), mean ± SD	10.9 ± 7.4	14.3 ± 11.6
Obesity (BMI > 30 kg/m²), *n* (%)	72 (45.3)	6 (37.5)
Family history of premature atherosclerotic disease, *n* (%)	33 (20.5)	6 (37.5)
Familial hypercholesterolaemia, *n* (%)	4 (2.5)	13 (81.3)
Diabetes mellitus, *n* (%)	121 (75.2)	6 (37.5)

proportion of study subjects had a history of percutaneous coronary intervention (33.2%) and/or coronary artery bypass grafting (21.0%). The most frequent cardiovascular risk factors were hypertension (77.6%) and diabetes mellitus (64.4%). The prevalence of diagnosed FH in this cohort was 20.6%.

Most patients (50.0%) were taking atorvastatin, followed by rosuvastatin (30.8%), simvastatin (18.8%) and pravastatin (0.4%). All were on the maximum-tolerated dose of statin therapy according to their physician's assessment. The number of patients on different statins is shown in Fig. 1.

Only 68 (13.8%) of the patients were prescribed ezetimibe and none received ezetimibe monotherapy (Table 5). The reported reasons for not using ezetimibe included that ezetimibe use was not considered necessary by the prescribing physician (48.7%), financial constraints relating to cost or reimbursement (31.7%), physician choice (8.3%) and other (11.3%). Most patients prescribed ezetimibe were also receiving high-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) and were defined as the maximum-treatment group.

Only 161 of the 491 (32.8%) patients who were taking the maximum-tolerated statin dose, with or without ezetimibe, reached the LDL-C goal of < 1.8 mmol/l. This percentage was even lower (16.2%) in patients on ezetimibe. In the group of maximally treated patients (high-dose statin plus ezetimibe) the at-goal rate was 13.2%.

In the 330 patients not at LDL-C goal, the LDL-C level was between 2.5 and 5.0 mmol/l in most patients (56.4%). Less than 20% (18.8%) of these patients were receiving maximal lipid-lowering therapy. LDL-C level higher than 5 mmol/l despite aggressive therapy was relatively uncommon and was found in only 16 (4.8%) patients. More females than males (nine vs seven) had an LDL-C level of > 5 mmol/l on treatment, although our study overall had recruited significantly more males than females.

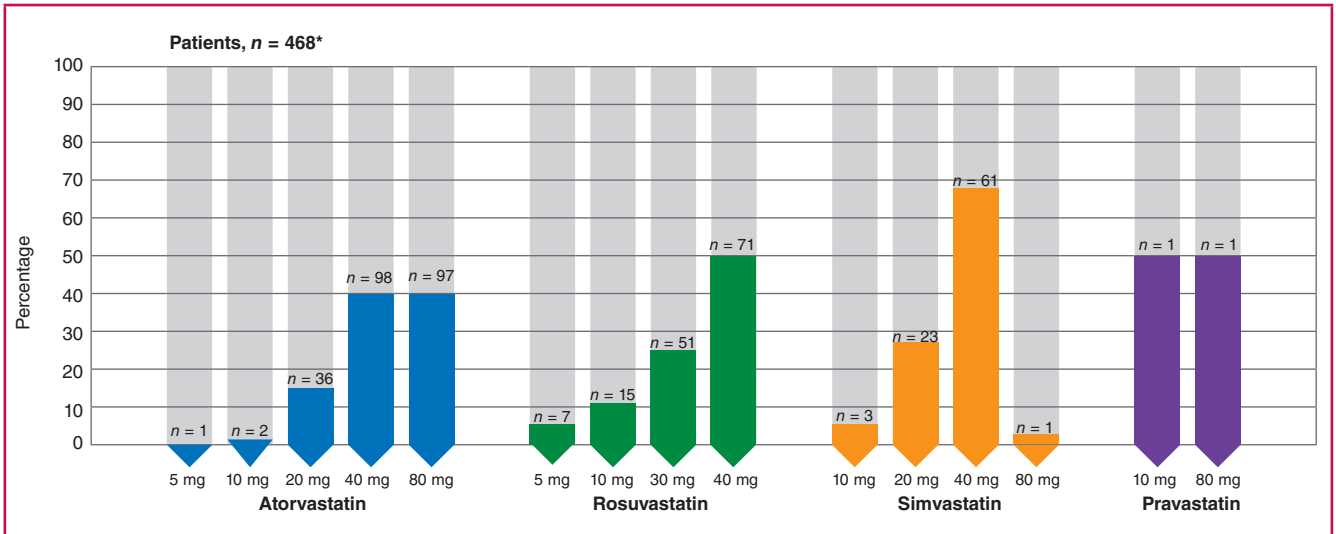

Fig. 1. Statin doses (n = 468*).

Table 7. Rosuvastatin dose equivalent based on statin potency ± ezetimibe use and LDL-C goal attainment*

Rosuvastatin dose equivalents (mg)	*(n = 468**)* n *(% of study population)*	*Reached LDL-C goal (*n *=146)* n *(% on dose at goal)*
2.5	4 (0.8)	2 (50)
5	27 (5.8)	12 (44)
10	105 (22.4)	39 (37)
20	144 (30.8)	55 (38)
40	128 (27.4)	29 (23)
80	7 (1.5)	2 (29)
160	6 (1.3)	2 (33)
320	47 (10.0)	5 (11)

*The effect of adding ezetimibe to a statin was estimated by doubling the rosuvastatin dose equivalent three times – patients taking rosuvastatin 40 mg/d and ezetimibe are therefore estimated to be taking a rosuvastatin dose equivalent of 320 mg/d.

The patients with LDL-C > 5.0 mmol/l were younger than those who reached their LDL-C goal (mean age 53.9 ± 10.9 vs 62.9 ± 10.5 years). These patients had in general been on treatment for longer periods of time [14.3 (11.6) vs10.9 (7.4) years] and the majority (81.3%) had been diagnosed with FH (Table 6). Only four patients with LDL-C > 5.0 mmol/l were receiving maximal lipid treatment. Very low LDL-C (< 1.0 mmol/l) level was uncommon and was only seen in 13.7% of patients.

Using the rosuvastatin and ezetimibe equivalent dose adjustments, most patients received the equivalent of 20 mg rosuvastatin (30.8%) followed by the 40 mg equivalent dose (27.4%) (Table 7).

Modelling analysis

Model 1: This model estimated the impact of up-titrating all patients who were not receiving ezetimibe to a maximal statin dose. We included all patients not at goal, who were not on ezetimibe and who were not receiving a rosuvastatin dose equivalent of 40 mg in this simulation. For each patient we calculated how many doublings they were away from the rosuvastatin 40-mg dose equivalent. For example, a patient who was on rosuvastatin 20 mg was one doubling away from rosuvastatin 40 mg, a patient on atorvastatin 20 mg (equivalent to rosuvastatin 10 mg) was two doublings away. The number of doublings was calculated by dividing 40 by the current dose equivalent and then deriving the log base 2. We then multiplied the result for the number of doublings required by 6% and subtracted this percentage from the current LDL-C level.

For example, a patient on atorvastatin 5 mg with an LDL-C of 3.5 mmol/l would be receiving a rosuvastatin dose equivalent of 2.5 mg. This patient would be four doublings (40/2.5 = 16 and $\log_2 16 = 4$) away from a rosuvastatin dose equivalent of 40 mg. Maximising the statin dose in this patient would result in an additional 24% (4 × 6%) reduction in LDL-C level and the estimated LDL-C level on maximal statin therapy would be 2.66 mmol/l.

Maximising the statin dose in the 171 patients eligible for this intervention would result in an additional 31 (18.1%) patients reaching LDL-C goal.

Model 2: This model estimated the impact of maximising the statin dose (if required) and then adding ezetimibe. We included all patients not at target who were not receiving ezetimibe, irrespective of statin dose in this analysis. In a first step we maximised the statin dose as shown above (for those who needed it) and then estimated the effect of ezetimibe by lowering the LDL-C level by a further 18%.

We included 265 patients in this analysis. This strategy would allow 92 (34.7%) additional patients to reach their LDL-C goal.

Model 3: With this model we evaluated the impact of maximising the statin dose, adding ezetimibe and then a PCSK9 inhibitor. In the first step we estimated the effect of increasing the statin dose to the maximum and adding ezetimibe to all patients who were not taking ezetimibe. We assumed that PCSK9 inhibitors would reduce the LDL-C level by a further 60% and calculated at-target rates following addition of a PCSK9 inhibitor.

Using this strategy, most patients not at goal (310 of 322, 96.3%) were able to reach their LDL-C target.

Model 4: In our last model we included all patients not at target and estimated the impact of adding a PCSK9 inhibitor without changing any of the other lipid-lowering therapy. With this intervention 92.9% (299 of 322 patients) would be at LDL-C goal.

Discussion

As CARDIO TRACK targeted a very high-risk population, the very high prevalence of diabetes mellitus (64.4%) and hypertension (77.6%) were not surprising. A significant number of patients (16.3%) were still smoking despite their very high-risk status.

The majority of the study population did not reach their LDL-C goal of < 1.8 mmol/l despite treatment with maximum-tolerated doses of high-intensity statins. The reasons for this are likely multifactorial.

Assuming that high-intensity statins reduce LDL-C level approximately 50% from baseline, then many patients with an untreated LDL-C > 3.6 mmol/l are not likely to reach target on a statin alone. Poor adherence to lipid-lowering therapy is also common and although we attempted to exclude patients with a history of non-adherence, we did not objectively assess adherence in this study. In a recent analysis of patients with probable FH in the ICPLS study, the real-world observed LDL-C reductions from baseline were also significantly lower than those projected based on reported statin potency.[14]

In an observational study of patient records from a German claims database, Kostev and colleagues reported that only 15% of 49 406 very high-risk patients with dyslipidaemia achieved a target LDL-C level of < 1.8 mmol/l despite high-dose statin use and a medication dispensing rate above 80%.[15] Furthermore, this study was based in Germany, making generalisability to a heterogeneous South African population challenging.

Ezetimibe was underused in our study population. Multiple other trials conducted in very high-risk populations also show a low use of statin plus ezetimibe combination therapy. In the FOURIER trial that evaluated the addition of evolocumab to conventional lipid-lowering therapy in patients with established atherosclerotic cardiovascular disease, only 5% of the study population were on ezetimibe treatment at enrollment.[16] Similarly, in the alirocumab ODYSSEY OUTCOME trial, only 3% of patients with an acute coronary syndrome within the last year were on ezetimibe.[17]

The most current South African dyslipidaemia guidelines recommend ezetimibe as a second-line treatment in combination with a statin when the LDL-C target is not achieved with the highest tolerated statin dose, when there is intolerance to statins or when there is a contra-indication to a statin.[18] However, the guidelines in place at the time of the study was conducted did not strongly endorse ezetimibe, as no cardiovascular outcome evidence was available for ezetimibe at the time the guidelines were compiled.[19] Lack of cardiovascular outcome data may have dissuaded some practitioners from prescribing ezetimibe.

Although one would expect a greater proportion of study participants receiving ezetimibe, especially when added to the highest possible statin dose, to reach LDL-C target, this was not the case. This finding is not unexpected as the authors frequently observe in clinical practice that clinicians are more likely to prescribe ezetimibe to patients who were far from their LDL-C goal. We have also noted that many funders in South Africa will not reimburse ezetimibe if patients are close to target. The use of ezetimibe may well increase as single-pill combination tablets of ezetimibe with a potent statin (atorvastatin or rosuvastatin) become available in South Africa, and especially if these combination tablets are less costly than prescribing two individual medications.

In our modelling analysis, we evaluated the impact of four different treatment strategies in bringing patients to goal. Because doubling the dose of a statin on average only decreases LDL-C level by a further 6%, the statin maximisation strategy was able to bring only 18% of those not at goal to goal. Adding ezetimibe following statin maximisation would allow 34% of patients previously not at goal to achieve goal. Because PCSK9 inhibitors reduce LDL-C level on average by about 60% when added to statin therapy, the addition of a PCSK9 inhibitor to a statin would allow over 90% of patients to reach goal. Most patients receiving a PCSK9 inhibitor would be able to reach goal without a statin dose increase or the addition of ezetimibe.

A simulation of various lipid-lowering strategies in American patients with atherosclerotic cardiovascular disease using data from a large administrative database showed that statin intensification would bring about 67.3% of patients to an LDL-C target of 1.8 mmol/l, while approximately 14% of patients would require a PCSK9 inhibitor.[20] In our cohort, many more patients would require PCSK9 inhibitors to reach target as we selected a population that was already receiving the maximal tolerated statin dose and specifically included patients with FH. As PCSK9 inhibitors are costly monoclonal antibodies, access to these drugs will be limited once they are commercially available in South Africa.

The 2018 update of the South African dyslipidaemia guidelines recommends considering PCSK9 inhibitor therapy in three groups of patients: first, in patients with atherosclerotic cardiovascular disease (coronary artery disease, symptomatic peripheral artery disease, ischaemic stroke) at very high risk who have substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy;[18] second, in patients with FH without clinically diagnosed atherosclerotic cardiovascular disease, at high or very high cardiovascular risk, and with substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy;[18] last, in patients with atherosclerotic cardiovascular disease and at very high risk who do not tolerate appropriate doses of at least three statins and who have elevated LDL-C levels despite alternative lipid-lowering therapies, such as ezetimibe.[18] Initial priority will need to be given to those patients with the highest baseline risk and LDL-C level in whom the number needed to treat will be the lowest.

Limitations

Potential study sites were conveniently sampled and patients attending these sites may not be fully representative of the spectrum of South African patients with dyslipidaemia. Only one study site was in the public sector and this site was based at a tertiary-level teaching hospital. Public sector patients are therefore not adequately represented in this study.

We were not able to objectively assess adherence to lipid-lowering therapy and incomplete adherence may well have been a contributing factor in some patients not at goal. We were unable to describe the specific statin dose for 23 patients because the information was not collected in the case report forms. This was an error that we detected after completion of the study and logistical issues precluded us from obtaining missing information from sites. In our opinion it is improbable that this would make a material difference to the results, discussion and conclusion of this study.

For our modelling analysis, we made several assumptions, including that patients will adhere to the prescribed therapy perfectly and that it will be possible to up-titrate all patients to the maximum statin dose. Because responses to lipid-lowering therapies may be variable, some patients may show larger or smaller decreases in LDL-C level at the various stages of our titration algorithm, but in a large population we would expect the average response to be close to previously published values. Incomplete adherence would reduce the number of patients reaching target at the various steps of our titration algorithm, as would an inability to titrate all patients to the maximum statin dose.

Conclusion

The majority of study participants were not at LDL-C goal despite maximum-tolerated statin with or without ezetimibe therapy, highlighting the importance of further treatment intensification in this high-risk population. Currently PCSK9 inhibitors, in combination with statin, is the most effective therapeutic strategy to reach LDL-C goals, but because of the anticipated high cost of the drug, access will be limited in South Africa. Despite the under-usage of ezetimibe in this study, the addition of ezetimibe to existing maximum-tolerated statin would result in a larger proportion of the study population reaching target LDL-C goals, therefore contributing to a greater reduction in atherosclerotic cardiovascular disease.

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PN, AvT and MGM are employees of Sanofi. PN, AvT and MGM do not own stocks in Sanofi or Regeneron. Sanofi manufactures and markets lipid-lowering therapies. Sanofi and Regeneron manufacture and market a PCSK9 inhibitor.

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Effect of invasive strategy on long-term mortality in elderly patients presenting with acute coronary syndrome

Samet Yilmaz, Mehmet Koray Adali, Oguz Kilic, Aysen Til, Yalin Tolga Yaylali

Abstract

Objective: The elderly have the highest incidence of cardiovascular disease and frequently present with acute coronary syndrome (ACS). In this study, our aim was to evaluate the effect of an invasive strategy on long-term mortality in patients of 80 years and older presenting with ACS.

Methods: Patients who were admitted to hospital with ACS were recruited using appropriate ICD codes in the computerised hospital data system. After exclusion of patients below 80 years old, the remaining 156 patients were involved in the final analyses. Ninety-four of 156 patients (60.3%) underwent coronary angiography and they constituted the invasive-strategy group, whereas the remaining 62 (39.7%) patients were treated medically and they constituted the conservative-strategy group.

Results: Median follow-up duration of patients was 8.5 (0–61) months. Total mortality at the end of the follow-up period was 24 (25.5%) patients in the invasive-strategy group and 30 (48.4%) in the conservative-strategy group (p = 0.006). According to Cox regression analysis, the invasive strategy (OR: 0.26, 95% CI: 0.12–0.56, p = 0.001), presentation with ST-segment elevation myocardial infarction (OR: 7.76, 95% CI: 1.74–34.57, p = 0.002), low ejection fraction below 40% (OR: 3.11, 95% CI: 1.43–6.76, p = 0.004), heart rate (OR: 0.98, 95% CI: 0.96–0.99, p = 0.013) and GRACE risk score between 150 and 170 (OR: 7.76, 95% CI: 1.74–34.57, p = 0.002) were related to long-term mortality.

Conclusions: Our results show the benefit of the invasive strategy on mortality rate in elderly patients over 80 years old and presenting with ACS.

Keywords: elderly, acute coronary syndrome, mortality

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Cardiology Department, Pamukkale University Hospitals, Pamukkale, Denizli, Turkey
Samet Yilmaz, MD, sametyilmazmd@gmail.com
Mehmet Koray Adali, MD
Oguz Kilic, MD
Yalın Tolga Yaylali, MD

Public Health Department, Pamukkale University, Pamukkale, Denizli, Turkey
Aysen Til, MD

With the aging of societies, the elderly population is increasing. Acute coronary syndrome (ACS) is not only the causative factor for mortality in younger people but is also one of the major causes of death in elderly people.[1] Coronary atherosclerosis is a dynamic process and progresses over time, so aging is a well-known risk factor for coronary artery disease.

Patients over 80 years account for more than one-third of those presenting with ACS and for more than 50% of in-hospital mortality due to ACS.[2] However, randomised, controlled trials have given less importance to elderly patients. For example, in the TRITON-TIMI 38 study, 13% of the patients and in the PLATO study, 15% of the patients were over the age of 75 years.[3,4] Therefore scientific evidence concerning elderly patients in ACS is scarce.

There are no specific guidelines concerning the treatment of elderly patients, hence the treatment strategy is not clear in this population.[5] Elderly patients diagnosed with ACS represent a high-risk population and therefore they should be treated more aggressively.

Over the last decade, an almost linear decrease in rates of mortality after ACS has been reported in all age classes, including the very elderly, in association with both the increased use of early percutaneous coronary intervention (PCI) and recommended medications.[6] Registry data from Europe showed that, over the last 15 years, the progressive switch from a conservative treatment to a more invasive approach may have contributed to reduction in mortality rates across the ACS spectrum, irrespective of age and gender.[7,8]

In this trial, our aim was to demonstrate the effect of the invasive strategy on long-term mortality rates in patients 80 years and older presenting with ACS.

Methods

Patients who were hospitalised due to a diagnosis of ACS between August 2014 and October 2017 were retrospectively screened for this trial. Patients who were admitted to hospital with ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (USAP) were selected using appropriate ICD codes in the computerised hospital data system. After the exclusion of patients below 80 years, the remaining 156 patients were involved in the final analyses.

This study was in compliance with the principles outlined in the Declaration of Helsinki. It was approved by the local ethics committee.

STEMI was defined by characteristic symptoms of myocardial ischaemia in association with persistent electrocardiographic ST elevation and the subsequent release of biomarkers of myocardial necrosis. Diagnostic ST elevation in the absence of left ventricular (LV) hypertrophy or left bundle branch block is defined by the European Society of Cardiology/American Heart Association/World Heart Federation Task Force as is the

universal definition of myocardial infarction as new ST elevation at the J point in at least two contiguous leads of 2 mm (0.2 mv) in men or 1.5 mm (0.15 mv) in women in leads v2–v3 and/or of 1 mm (0.1 mv) in other contiguous chest leads or the limb leads.[9,10]

In the spectrum of ACS, USAP/NSTEMI was defined by electrocardiographic ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g. troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent).[11] NSTEMI was diagnosed by the presence of positive cardiac enzymes, whereas USAP was not associated with elevated cardiac biomarkers.

Pamukkale University hospital is a tertiary centre having the capability of coronary angiography and PCI 24 hours a day, seven days a week. Patients with a suspicion of ACS were evaluated by emergency department physicians and cardiologists until the final diagnosis.

Patients' demographic and clinical features, and laboratory parameters were obtained retrospectively from the hospital database. Hypertension was defined as documentation of a systolic blood pressure of 140 mmHg and/or a diastolic blood pressure of 90 mmHg in at least two measurements or active use of any antihypertensive agent. Diabetes mellitus was defined as a fasting plasma glucose level over 126 mg/dl (6.99 mmol/l) or glucose level over 200 mg/dl (11.1 mmol/l) at any measurement or active use of an antidiabetic agent. Smokers were defined as patients who continued smoking at presentation.

All patients got in-hospital medication according to current guidelines.[12,13] A loading dose of 300 mg acetylsalicylic acid was given to all patients after the diagnosis of ACS. Clopidogrel (300 or 600 mg loading dose) or ticagrelor (180 mg loading dose) were given in addition to acetylsalicylic acid according to the preference of the patient's physician. Unfractionated heparin or low-molecular weight heparin were given according to the patient's weight.

The decision to perform coronary angiography and the timing of the procedure were determined by the patient's physician. The standard Judkins technique was used for visualisation of the coronary arteries. In-hospital and long-term mortality data were obtained from hospital records and national mortality records.

The primary endpoint was defined as all-cause mortality at the prespecified time points. These were: short term (30-day mortality), midterm (T1), defined as the time between 31 days and six months, T2, defined as the time between 31 days and 12 months, and long term, defined as the time period beyond 12 months.

Statistical analysis

The analyses were carried out using the SPSS 24 (SPSS Inc, Chicago, IL). To test the distribution pattern, the Kolmogorov–Smirnov and Shapiro–Wilk methods, and Skewness and Kurtosis results were used. Continuous data, which were not distributed normally, are presented as median ± interquartile range (IQR); categorical variables are given as percentages. Categorical variables were compared with the chi-squared test. Yates' correction was used where necessary. Fisher's exact test was used when expected frequencies were ≤ 5. Continuous variables were compared with the Mann Whitney *U*-test. Cox regression analysis was used to assess the effect of the strategy on mortality rate. All parameters in the univariate analysis, which has a *p*-value < 0.25 and variables, which are the known risk factors of coronary artery disease, were selected in the multivariate model. A *p*-value of < 0.05 was considered statistically significant.

Results

A total of 156 patients (80 male, 51.2%) with a median age of 83 ± 5 years were included in this study. Ninety-four of 156 patients (60.3%) underwent coronary angiography and they constituted the invasive-strategy group, whereas the remaining 62 (39.7%) were treated medically and they constituted the conservative-strategy group. In the invasive group, 54 (34.6%) patients underwent PCI, 18 (11.5%) underwent coronary artery bypass grafting (CABG) surgery and the remaining patients did not undergo revascularisation because their lesions were not amenable to either the percutaneous or surgical procedure.

Patients' demographic features and clinical characteristics are presented in Table 1. Patients in the invasive group were younger and more were hypertensive than patients in the conservative group ($p = 0.002$ and $p = 0.015$, respectively). Serum creatinine levels at admission were significantly higher in the conservative-strategy group (1.1 ± 0.6 vs 0.9 ± 0.4 mg/dl, $p = 0.042$). However there was no difference in terms of cardiac enzymes or GRACE risk scores between the groups. Compared with the conservative group of patients, the invasive group presented more often with classical ACS symptoms such as chest pain (89.4 vs 69.4%, $p = 0.002$), while they had dyspnoea or other symptoms less frequently (10.6 vs 30.6%, $p = 0.002$).

Median follow-up duration of patients was 8.5 (0–61) months. A total of 16 (17%) patients in the invasive group and 24 (38.7%) in the conservative group died during the one-year follow up ($p = 0.004$) (Fig. 1). Mortality rates at the prespecified time points are reported in Table 2. Total mortality at the end of the follow-up period was 24 (25.5%) patients in the invasive-strategy group and 30 (48.4%) in the conservative-strategy group ($p = 0.006$) (Fig. 2).

Eighty-two (52%) patients had coronary artery disease history before the enrollment and 28 (34%) of them died during follow up. Seventy-four patients (48%) had no coronary artery disease history and 26 (35%) of them died during follow up. There was no statistically significant difference regarding presence of coronary artery disease and mortality ($p = 0.897$).

Two models were generated in Cox regresssion analysis to find factors related to mortality. The models and included factors are presented in Table 3. According to model 1, the invasive strategy [odds ratio (OR): 0.25, 95% confidence interval (CI): 0.08–0.74, $p = 0.012$], male gender (OR: 3.93, 95% CI: 1.36–11.35, $p = 0.011$), presence of hypertension (OR: 2.65, 95% CI: 1.11–6.32, $p = 0.027$), low ejection fraction below 40% (OR: 4.49, 95% CI: 1.66–12.10, $p = 0.003$), GRACE risk score below 150 (OR: 0.18, 95% CI: 0.03–0.86, $p = 0.032$) and sinus rhythm at admission electrocardiography (ECG) (OR: 0.21, 95% CI: 0.05–0.85, $p = 0.029$) were found to be related to long-term mortality rate.

According to model 2, the invasive strategy (OR: 0.26, 95% CI: 0.12–0.56, $p = 0.001$), presentation with STEMI (OR: 7.76, 95% CI: 1.74–34.57, $p = 0.002$), low ejection fraction below 40% (OR: 3.11, 95% CI: 1.43–6.76, $p = 0.004$), heart rate (OR: 0.98, 95% CI: 0.96–0.99, $p = 0.013$) and GRACE risk score between 150 and 170 (OR: 7.76, 95% CI: 1.74–34.57, $p = 0.002$) were related to long-term mortality rate.

Table 1. Patients' clinical characteristics by adopted strategy

Clinical characteristics	*Total (n = 156)*	*Invasive strategy 94 (60.3%)*	*Conservative strategy 62 (39.7%)*	p-*value*
Demographic chracteristics				
Age (median,IR)	156	83.0 (4)	85.0 (6)	0.002
Men, *n* (%)	80	50 (53.2)	30 (48.4)	0.557
Risk factors, *n* (%)				
Smoking	68	44 (46.8)	24 (38.7)	0.318
Dyslipidaemia	36	22 (23.4)	14 (22.6)	0.905
Hypertension	99	52 (55.3)	47 (75.8)	0.015
Diabetes	61	37 (39.4)	24 (38.7)	0.935
Biochemical risk profile (median, IR)				
CKMB (ng/ml)	156	15.8 (73.9)	9.0 (25.2)	0.275
Troponin I (ng/ml)	156	0.5 (2.4)	0.2 (1.6)	0.213
Total cholesterol (mg/dl)	156	164.0 (62.0)	166.5 (64.0)	0.841
(mmol/l)		4.25 (1.61)	4.31 (1.66)	
HDL cholesterol (mg/dl)	156	41.0 (15.0)	43.0 (19.0)	0.859
(mmol/l)		1.06 (0.39)	1.11 (0.49)	
Triglycerides (mg/dl)	156	99.0 (54.0)	107.5 (105.0)	0.488
(mmol/l)		1.12 (0.61)	1.21 (1.19)	
Serum creatinine (mg/dl)	156	0.9 (0.4)	1.1 (0.6)	0.042
Admission haemoglobine (g/dl)	156	12.3 (2.5)	12.1 (2.4)	0.518
Serum glucose (mg/dl)	156	123.0 (63.0)	121.0 (57.0)	0.815
(mmol/l)		6.83 (3.5)	6.72 (3.16)	
Clinical risk profile				
SBP (mmHg) (median, IR)	156	128.0 (32.5)	128.0 (36.5)	0.882
Heart rate (bpm) (median, IR)	156	80.0 (20.0)	80.0 (25.0)	0.087
GRACE risk score classes, *n* (%)				
≤ 150	43	30 (31.9)	13 (21.0)	0.320
151–174	75	42 (44.7)	33 (53.2)	
≥ 175	38	22 (23.4)	16 (25.8)	
Cardiac arrest at admission, *n* (%)	4	2 (2.1)	2 (3.2)	0.671
Ejection fraction classes, *n* (%)				
≤ 40%	61	33 (35.1)	28 (45.2)	0.208
> 40%	95	61 (64.9)	34 (54.8)	
Presentation symptoms, *n* (%)				
Chest pain	127	84 (89.4)	43 (69.4)	0.002
Dyspnoea	29	10 (10.6)	19 (30.6)	
ECG results, *n* (%)				
Sinus rhythm	131	76 (80.9)	55 (88.7)	0.390
Atrial fibrillation	20	14 (14.9)	6 (9.7)	
Atrioventriculer block	5	4 (4.3)	1 (1.6)	

IR, interquartile range; CKMB, creatine kinase myocardial band; HDL, high-density lipoprotein; SBP, systolic blood pressure; ECG, electrocardiography.

Discussion

Over a median follow up of 8.5 months, the invasive strategy significantly reduced total mortality rates compared to the conservative strategy in ACS patients who were older than 80 years. Other than the conservative strategy, older age, presence

Table 2. Patients' outcome according to invasive or conservative strategy

Outcome	*Invasive 94 (60.3%)*	*Conservative 62 (39.7%)*	p-*value*
Mortality, *n* (%)			
30-day cumulative	0 (0)	11 (17.7)	< 0.001
T1 time point	13 (13.8)	8 (15.7)	0.762
T2 time point	16 (17.0)	13 (25.5)	0.223
12-month cumulative	16 (17.0)	24 (38.7)	0.004
Total	24 (25.5)	30 (48.4)	0.006

T1, 31 days to 6 months; T2, 31 days to 12 months.

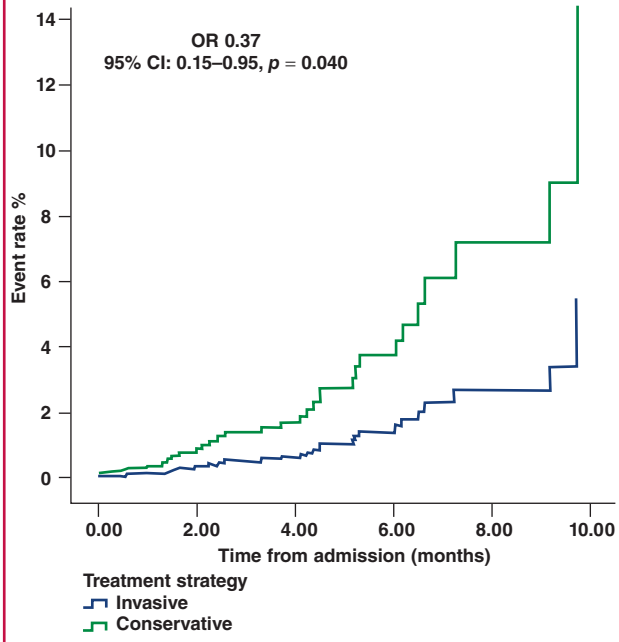

Fig. 1. One-year mortality rates based on treatment strategy.

of hypertension, low ejection fraction below 40%, high GRACE risk score and presentation with STEMI were also found to be related to long-term mortality rate.

Age is an important risk factor for ACS, and advanced age is also strongly associated with mortality in the presence of ACS.[14] The GRACE investigators showed that, among patients presenting with NSTEMI and referred for PCI or CABG, six-month mortality rate increased with age (1.6, 4.3 and 7.0% in patients < 70 years, 70–80 years and > 80 years, respectively).[15] In 47 407 consecutive patients who underwent PCI and were prospectively enrolled in the PCI registry of the EHS programme, in-hospital mortality rate was 1.7% in ACS patients less than 75

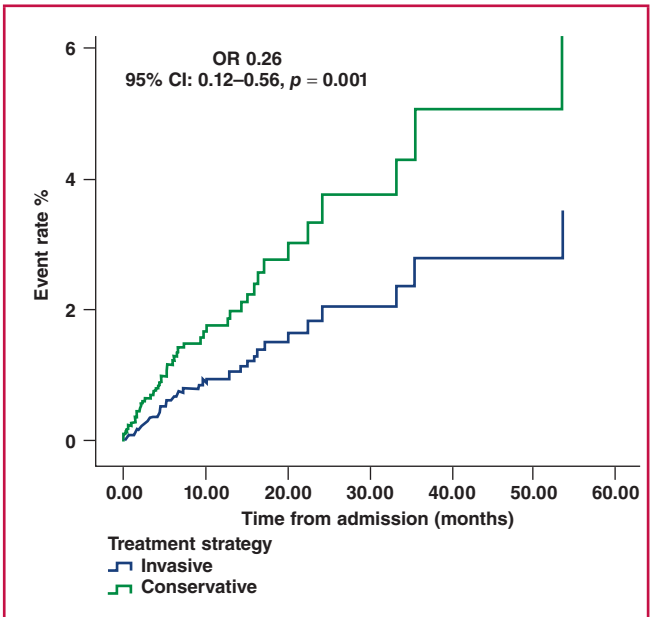

Fig. 2. Five-year mortality rates based on treatment strategy.

Table 3. Death predictors at the prespecified by Cox multivariate analysis

Mortality	*OR*	*95% CI*	p-*value*
Model 1			
Invasive strategy*			
Male	0.25	0.08–0.74	0.012
Hypertension	3.93	1.36–11.35	0.011
Ejection fraction ≤ 40%***	2.65	1.11–6.32	0.027
GRACE risk score	4.49	1.66–12.10	0.003
< 150****	0.18	0.03–0.86	0.032
150–175****	0.32	0.10–0.96	0.043
ECG sinus rhythm	0.21	0.05–0.85	0.029
Model 2			
Invasive strategy*	0.26	0.12–0.56	0.001
STEMI**	7.76	1.74–34.57	0.002
Ejection fraction ≤ 40% ***	3.11	1.43–6.76	0.004
Heart rate (bpm)	0.98	0.96–0.99	0.013
GRACE risk score 150–175****	0.32	0.15–0.70	0.004

OR, odds ratio; CI, confidence interval.
*Conservative strategy as ref. **USAP as ref. ***Ejection fraction > 40% as ref. ****Grace > 175 as ref.
Model 1: Treatment protocols, gender, diabetes, hypertension, dyslipidaemia, smoking, diagnosed, ejection fraction, ECG results, presentation symptoms, GRACE risk score.
Model 2: Treatment protocols, diagnosed, ejection fraction, heart rate, ECG results, smoking, admission SBP, presentation symptoms, GRACE risk score, CKMB peak value, troponin peak value.

years compared to 5.2% in those 75 years or older.[16] In another study in 1 470 NSTEMI patients from the Taiwan nationwide registry, older age ≥ 75 years increased mortality rate 4.9 times compared to patients 45–64 years of age.[17]

Our study represents the high risk elderly patients admitted with a diagnosis of ACS face in a contemporary cardiology clinic. About 71% of our patients were characterised by a GRACE risk score higher than 150, and more than 70% had a LV ejection fraction lower than 50%. As a treatment strategy, about 60% of our patients were managed invasively. In the literature, angiography rate in this population was slightly lower than in our study. In European and US registries, the reported proportion of elderly patients assigned to an invasive strategy was 50 to 33% in patients aged beyond 70 and 80 years, respectively.[15]

Our analysis of elderly patients with ACS demonstrated that an invasive strategy was associated with a lower mortality rate at follow up of a maximum of 61 months in comparison with an initial conservative strategy. Almost twice the risk of mortality has been seen with the conservative strategy. Similar to our results, Tegn *et al*. reported in their After Eighty study, an open-label, multicentre study targeting NSTEMI patients older than 80 years, that an invasive strategy was superior to a conservative strategy in reduction of composite events of death, myocardial infarction, stroke and the need for urgent revascularisation (40.6 vs 61.4%, hazard ratio 0.53, 95% CI: 0.41–0.69; $p = 0.0001$) at a median follow up of 1.53 years.[18] However in another study from Saudi Arabia, PCI had no effect on mortality rate in elderly patients with ACS.[19]

During the follow-up period, 75% of the STEMI patients in our study died. This value was 32% in the NSTEMI/USAP patients. This shows that STEMI has a worse prognosis than other types of ACS in elderly patients. Similar to our results, in another study, it was shown that STEMI increased mortality risk about two-fold compared to NSTEMI at older ages.[20] In another study from Switzerland from 2001 to 2012, in-hospital mortality rate decreased and PCI use was significantly increased in older patients.[21]

Ischaemic heart disease is the leading cause of death globally.[22] Because of the growth of the elderly population, the World Health Organisation predicts that coronary heart disease deaths will increase by 120 to 137% during the next two decades, and a person aged over 80 years can expect about nine remaining years of life.[23] For this reason, a strategy on how to treat very elderly patients is essential. The results from the present study support an invasive strategy in octogenarians presenting with ACS.

Our study has some limitations. First, it has a retrospective, cross-sectional design with single-centre data. Due to the retrospective retrieval of the patient data and the low patient numbers, our study cannot be generalised to all elderly populations. Second, diagnosis of ACS in the elderly population is challenging and multiple co-factors may affect cardiac enzyme elevation, so some patients could be misdiagnosed. Finally, the presence of multiple co-morbidities and the frailty of patients may affect long-term mortality rates in elderly patients.

Conclusion

Guideline-based therapy should be the basic strategy for all age groups in the presence of ACS. Within the indications, an invasive strategy should without doubt be applied in elderly patients. Advanced age of the patient should not be the reason for not receiving these treatments.

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IV drugs can rapidly restore normal heart rhythm without sedation, shocks

Electrical and intravenous drug cardioversion were equally efficacious in treating acute atrial fibrillation, found a large, randomised, controlled trial.

A large, randomised, controlled trial looked at cardioversion, a medical procedure that quickly brings heart rhythm back to normal. Cardioversion can be done with a mild electric shock or with fast-acting drugs delivered through an IV. 'These methods allow us to quickly get patients back to their normal heart rate and send them home after four to six hours in the emergency department,' said Dr Ian Stiell, lead author and senior scientist at the Ottawa Hospital and distinguished professor at the University of Ottawa.

Acute atrial fibrillation is a rapid, irregular heartbeat that must be treated within 48 hours to avoid complications such as stroke and heart failure. The study team estimates that acute atrial fibrillation accounts for 430 000 emergency department visits every year in Canada and the USA.

The researchers recruited 396 patients with acute atrial fibrillation from 11 Canadian emergency departments. Cardioversion is a commonly used treatment in this country. Patients were randomly assigned to one of two kinds. The first group received only electrical cardioversion. Patients are sedated during this procedure, so they do not feel the shock. The second group received a drug called procainamide through an IV. If the drug did not reset the patient's heart rhythm within 30 minutes, they received electrical cardioversion.

In the shock-only group (192 patients), 92% returned to their normal heart rhythm (176) and 95% were discharged home (183). In the drug-then-shock group (204 patients), 96% returned to their normal heart rhythm (196), 97% were discharged home (198), and 52% recovered their normal heart rhythm with the drug alone (106).

Both kinds of cardioversion were equally good at restoring normal heart rhythm and getting patients home the same day. The drug–shock strategy was more effective for patients experiencing atrial fibrillation for the first time, and for patients younger than 70 years.

The two methods were equally safe, none of the patients had any serious side effects. Two weeks after the treatment, no patients had had a stroke, 95% still had normal heart rhythm, 11% returned to the emergency department because of atrial fibrillation, 3% had an additional round of cardioversion, and 2% were admitted to hospital.

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Clinical spectrum and prevalence of congenital heart disease in children in Botswana

Tiny Mazhani, Andrew P Steenhoff, Endale Tefera, Thuso David, Zaakir Patel, Warona Sethomo, Marek Smieja, Loeto Mazhani

Abstract

Background: Reliable data on congenital heart disease (CHD) from diverse settings is important both for planning health systems in each country and to elucidate possible aetiologies of CHD in different settings. There is a lack of data on the clinical spectrum and prevalence of CHD in Botswana. The aim of this study was to describe the clinical spectrum and prevalence of CHD in Botswana.

Methods: This was a retrospective, descriptive, cross-sectional study of all children from birth to 15 years who had had an echocardiogram performed as an in- or out-patient at Princess Marina Hospital (PMH) between 1 January 2010 and 31 December 2012.

Results: Of 377 enrollees, 140 (40%) had normal echocardiographs, 170 (45%) had CHD, and 57 (15%) had an acquired lesion. In the CHD patients, median age was 0.9 years (Q1: 0.2, Q3: 4.1) and 85 (50%) were male. Ventricular septal defect (VSD) (29%), patent ductus arteriosus (18%), atrioventricular septal defect (AVSD) (10%) and tetralogy of Fallot (TOF) (6%) were the predominant pathologies. VSD was the most common acyanotic lesion and TOF the most common cyanotic lesion. The estimated prevalence of CHD was between 2.8 and 4.95 per 1 000 live births.

Conclusions: The clinical spectrum of CHD in Botswana is similar to that observed in other African countries and in the Western world, with VSD the most common acyanotic lesion and TOF the most common cyanotic lesion. The prevalence of CHD was 2.8–4.95 per 1 000 live births, in keeping with other settings. This is the first study to describe CHD in Botswana, and it aimed to stimulate subsequent studies in this field.

Department of Paediatric and Adolescent Health, Faculty of Medicine, University of Botswana, Gaborone, Botswana
Tiny Mazhani, MMed, MD, tinym106@yahoo.com
Andrew P Steenhoff, MD
Endale Tefera, MD
Thuso David, MD
Zaakir Patel, MD
Warona Sethomo, MD
Loeto Mazhani, MD

Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, USA
Andrew P Steenhoff, MD

Department of Paediatrics, Princess Marina Hospital, Gaborone, Botswana
Loeto Mazhani, MD

McMaster University, Hamilton, Ontario, Canada
Marek Smieja, MD, PhD

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Congenital heart disease (CHD) is defined as a gross structural abnormality of the heart or intrathoracic great vessels.[1] Although this abnormality is present at birth, it may initially be clinically silent and present with symptoms only later in life.[2] The prevalence and pattern of CHD varies within and between countries.[3] Reported estimates vary widely and there may be differences between low-, middle- and high-income countries. Reliable data on CHD from diverse settings are important for both planning health systems in each country and to elucidate possible aetiologies of CHD in different settings.[4]

In Botswana, as is the case in many low- and middle-income countries (LMIC), the clinical spectrum and prevalence of CHD is unknown as there are no published data on the epidemiology of CHD. The majority of Botswana's population receives clinical care from the government-funded public health system. As in many LMICs, Botswana's public health system faces challenges both in diagnosing and managing CHD. However, there is some in-country expertise, including echocardiography, to both diagnose and medically manage CHD. Additionally, for those patients with a correctable lesion, Botswana's middle-income status enables Batswana citizens to be referred to other countries for cardiac intervention and surgery. In this article we seek to begin to address the paucity of data on CHD in Botswana. Our objective was to describe the clinical spectrum and prevalence of CHD in Botswana.

Methods

This was a retrospective, descriptive, cross-sectional study of all children who had had an echocardiogram performed as an in- or out-patient at Princess Marina Hospital (PMH). The study period was from 1 January 2010 to 31 December 2012. The project was reviewed and approved by ethics boards at the Botswana Ministry of Health, PMH and the University of Botswana.

PMH is a 525-bed tertiary hospital located in Gaborone, Botswana's capital city. PMH is the main tertiary referral centre for district hospitals and clinics located in southern Botswana. For paediatric cardiology during the study period, the PMH paediatric cardiac clinic was the only referral centre for the entire country. The paediatric cardiac clinic saw out-patients three times a week and did in-patient consultations daily. It was

staffed by two general paediatricians with training in paediatric echocardiography and cardiology.

The clinic screened referrals for cardiac disease and managed children with known cardiac conditions, including CHD. Initial assessment of patients included history, physical examination, chest radiography and electrocardiography. Echocardiography was performed at the discretion of the attending paediatrician if any of the initial investigations suggested heart disease.

Patients diagnosed with CHD were managed medically, with repeat clinic follow-up visits, including echocardiograms as required. Patients requiring surgical correction were referred to South Africa and, following post-surgery hospital discharge, were managed back in Botswana.

Inclusion criteria were patients younger than 15 years of age who were seen at the PMH paediatric cardiac clinic and who had had at least one echocardiogram. Patients were identified by reviewing clinic echocardiography reports and applying the inclusion criteria. Duplicate records were deleted and only the initial echocardiography report was retained. The list of data points extracted included: age, gender, weight, and indication for and result of the echocardiogram.

During data collection we noted that from May 2014, all paediatric echocardiographs were performed by one paediatrician. Given that this paediatrician's record keeping was good, all echocardiograph reports performed after May 2014 were available for analysis. This presented an excellent opportunity to assess whether the spectrum of CHD that had been sampled between 1 January 2010 and 31 December 2012 was similar to that seen in 2014. Hence we included a comparator group for three months of 2014 (from 1 September to 30 November 2014) to assess for possible sampling bias.

Statistical analysis

Data were summarised using standard descriptive statistics and analysed using STATA version 12.0 (College Station, TX). A p-value of < 0.05 was deemed significant.

To estimate the prevalence of CHD, we took two approaches: first, for the three years from 2010 to 2012 with records from a single paediatrician, we calculated the number of new CHD patients seen per year. Given that this figure reflected the echocardiography reports of one of two paediatric cardiologists, we doubled this number to estimate the real number seen by two paediatric cardiologists per year. Using Botswana's 2012 annual birth cohort of 40 856 from the Botswana Vital Statistics Report as the denominator, we then estimated the prevalence of CHD.

For the comparator group, we used the same calculation to estimate the prevalence of CHD: for three months of 2014, we noted the number of unique patients with CHD. To adjust for the fact that patients return every three to six months for review at the clinic and that for these three months in 2014, the paediatric cardiologist was not on leave, we multiplied this by two to estimate the number of new unique CHD patients seen in the year 2014. This number was then used as the numerator, with the denominator the annual birth cohort, to estimate the prevalence of CHD in 2014.

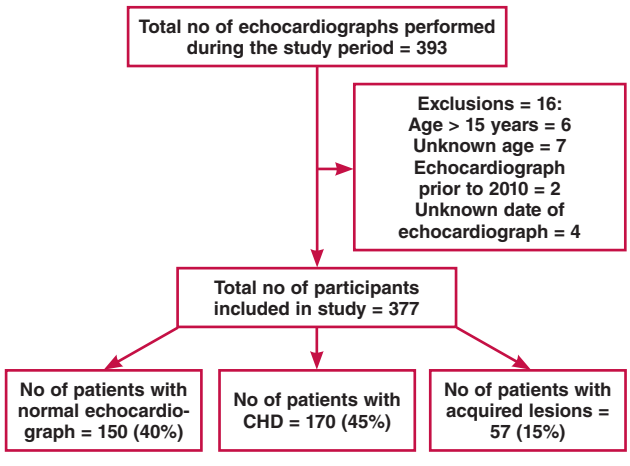

Fig. 1. Flow diagram of enrolled participants.

Results

Overall, 377 subjects met study inclusion criteria (Fig. 1). Of these, 170 (45%) had CHD, 150 (40%) had normal echocardiographs and 57 (15%) had acquired cardiac disease.

Demographics are summarised in Table 1. The median age of the study population was 1.3 years (interquartile range 2 months to 5.4 years) with a fairly even age distribution among children with CHD, whereas children with acquired heart disease tended to be in the oldest age group of 5 to 15 years (46%). Almost a quarter (24%) of patients with CHD had a weight-for-age less than the third standard deviation.

Indications for echocardiography are summarised in Table 2. The most common recorded indication was a known risk factor for CHD, including trisomy 21 (n = 10, 11%) and other dysmorphic features (n = 7, 7%). However, CHD risk factors were not specified in the majority of patients.

The distribution of CHD types is summarised in Fig. 2. The most common acyanotic congenital cardiac lesion was ventricular septal defect (VSD) (50/170; 29%). The most common cyanotic congenital cardiac lesion was tetralogy of Fallot (TOF) (11/170; 6%).

Of the 50 VSDs, VSD type was recorded in 23 (46%) cases: 8/23 (35%) were muscular, 8/23 (35%) were membranous, 5/23 (22%) were outlet and 2/23 (9%) were inlet. VSD size was small

Table 1. Clinical characteristics of children with normal versus abnormal echocardiographs

	Whole study population (n = 377) (%)	*Normal echocardiogram (n = 150) (%)*	*Abnormal echocardiogram (n = 227) (%)*	
			CHD (n = 170) (%)	*Acquired (n = 57) (%)*
Male gender*	188 (50)	74 (49)	85 (50)	29 (51)
Age group				
0–3 months	102 (27)	47 (31)	50 (28)	5 (9)
> 3 m–1 years	82 (22)	34 (23)	39 (23)	9 (11)
> 1–5 years	90 (24)	25 (17)	48 (28)	17 (30)
> 5–15 years	103 (27)	44 (29)	33 (19)	26 (46)
Weight for age				
Normal (> 0 SD)	80 (21)	36 (24)	34 (20)	10 (18)
0 to –3 SD	157 (42)	59 (39)	70 (41)	28 (49)
< –3 SD	72 (19)	26 (17)	40 (24)	6 (11)
Unknown	68 (18)	29 (19)	26 (15)	13 (23)

*There were five patients with unknown gender, the rest were female (n = 184).

Table 2. Indications for echocardiography

Indication	*Number (n = 377)*	*Percentage**
Risk factors for CHD	95	25
Suspected CHD	75	20
Follow up	66	17
Murmur	59	16
Post-operative	35	9
Cardiomegaly	32	8
Heart failure	7	2
Unknown	8	2

*Total approximated percentages = 99% due to rounding.

in 24/50 (48%), moderate in 10/50 (20%), large in 4/50 (8%) and not recorded in 12/50 (24%).

Of 31 patent ductus arteriosus (PDA) lesions, the size was small in 12 (38%), moderate in four (13%), large in 10 (32%) and not recorded in five (16%).

Gender and age differences between the most common congenital and acquired cardiac lesions are compared in Table 3. There was a slight male predominance in children with atrio-ventricular septal defect (AVSD) (58%) and cor pulmonale (80%). The median age of children with CHD was lower than children with an acquired cardiac lesion (0.9 vs 3.2 years; p = 0.001 by two-sample Wilcoxon rank-sum). Among CHD lesions, patients with TOF had the highest median age (5.4 years), whereas all other patients with CHD lesions had a median age of 2.4 years or younger.

From 2010 to 2012, 170 patients with CHD were seen at the PMH cardiac clinic, equating to 57 per year. As 57 CHD cases per year reflects only the echocardiography reports of one of two paediatric cardiologists, we doubled this number to estimate the real number seen by two paediatric cardiologists (114 in one year). Using Botswana's 2012 annual birth cohort of 40 856 from the Botswana Vital Statistics Report, the estimated prevalence of CHD was 114/40 856 = 2.8/1 000 live births.

For the comparator group in the three months of 2014, 99/172 patients seen at PMH cardiac clinic had CHD. This was an estimate of 198 cases seen in one year. Using Botswana's 2012 annual birth cohort of 40 856 (as numbers were not available for 2014), the estimated prevalence of CHD was 198/40 856 = 4.95/1 000 live births.

Discussion

This is the first study exploring the clinical spectrum and prevalence of CHD in children in Botswana. The project focused on PMH, the referral site for paediatric cardiology for the country. The estimated prevalence of CHD was between 2.8 and 4.95/1 000 live births.

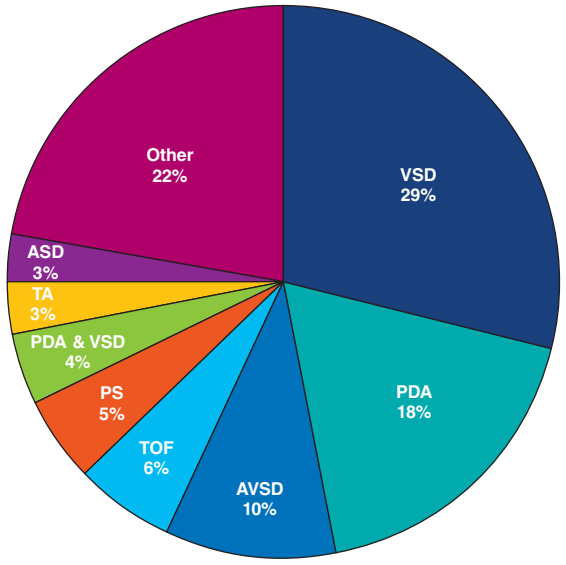

Fig. 2. Pie chart showing the distribution of CHD by pathology for the study group (n = 170).

Note: other includes four (2%) each of AR; three (2%) each of DORV (with PS), D-TGA, HLHS; two (1%) each of L-TGA, TR, CHD > two lesions; and one (0.6%) each of PAPVD, PS (with intra-cardiac shunt), AS, CoA (with VSD), MS, DORV (without PS), TAPVR, truncus arteriosus, single ventricle, primary pulmonary hypertension, mitral insufficiency, PR, PDA + ASD, and shone complex.

ASD, atrial septal defect; AVSD, atrioventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TA, tricuspid atresia; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 3. Distribution of congenital and acquired heart disease according to gender and age

Cardiac lesion	*Number (%)*	*Boys (% found in boys)*	*Age (years) Median (Q1, Q3)*
Congenital	n = 170	n = 85	
VSD	50 (29)	24 (48)	1.9 (0.2–5.1)
PDA	31 (18)	13 (42)	0.2 (0.1–0.7)
AVSD	17 (10)	10 (58)	0.4 (0.1–0.8)
TOF	11 (6)	6 (54)	5.4 (1.6–11.3)
PS	9 (5)	5 (55)	2.2 (0.6–4.7)
VSD + PDA	6 (4)	3 (50)	0.4 (0.2–0.9)
TA	5 (3)	2 (40)	0.9 (0.5–1.8)
ASD*	5 (3)	2 (40)	0.3 (0.1–0.5)
Others#	36 (21)	20 (56)	3.3 (0.1–5.8)
Total	170	85 (50)	0.9 (0.2–4.1)
Acquired	n = 57	n = 29	
Cardiomyopathy	22 (39)	9 (41)	5.4 (0.9–10.8)
Pericardial effusion	17 (29)	8 (47)	1.4 (0.6–5.3)
Cor pulmonale	10 (17)	8 (80)	3.5 (1.4–7.1)
Rheumatic heart disease	7 (12)	3 (42)	11.0 (5.2–14.5)
Malignancy	1 (2)	1 (100)	0.1 (0.1–0.1)
Total	57	29 (51%)	3.2 (1.2–10.8)

SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile.
*ASD includes ostium secundum and ostium primum.
#Other congenital heart disease includes: DORV (four), AR (four), D-TGA (three), HLHS (three), L-TGA (two), TR (three), CHD > two lesions (two), mitral insufficiency (two), PAPVD (one), PS with intracardiac shunt (one), AS (one), Ao co-arctation (one), MS (one), TAPVR (one), truncus arteriosus (one), single ventricle (one), primary pulmonary hypertension (one), PR (one), PDA +ASD (one), Shone complex (one), VSD +ASD (not AV canal) (one), aortic root dilatation (one).
AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrio-ventricular septal defect; CoA, co-arctation of the aorta; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; MS, mitral stenosis; PAPVD, partial anomalous pulmonary venous drainage; PDA, patent ductus arteriosus; PR, pulmonary regurgitation; PS, pulmonary stenosis; TA, tricuspid atresia; TAPVR, total anomalous pulmonary venous return; L-TGA, levo-transposition of the great arteries; D-TGA, dextro-transposition of the great arteries; TOF, tetralogy of Fallot; TR, tricuspid regurgitation; VSD, ventricular septal defect.

VSD was the most common acyanotic lesion. In descending order of prevalence, other common acyanotic lesions were PDA, AVSD, pulmonary stenosis (PS), PDA in combination with a VSD, and atrial septal defect (ASD). TOF was the most common cyanotic lesion followed by truncus arteriosus (TA).

The majority of African countries report VSD, TOF and PS as the most common lesions. A summary of the most prevalent CHD lesions by country is as follows: VSD and TOF in Cameroon and Nigeria,[3,5] VSD, PS and ASD in Egypt,[6] VSD, TOF and PDA in Zimbabwe,[7] VSD, TOF, PS, PDA, AVSD and ASD in Sudan,[8] and VSD, TOF and PS in Mauritania.[9] Worldwide the prevalence of CHD types in descending order of prevalence is VSD, ASD, PDA, PS, TOF, co-arctation of the aorta (CoA), transposition of the great arteries (TGA) and aortic stenosis (AS).[4]

VSD is the most common CHD lesion found in both African and Western countries.[10] In the 46% of patients where VSD type was recorded, muscular and membranous VSDs were most common in Botswana. Globally, peri-membranous VSDs are most common (70%).[11] Outlet (infundibular or conal) defects account for 5–7% of VSDs in Western countries, but can be as high as 30% in far Eastern countries.[11] Globally, inlet (or atrioventricular canal) defects account for 5–8%, while trabecular (muscular) VSDs account for 5–20% of VSDs.[11]

The fact that ASD did not appear as the second or third most common congenital heart disease actually underlines the most important bias associated with hospital-based studies. Because ASD is mostly asymptomatic in childhood and its murmur is also a soft pulmonic ejection murmur (flow murmur), it is the most common CHD diagnosed in adults for the first time. Silent PDAs (PDA < 1.5 mm, no murmur) may also not present to medical attention. Therefore, sampling a group of newborns or children from different communities based on certain attributes and carrying out echocardiography would be a reliable way of calculating the prevalence.

AVSD was the third most common lesion in our study. It was the fifth most common lesion in a Sudanese study[8] but was not found to be very prevalent in most other African studies. In a meta-analysis of worldwide CHD, articles studying only specific groups such as trisomy 21 were excluded. Eighteen patients in our study were found to have trisomy 21 and 10 (56%) had an AVSD. This may explain why our cohort was relatively 'enriched' for AVSD patients compared to these other studies.

TOF was the fourth most common CHD lesion, and the most common cyanotic lesion. In most African countries such as Cameroon, Nigeria, Zimbabwe, Sudan and Mauritania, TOF was the second most prevalent lesion and the most common cyanotic lesion.[5,7-9,12,13] We report an older age of patients with TOF in our study with a mean age of 6.1 years, however this likely reflects a survivor effect as patients with TOF in Botswana are referred for corrective cardiac surgery.

A small proportion of patients had acquired cardiac lesions. These included cardiomyopathy, pericardial effusion, cor pulmonale, rheumatic heart disease (RHD) and malignancy, in descending order of prevalence. As anticipated, the median age of CHD (0.9 years) was significantly lower than that of acquired heart disease (3.2 years). Nearly a third of children with pericardial effusions were underweight, likely in keeping with having tuberculosis, which accounts for the majority of pericardial effusions in Botswana. Only seven patients had RHD, suggesting a low prevalence of this condition. Similarly, Cilliers in neighbouring South Africa has reported a marked decline over the past two decades in the incidence of children with both acute rheumatic fever and RHD.[14] We assume that the low prevalence of RHD was due to an improvement in the socio-economic circumstances in Botswana, including ready access to first-line antibiotics, as has been the case globally.

When recorded, the most common indication for requesting echocardiography was presence of a risk factor for CHD. The most common recorded risk factor was trisomy 21. By comparison, in the Niger Delta region of Nigeria, a murmur was the most common indication for an echocardiograph.[15]

In our study, there was a skewed distribution of ages, with most subjects being young and a few being older. This resulted in a non-normal age distribution for the study cohort; the median age for the total study group was 1.3 years (interquartile range 0.2–5.4). Close to one-third (27%) of the entire study population was less than three months of age.

In most longitudinal series of CHD, approximately two to three per 1 000 newborns with CHD will be symptomatic in the first year of life. By one week of life, the diagnosis is often established in 40–50% of patients, while the diagnosis will be established in 50–60% of patients by one month of life.[5]

The mean age of patients with CHD was 2.8 years in our study, which may suggest a slightly delayed age of diagnosis. However, it was a challenge in our cohort to accurately determine the precise age of first presentation for most patients, because most had had previous echocardiographs prior to the study period. In patients who had had multiple echocardiographs, the report for the first echocardiograph was chosen.

The majority of patients with acquired lesions were older than five years, as anticipated. We therefore expect that the mean and median ages of CHD patients reported in our study, although correct for our study cohort, are in fact higher than would be found in a prospective cohort study where the age of first echocardiogram and therefore first diagnosis of CHD would be lower, and likely more similar to the younger ages reported in the literature. This speaks to the need for future prospective cohort studies.

Limited antenatal screening for CHD in Africa has led to the majority of congenital cardiac lesions being diagnosed postnatally. The onset of permanent sequelae can be prevented by early diagnosis of simple cardiac lesions, but this remains a challenge in Africa.[16] In Malawi the age of presentation for both congenital and acquired heart disease was late.[17] The mean age of presentation for a VSD was 3.2 years, while for RHD it was 11.5 years. Consequently a large number of patients with left-to-right shunts had pulmonary hypertension at the time of diagnosis.[17] Studies from both Nigeria and Cameroon also found patients who presented late with Eisenmenger complex and shunt reversal.[5,12] In our study only one patient was found to have Eisenmenger complex.

There were no significant gender differences in our study population. In India however Sawant *et al.* found a male predominance of CHD, which was similar to two other studies in India with similar findings.[18]

The estimated national prevalence of CHD in the study group was 2.8 per 1 000 live births. This was an underestimate due to the limitations of our study design that entailed capturing data from only one of two paediatric cardiologists during the study period; hence the need for the comparator group. The estimated national prevalence of CHD as estimated from the comparator

group was 4.95 per 1 000 live births, which is comparable to studies done in the Western world, with an incidence of CHD between three and 12 per 1 000 live births.[10]

This study had some limitations. The spectrum of CHD described is of symptomatic children presenting to a national referral centre paediatric cardiology clinic. Hence patients with asymptomatic or milder lesions such as ASDs are likely under-represented. VSD type was documented in 46% of our patients, likely because many patients had their initial echocardiograph prior to the study period, and subsequent follow-up echocardiographs were less detailed. The mean age of patients with a VSD was 3.3 years; this was the age when the echocardiograph was performed and not necessarily the age of presentation. From our study, we were unable to determine the number of VSDs that closed spontaneously. Similarly, future studies should also document type and size of ASD and AVSD.

Our approach to estimating the national prevalence of CHD has both advantages and disadvantages. The advantage is that PMH was the only centre performing echocardiographs in children in the country during the study period. The disadvantages are mainly due to the possible referral bias. Patients from peripheral parts of the country may never have arrived at the PMH cardiac centre. Additionally, patients who had asymptomatic or small ASDs, VSDs that closed spontaneously or silent PDAs, or those who died before coming to medical attention would have been missed. This figure would therefore be an underestimation. Additionally the inadvertent inclusion of non-citizens with CHD who reside in but were born outside Botswana may lead to an overestimation of CHD. Future studies are required to give us a more accurate reflection of the prevalence of CHD in Botswana.

Conclusions

The clinical spectrum of CHD is similar to that observed in other African countries and in the Western world, with VSD the most common acyanotic lesion and TOF the most common cyanotic lesion. The prevalence of CHD in Botswana was 2.8–4.95 per 1 000 live births, in keeping with other settings. This is the first study to describe CHD in Botswana, and it aimed to stimulate subsequent studies in this field. Findings will also assist national policies in prioritising non-communicable diseases such as CHD.

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Review Article

Subclinical anthracycline therapy-related cardiac dysfunction: an ignored stage B heart failure in an African population

Wan Zhu Zhang, Feriel Azibani, Karen Sliwa

Abstract

Anthracyclines are potent antineoplastic agents with a proven efficacy in the treatment of many paediatric and adult haematological and solid-organ cancers. Anthracycline therapy-related cardiac dysfunction (ATRCD) is the commonest and most well-studied chemotherapy-induced cardiovascular toxicity. Therefore patients who received anthracycline therapy are considered in stage A heart failure. Recent study findings suggest that anthracycline cardiotoxicity represents a continuum that begins with subclinical myocardial cell injury, followed by an early asymptomatic decline in left ventricular ejection fraction that can progress to symptomatic heart failure if left untreated. In Western countries, ATRCD has been reported in 57% of anthracyclines-treated patients. However, data on incidence and spectrum of ATRCD in Africa are not available. This literature review aimed to highlight the concept of subclinical ATRCD as a stage B heart failure in the spectrum of ATRCD, and the importance of early detection. We emphasise the potential burden and risk of subclinical ATRCD in the African population, with the ultimate aim of drawing the attention of health workers in Africa to improve care of the relevant population.

Keywords: subclinical anthracycline therapy-related cardiac dysfunction, stage B heart failure, African population

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Anthracyclines are potent antineoplastic agents with proven efficacy in the treatment of many paediatric and adult haematological and solid-organ cancers. Anthracycline therapy-related cardiac dysfunction (ATRCD) is the most notorious and well-studied chemotherapy-induced cardiovascular toxicity. This dose-dependent ATCRD was first described in 1971 in a cohort of 67 patients treated with Adriamycin for a variety of tumours.[1] The clinical significance of anthracycline cardiotoxicity is growing with the increasing number of cancer survivors worldwide. ATRCD is defined as a decrease in left ventricular ejection fraction (LVEF) of > 10%, to a value < 53%.[2]

Anthracycline toxicity may be acute, early or late. Acute toxicity, which develops in 1% of patients immediately after infusion, is uncommon and generally reversible.[3] Early effects occur within the first year of treatment, while late effects manifest after several years (median of seven years after treatment).[4,5] Early- and late-onset cardiac dysfunction are more likely to be irreversible.[5]

In the literature there is wide variation in the reported frequency of clinical cardiotoxicity. Differences in study population, treatment protocols and duration of follow up could account for this wide variability. The prevalence of late asymptomatic ATRCD has been reported to be more than 57% at a median of 6.4 years after treatment among survivors of childhood cancers,[6] and the incidence of symptomatic heart failure as high as 16%, 0.9 to 4.8 years after treatment.[7]

According to the American College of Cardiology and American Heart Association guidelines,[8] patients who received cardiotoxic agents are considered in stage A heart failure. This identifies patients who are at a high risk for developing heart failure with no evidence of cardiac structural disorder. Stage B refers to patients with cardiac structural disorder but who have never developed symptoms of heart failure. Stage C denotes patients with symptoms of heart failure associated with underlying structural heart disease, and stage D designates the patient with end-stage disease who requires specialised treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation or hospice care. This

Hatter Institute For Cardiovascular Research In Africa, University of Cape Town, Cape Town, South Africa
Wan Zhu Zhang, MMed, zhangwanzhu2012@gmail.com
Feriel Azibani, PhD
Karen Sliwa, PhD

Uganda Heart Institute, Kampala, Uganda
Wan Zhu Zhang, MMed, zhangwanzhu2012@gmail.com

Table 1. Classification of heart failure (HF)

Stage of HF	*Definition*
A	High risk for developing HF with no evidence of cardiac structural disorder
B	Cardiac structural disorder but has never developed symptoms of HF
C	Symptoms of HF associated with underlying structural heart disease
D	End-stage disease requiring specialised treatment strategies

approach to the classification of heart failure emphasises both the evolution and progression of the disease (Table 1).

This literature review aimed to highlight the concept of subclinical ATRCD as a stage B heart failure, underline the importance of its early detection, and emphasise the potential burden and risk of subclinical ATRCD in the African population. Our ultimate aim was therefore to draw the attention of African clinicians in order to improve care of the relevant population.

Concept of subclinical ATRCD

Anthracycline inhibits topoisomerase II (Top2), an essential enzyme for unwinding deoxyribonucleic acid strands during deoxyribonucleic acid replication or transcription.[9] High cumulative use of anthracyclines induces deleterious effects on cardiomyocytes, endothelial cells, fibroblasts and cardiac stem cells (Fig. 1). In the cardiac tissue, anthracycline targets Top2β, the primary Top2 isoform in the heart, triggering profound changes in the transcription, leading to defective mitochondrial biogenesis and reduced levels of anti-oxidative enzymes, manifested as increased production of reactive oxygen species and cardiomyocyte death.[10]

Anthracycline has also been shown to reduce coronary branching, capillary density and the expression of myocardial vascular growth factors.[11] The number of cardiac progenitor cells and their ability to differentiate into endothelial cells, smooth muscle cells or myocytes is also diminished.[11] Therefore the ability of the heart to adapt to any additional stress is impaired after exposure to anthracyclines.

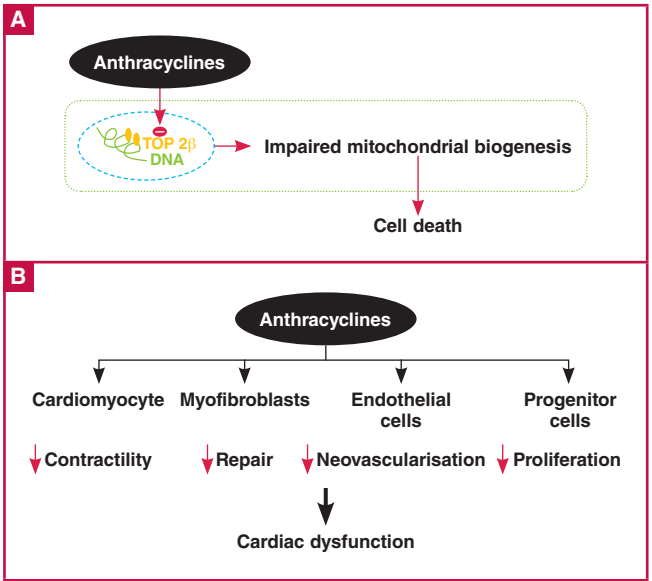

Fig. 1. Mechanism of anthracycline cardiotoxicity. A: In cardiac tissue, anthracycline inhibits topoisomerase II β (Top2β), triggering profound changes in transcription, leading to defective mitochondrial biogenesis, increased production of reactive oxygen species and cardiomyocyte death. B: Anthracycline induces deleterious effects on cardiomyocytes, endothelial cells, fibroblasts and cardiac progenitor cells, affects cardiac contractility and attenuates repair, neovascularisation and proliferation after injury, thus resulting in cardiac dysfunction.

Recent study findings suggest that anthracycline cardiotoxicity represents a continuum that begins with subclinical myocardial cell injury, followed by an early asymptomatic decline in LVEF, which can progress to symptomatic heart failure if left untreated.[12] Not all subclinical LV dysfunctions (stage B heart failure) will become stage C or D heart failure. However, these insults enhance cardiac susceptibility to further cardiovascular stresses (such as pregnancy, surgery, hypertension) or injuries (radiation, ischaemia) and, ultimately, increase the risk of premature cardiovascular (CVD) mortality. This phenomenon has been labelled the multiple-hit hypothesis[13] (Fig. 2).

Cardinale *et al.*[12] suggested that late-onset anthracycline cardiotoxicity likely reflects the timing of detection, rather than the timing of the occurrence of cardiotoxicity. These findings, together with the multiple-hit hypothesis, highlight an urgent need for the surveillance and management of anthracycline cardiotoxicity.

Periodic echocardiographic monitoring has been advocated for this vulnerable population.[2] To further improve early detection of subclinical LV functional deterioration, guidelines from onco-cardiologists advise the use of advanced cardiac imaging (global longitudinal strain, GLS), often combined with the use of circulating levels of cardiotoxicity biomarkers such as cardiac troponin.[14] It is therefore recommended to evaluate at baseline (initiation of anthracycline regimen) LVEF, GLS and circulating cardiac troponin levels. If any of these three parameters are abnormal, a cardiology consultation is recommended.

Follow up is recommended at the completion of anthracycline therapy and six months later for doses < 240 mg/m^2 or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS and troponin level are recommended before each additional 50 mg/m^2.[2] According to recommendations from the American

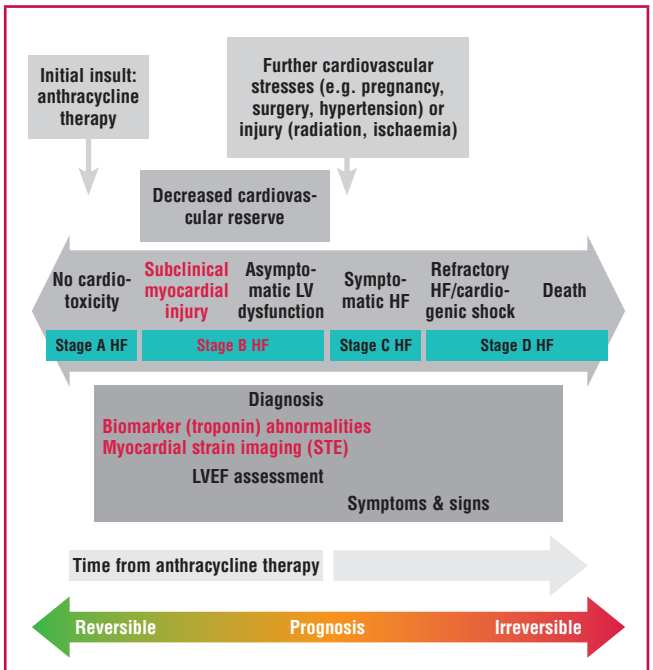

Fig. 2. Spectrum of ATRCD and the multiple-hit hypothesis. HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; STE, speckle-tracking echocardiography.

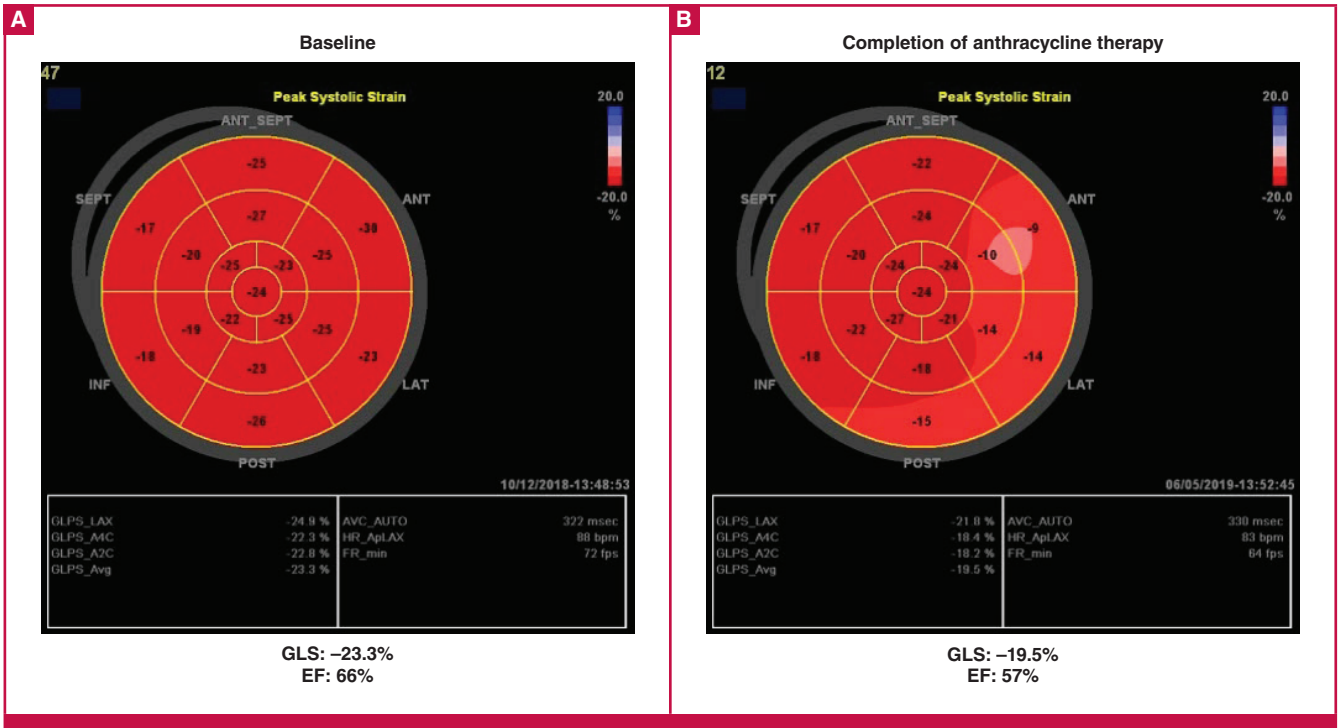

Fig. 3. Strain images of a patient who was diagnosed with subclinical ATRCD by GLS.

Society of Echocardiography and the European Association of Cardiovascular Imaging, a relative percentage decrease of GLS > 15% (Fig. 3) compared with baseline and/or positive troponin I levels during follow up will be considered subclinical ATRCD.[2]

Only a few studies have reported the incidence of subclincal ATRCD. Boyd *et al.*[15] used two-dimensional strain analysis to detect subclinical LV systolic dysfunction in 140 breast cancer patients early (within three month) after anthracycline chemotherapy. Subclinical LV dysfunction (> 11% reduction in GLS) occurred in 22% of their patient cohort. In another cohort of 159 patients receiving anthracycline, trastuzumab (a monoclonal antibody for treating HER2 receptor-positive breast cancer) or both,[16] decreased GLS (by > 11%) was found in 33% of patients seven months after the completion of the chemotherapy treatment. Interestingly, LVEF remained within normal ranges in both studies.

African populations who are at risk of developing ATRCD

Cancer is emerging as a major public health problem in sub-Saharan Africa (SSA) because of population aging and growth, as well as increased prevalence of key risk factors, including those associated with social and economic transition. A high residual burden of infectious agents (HIV/AIDS, human papillomavirus, hepatitis B virus) in certain SSA countries unquestionably drives the rates of certain cancers. Indeed, about one-third of all cancers in the region are estimated to be infection related.[17] Breast and cervical cancer in women and prostate cancer in men are the major cancers with a poor outcome in SSA.[17]

The growing prevalence and pattern of cancer in SSA determine the large role of anthracycline in cancer treatment in SSA. In the developed world, anthracycline has been used much less frequently, being partially replaced by novel, less cardiac-toxic anti-tumour drugs when treating certain types of cancer.[18] However, most of these novel drugs are costly and so not available in SSA.

Following the launching of the African Cancer Network Project in 2012, more than 100 cancer treatment institutions were set up by 2015.[19] More and more African cancer patients are able to receive anthracycline-based chemotherapy. Although there are no reliable data on how many patients are receiving these anti-tumour drugs in Africa, it has been estimated that about 60% of cancer patients in the Uganda Cancer Institute (UCI) are treated with anthracycline. The common cancers treated with anthracyclines at UCI include breast cancer (68.75%), non-Hodgkin's lymphoma (13.13%), Hodgkin's lymphoma (5.6%), advanced hepatocellular cancer (3.7%), soft tissue sarcomas (3.7%) and leukaemia (3.1%). Moreover, 80% of this population that are at risk of cardiotoxicity are women.[17]

Association of anthracycline cardiotoxicity risk with ethnicity and gender

Studies investigating sexual dimorphism of anthracycline cardiotoxicity are sparse. Yet growing evidence, mainly obtained in experimental studies, pinpoints a sexual dimorphism of doxorubicin cardiotoxicity, with females being protected compared to males.[20] This protection includes the essential targets of anthracycline, that is energy metabolism, energetic signalling pathways and oxidative stress.[20]

In a review article of anthracycline cardiotoxicity in childhood cancer survivors, Armstrong *et al.*[21] identified 17 studies evaluating gender as a risk factor for cardiotoxicity after anthracyclines and found five, including four high-quality studies, to validate that females experienced a poorer outcome than males. It has been suggested that doxorubicin cardiotoxicity

is higher in prepubertal girls, and this could be explained by the lack of protection from female hormones. Further studies are needed to understand in more detail the mechanism of female protection.

Black race was found to be a risk factor for developing ATRCD in both childhood cancer survivors[22] and adult cancer patients.[23] In an *in vitro* study, Huang *et al*.[24] used EBV-transformed B-lymphoblastoid HapMap cell lines derived from an African- and a European-descent cell line, in order to evaluate population- and gender-specific differences in cell cardiotoxicity after daunorubicin and other drug (carboplatin, cisplatin, etoposide) treatment. Interestingly, African-descent cell lines were found to be more prone to develop cytotoxicity linked to daunorubicin.

In Africa, two published studies done in Cote d'Ivoire and Morocco reported a high incidence of cardiotoxicity in adult cancer patients on anthracycline treatment. Elalouani *et al.* who conducted the first prospective cohort study in Morocco, investigating the frequency of anthracycline-induced cardiotoxicity, noted that 56% of the 70 patients developed a decrease in cardiac function and 4% of cases developed severe cardiotoxicity.[25] In the prospective cohort study performed at Abidjan Institute of Cardiology over 10 months, 45 adult patients were followed up and four patients (8.8%) developed significant cardiotoxicity.[26]

Cardiovascular care in African cancer patients: current status, challenges and opportunities

Despite an increased risk of developing asymptomatic subclinical ATRCD in Africa, there is a noted paucity of information on burden of subclinical anthracycline-induced cardiotoxicity and related predictors among adult cancer patients receiving anthracycline chemotherapy. This large gap in knowledge has led to a lack of local guidelines for monitoring and management of ATRCD.

The majority of patients receive only screening echocardiography before chemotherapy with no follow-up cardiac screening. This may leave many anthracycline-treated patients with undetected stage B heart failure (asymptomatic subclinical cardiac dysfunction) at risk of developing stage C or D heart failure when they encounter another cardiovascular risk later in life.

Strain echocardiography (GLS) and biomarkers (troponin) are verified diagnostic tools for this stage B heart failure. GLS is becoming routinely used in this population in the developed world but not in Africa, for a number of reasons. Indeed, many cardiologists are not trained to use this methodology, and few patients can afford the cost of serial echocardiography studies. When strain echocardiography is not available, conventional echocardiography parameters, which measure the longitudinal motion of the left ventricle [mitral annular plane systolic exertion (MAPSE), peak systolic mitral annular velocity by tissue Doppler (S′)], may potentially be useful in Africa.[27] However, their roles in detecting subclinical ATRCD have not been studied.

Compared to strain echocardiography, biomarker tests are cheaper and less skill-dependent, therefore more practical in African settings. Troponin, a biomarker of cardiac injury, has been found to have high negative predictive value in detecting subclinical ATRCD.[28] Natriuretic peptides, biomarkers of cardiac load, are the next most commonly researched biomarkers in the context of ATRCD, apart from troponin. However, their roles in detecting subclinical ATRCD are less defined due to conflicting results from different trials. Myeloperoxidase is regarded as a marker of oxidative stress. In a recent study of multiple biomarkers, myeloperoxidase levels rose early, persisted throughout the course of therapy, and were associated with cardiotoxicity.[29]

Despite the challenges of implementing internationally recommended cardiac care protocols for cancer patients in SSA, conventional echocardiography combined with biomarker tests may be potentially useful for African patients. These tools have not been studied in SSA populations. Detecting subclinical ATRCD in a low-income country (SATRACD study) is an ongoing observational cohort study that will diagnose subclinical ATRCD in Ugandan cancer patients using international guidelines. The primary goal of this study is to determine the burden and risk factors of subclinical ATRCD in the study population, evaluating the role of conventional echocardiography parameters and biomarkers in detecting subclinical ATRCD in Ugandan cancer patients.

Conclusion

Due to the growing prevalence and unique pattern of cancer populations in Africa and progress in oncology treatments, there is increasing exposure of cancer patients to anthracycline. Subclinical ATRCD is a silent risk factor for heart failure in cancer survivors. Therefore subclinical ATRCD should no longer be ignored in Africa.

Oncologists and cardiologists in Africa have a responsibility to provide standard of care for patients receiving anthracycline therapy by implementing international guidelines. Local research in this field is needed to evaluate the real burden and risk factors of anthracycline therapy-related stage B heart failure. Moreover, in order to promote the application of available resources in cardio-oncology clinical practice and help to establish national guidelines for cardiac monitoring and management of patients with ATRCD, research should investigate more easily accessible tools to diagnose early damage, such as biomarkers and conventional echocardiography parameters.

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Tunisia Country Report

PASCAR and WHF Cardiovascular Diseases Scorecard project

Habib Gamra, Jihene Maatoug, Jean M Fourie, Wihan Scholtz, Oana Scarlatescu, George Nel, Hassen Ghannem

Abstract

Data collected by the Pan-African Society of Cardiology for the World Heart Federation's scorecard project regarding the current state of cardiovascular disease prevention, control and management along with related non-communicable diseases in Tunisia are presented. Furthermore, the strengths, threats, weaknesses and priorities identified from these data are highlighted in concurrence with related sections in the incorporated infographic. Information was collected using open-source data sets available online and relevant government publications.

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On behalf of the World Heart Federation (WHF), the Pan-African Society of Cardiology (PASCAR) co-ordinated data collection and reporting for the country-level Cardiovascular Diseases Scorecard to be used in Africa.[1-3] The objectives of the scorecard have previously been published along with data from seven African countries.[3] The Tunisian Heart Foundation, a member of PASCAR and the WHF, along with epidemiologists from the University of Sousse, assisted in collating and verifying the data.

Based on the data collected, we summarise the strengths, threats, weaknesses and priorities identified, which need to be considered in conjunction with the associated sections provided in the infographic published with this report. Data sets used included open-source data from the World Bank, World Health Organization (WHO), Institute for Health Metrics and Evaluation and the International Diabetes Federation (IDF), along with other relevant and government publications.

The Tunisian Heart Foundation, Tunisia
Habib Gamra

Department of Epidemiology, Faculty of Medicine, Farhat Hached Hospital, University of Sousse, Sousse, Tunisia
Jihene Maatoug
Hassen Ghannem

Pan-African Society of Cardiology, Cape Town, South Africa
Jean M Fourie
Wihan Scholtz, wihan@medsoc.co.za
George Nel

World Heart Federation, Geneva, Switzerland
Oana Scarlatescu

Part A: Demographics

According to the World Bank (2018), Tunisia is a lower-middle-income country with 31% of its people living in rural areas.[4] As indicated by the National Institute of Statistics, 2.9% of the population was living in extreme poverty in 2015.[5] Life expectancy at birth in 2018 was 74 and 79 years for men and women, respectively.[4] The general government health expenditure was 4.1% of the gross domestic product (GDP) in 2017, while the country's GDP per capita was US$3 317.5 in 2019.[4]

Part B: National cardiovascular disease epidemic

The national burden of cardiovascular diseases (CVD) and risk factors for non-communicable diseases (NCD)

Tunisia's premature deaths, attributable to CVD (30–70 years old), was 11% in 2012,[6] while 44% of the estimated NCD deaths (86%) accounted for CVD in 2016.[7] In 2017, the age-standardised total CVD death rate was very high at 51.5%, compared to 31.8% for the Global Burden of Disease (GBD) data.[8] The percentage of disability-adjusted life years (DALYs) resulting from CVD for men was 23.8% and for women 19.4%, which is also higher than the GBD data of 14.66% for both genders. The prevalence of atrial fibrillation (AF) and atrial flutter was 0.3%, while that of rheumatic heart disease (RHD) was 0.01% compared to the GBD data of 0.53%. The total RHD mortality rate was 0.15% of all deaths, which is lower than the GBD data of 0.51% (Table 1).[8]

Tobacco and alcohol

Data on the prevalence of tobacco use for adult men and women (≥ 15 years old) in 2018 were 49.3 and 2.9%, respectively. In 2008, the prevalence of smoking in adolescents (13–15 years old) was 20.1 and 3.8% for boys and girls, respectively.[9] The proportion of premature CVD mortality attributable to tobacco is 5%, which is much lower than the global 10%,[10] while the estimated annual direct cost of tobacco use is unknown. The three-year (2016–18) average recorded alcohol consumption per capita (≥ 15 years) was 1.6 litres (Table 1).[9]

Table 1. Cardiovascular disease indicators for Tunisia

Indicators	*Male*	*Female*	*Total*	*Year*
Status of national cardiovascular disease epidemic				
Premature CVD mortality (30–70 years) (% deaths)	–	–	11	2012
Total CVD mortality (% of deaths)	50.7	52.5	51.5 (31.8)*	2017
Total RHD mortality (% of deaths)	0.12	0.19	0.15 (0.5)*	2017
DALYs attributable to cardiovascular diseases (%)	23.8	19.4	21.9 (14.7)*	2017
AF and atrial flutter (%)	0.3	0.3	0.3 (0.5)*	2017
Prevalence of RHD (%)	0.01	0.01	0.01 (0.5)*	2017
Tobacco and alcohol				
Prevalence of adult tobacco use (≥ 15 years) (%)	49.3 (36.1)**	2.9 (6.8)**	–	2018
Prevalence of youth (13–15-year-olds) tobacco use (%)	20.1 (18.2)**	3.8 (8.3)**		2010
Estimated direct (healthcare-related) cost of tobacco use in your population (in current US$)			–	–
Proportion of premature CVD mortality attributable to tobacco (%)	–	–	5 (10)**	2004
Recorded alcohol consumption per capita (≥ 15 years) (in litres of pure alcohol) (three-year average)			1.6	2016-18
Raised blood pressure and cholesterol				
Population with raised BP (SBP ≥ 140 or DBP ≥ 90 mmHg) (%)	23.8 (24.1)**	22.5 (20.1)**	–	2015
Population with raised TC (≥ 5.0 mmol/l) (%)	37.3	43.8	40.7 (38.9)**	2008
DALYs attributable to hypertension (%)	13.2	12.1	12.74 (8.7)*	2017
Mortality caused by hypertensive heart disease (% of deaths)	2.7	4.7	3.55 (1.7)*	2017
Physical activity				
Adolescents (11–17 years) who are insufficiently active (< 60 minutes of moderate- to vigorous-intensity PA daily) (%)	74.1	88.2	81.4	2010
Adults (age-standardised estimate) who are insufficiently active (< 150 minutes of moderate-intensity PA per week, or < 75 minutes of vigorous-intensity PA per week) (%)	26.4	34.1	30.4 (27.5)**	2016
Overweight and obesity				
Adults who are overweight (BMI ≥ 25–< 30 kg/m²) (%)	57.1	65.8	61.6 (38.9)**	2016
Prevalence of obesity (BMI ≥ 30 kg/m²) (%)	19.1	34.3	26.9 (13.1)**	2016
Diabetes				
Defined population with fasting glucose ≥ 126 mg/dl (7.0 mmol/l) or on medication for raised blood glucose (age-standardised) (%)	12.1 (9)*	12.9 (8)**	–	2014
Prevalence of diabetes (20–79 years) (%)	–	–	8.5 (9.3)#	2019

CVD, cardiovascular disease; RHD, rheumatic heart disease; DALYs, disability-adjusted life years; AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; PA, physical activity; BMI, body mass index.
*IHME global data exchange[8]
**WHO global data[9]
#*IDF Diabetes Atlas*.[11]

Raised blood pressure and cholesterol

In 2015, about 24% of men and 22.5% of women had raised blood pressure (BP) (systolic BP ≥ 140 or diastolic BP ≥ 90 mmHg) levels, which is more or less similar to the GBD data of 24.1 and 20.1% for men and women, respectively.[9] In 2017, the percentage of DALYs lost because of hypertension was 12.74%, while mortality rate caused by hypertensive heart disease was 3.55 versus 1.65% for global data (Table 1).[8] The percentage of individuals with raised total cholesterol levels (≥ 5.0 mmol/l) was 40.7% compared to Global Health Observatory (GHO) data (38.9%).[9]

Physical activity

Data for 11–17-year-old adolescents indicated that 81.4% were insufficiently active [< 60 minutes of moderate- to vigorous-intensity physical activity (PA) daily]. The age-standardised estimate for adults who were insufficiently active (< 150 minutes of moderate-intensity PA per week or < 75 minutes of vigorous-intensity PA per week) was 30.4%, which is higher than GHO data at 27.5% (Table 1).[9]

Overweight and obesity

In 2016, the prevalence of overweight [body mass index (BMI) ≥ 25–< 30 kg/m²] and obesity (BMI ≥ 30 kg/m²) in adults 25 years and older was almost 62 and 27%, respectively.[9] Compared to global data, both these indicators are much higher than the 38.9% for overweight and 13.1% for obesity.[9] More women than men were overweight (65.8 vs 57.1%) and obese (34.3 vs 19.1%), respectively (Table 1).

Diabetes

The percentage of the population defined with a fasting blood glucose level ≥ 7.0 mmol/l or on medication for raised blood glucose levels (age-standardised) in 2014 was 12.1% for men, and for women 12.9%. In 2019, the age-adjusted prevalence (20–79 years old) of diabetes was 8.5%, which is higher than that of Africa (3.9%), and slightly lower than the global level at 9.3% (Table 1).[11]

Part C: Clinical practice and guidelines

Health system capacity

The country had an average of 13 physicians and 25.1 nurses per 10 000 of the population in 2017, while there were 23 hospital beds for every 10 000 people in 2015.[9]

Data for locally relevant clinical tools to assess CVD risk,[12] and guidelines for the detection and management of AF and management of acute rheumatic fever are available.[13,14] Appropriate national guidelines are available for the treatment

of tobacco dependence.[15] However, locally relevant clinical guidelines for the management of pharyngitis and RHD as well as for CVD prevention are lacking. Tunisia does not have a registry for people with a history of rheumatic fever and RHD, although a system exists to measure the quality of care provided to people who had suffered acute cardiac events.[9] Standard treatment guidelines for diabetes mellitus and other NCD, or conditions such as hypertension have been developed.[16,17]

Essential medicines and interventions

In Tunisia, all the essential CVD medicines are available in the public sector,[9] as are warfarin and clopidogrel.[18] Data regarding total cholesterol measurement,[9] priority CVD risk stratification and secondary prevention of rheumatic fever and RHD are available at the primary healthcare level (Habib Gamra, pers commun).

Secondary prevention and management

The percentage of people with a history of CVD taking aspirin, statins and at least one antihypertensive agent is 38%.[19] In 2012, 32.9% of hypertensive persons received medical treatment,[20] however, the percentage of high-risk patients with AF receiving oral anticoagulants was unknown.

Part D: Cardiovascular disease governance

Strategies that address NCD, which include CVD and risk factors such as diabetes, have been developed, although not much work has been done in this area[21] since no dedicated budget is available to ensure implementation. However, Tunisia has an operational unit or department in the ministry of health (MoH) that is responsible for NCD.[22,23] Furthermore, the prevention and control of RHD in Tunisia is efficient through the acute articular rheumatism monitoring programme.[24] However, a national surveillance programme that includes CVD and their risk factors is lacking.

Regarding tobacco use, Tunisia has formulated a national tobacco control plan and multi-sectoral co-ordination mechanism for tobacco control.[15] Collaborative projects between the Tunisian MoH and that of higher education and scientific research and technology have been reported by Hassen Ghannem.[17] No information is available on the total annual government expenditure for cardiovascular healthcare.

Tunisia was part of the WHO-CHOICE project, which incorporated a cost-effectiveness modelling tool that gathers national data to be used for developing the most effective interventions for leading causes of the disease burden.[25] The model can be adjusted according to the specific needs of the country and assist policymakers in planning and prioritising services at a national level.[25] The benefits of CVD prevention and control for population health and the economy have also been modelled, according to Saidi *et al*.[12]

Assessment of policy response

No legislation exists in Tunisia mandating health financing for CVD or that of essential CVD medicines at affordable prices. However, van Mourik *et al*.[26] reported that Tunisia is one of the countries where medicines are provided free of charge in the public healthcare sector.

Legislation exists banning smoking in indoor workplaces and public areas, other public places, public transport, all forms of tobacco advertising, promotion and sponsorship, as do measures to protect tobacco-control policies from tobacco industry interference.[15] However, that mandating clear and visible warnings on at least half of the principal display areas of tobacco packs does not exist.

According to *The Report*, there seem to be policies that ensure equitable nationwide access to healthcare professionals and facilities in Tunisia,[27] including those ensuring screening of individuals at high risk for CVD.[28] However no sustainable funding from taxation is available for CVD.

Taxes on unhealthy foods or sugar-sweetened beverages have been introduced at 25% of the excise tax (*Discussion et adoption par l'assemblée des représentants du peuple dans sa séance du 9 décembre 2017*).[23,29] Tunisia is one of the few African countries with a policy that entirely reduced the affordability of tobacco products through increasing tobacco excise taxes.[22] In 2018, the excise tax of the final consumer price of tobacco products was 74%. No data were found on excise tax of the final consumer price of alcohol products, or legislation banning the marketing of unhealthy foods to minors, and clear and visible warnings on foods high in calories, sugar or saturated fats. No policy interventions were available promoting a diet that reduces CVD risk or those facilitating PA.[17]

Stakeholder action

In Tunisia, non-governmental organisation (NGO) advocacy for CVD policies and programmes as such has not been demonstrated.[21] No information about active involvement of patients' organisations in advocacy for CVD/NCD prevention and management is available or that regarding advocacy champions and or patient engagement for RHD groups. However, the involvement of civil society in the development and implementation of a national tobacco control plan is available.[10] A community-based intervention with multi-sectoral interventions was implemented in Tunisia, which demonstrated the effectiveness of reducing risk factors in the community, workplace and schools from 2010–2014.[30] However, the involvement of policymakers and political will was recommended to reinforce the intervention, have a better impact, and to ensure a long-term effect.[31]

Specific activities by cardiology professional associations aiming at a reduction in the premature CVD mortality rate of 25% by 2025 are also not known. In an interventional study at six workplaces, screening and health-promotion initiatives were suggested, 'to avert the excessive risk for CVD,' which included BP measurements.[32]

As part of the data collected for Tunisia, the following strengths, threats, weaknesses and priorities are summarised.

Strengths

Tunisia implemented a CVD registry in three geographical populations, which provided incidence and fatality data for the first time in 2001.[33] These authors suggested the data should be integrated into the local health system. A decrease in the incidence of RHD was reported by Belguith *et al*.[24]

WORLD HEART FEDERATION

PAN-AFRICAN SOCIETY OF CARDIOLOGY – PASCAR –

Tunisian Heart Foundation

Cardiovascular Disease Scorecards – Africa

TUNISIA – SEPTEMBER 2020

Status of Cardiovascular Disease (CVD) and Non-communicable diseases (NCD)

Country Demographics

World Bank Classification

Lower-middle income

31%

of population living in rural areas

60% (Sub-Sahara Africa)

TUNISIA

0.15%

of total mortality caused by **RHD**

Global data: **0.51%**

0.01%

Prevalence of rheumatic heart disease **(RHD)**

Global data: **0.53%**

5%

of premature CVD mortality attributable to **tobacco**

Global data: **10%**

MALE **49.3** % **2.9** FEMALE

Prevalence of **tobacco** use **age ≥15**

Global data: **36.1%** (male) **6.8%** (female)

3.55%

of deaths caused by **hypertensive heart disease**

Global data: **1.65%**

23.8% **22.5%**

MALE FEMALE

of population with raised **blood pressure** (SBP ≥140 or DBP ≥90)

Global data: **24.1%** (male) **20.1%** (female)

26.9%

Prevalence of obese adults (BMI of ≥30 kg/m2)

Global data: **13.1%**

51.49%

of **deaths** caused by CVD

Global data: **31.8%**

40.7%

of population with raised total **cholesterol** (≥5.0 mmol/L)

Global data: **38.9%**

8.5%

Prevalence of diabetes **(ages 20-79)**

3.9% (Africa)

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www.tunhf.org

TUNISIA

Health System Capacity

13.03
Number of physicians (per 10,000 population)

25.14
Number of nurses (per 10,000 population)

23
Number of hospital beds (per 10,000 population)

KEY: No data | Not in place | In process/ partially implemented | In place

Clinical Practice and Guidelines

Locally-relevant (national or subnational level):

- Clinical tool to assess CVD risk — In place
- Guidelines for treatment of tobacco dependence — In place

Clinical Guidelines for:

- The detection and management of atrial fibrillation — In place
- The detection and management of acute rheumatic fever — In place
- The detection and management of rheumatic heart disease — Not in place
- The detection and management of diabetes — In place
- CVD prevention (within the last 5 years) — Not in place
- A system to measure the quality of care provided to people who have suffered acute cardiac events — In place

TUNISIA

Cardiovascular Disease Governance

A national strategy or plan that addresses:

- CVDs and their specific risk factors — In place
- NCD and their risk factors — In place
- Rheumatic heart disease prevention and control as a priority — In place
- A national surveillance system that includes CVDs and their risk factors — Not in place

Stakeholder action

- Non-governmental organizations' advocacy for CVD policies and programmes — Not in place
- Civil society involved in developing and implementing of national CVD prevention and control plan — No data

For more information, please email info@worldheart.org info@pascar.org secretariat@tunhf.org

Source References: Global Health Data Exchange; WHO Global Health Observatory data repository; WHO NCD Document repository; Country specific publications.

The National Tunisian Registry of Atrial Fibrillation (NATURE-AF) collects data from patients with AF to define the prevalence of various cardiovascular incidences leading to death. NATURE-AF will reveal the outcomes, frequency and quality of oral anticoagulation in these patients. Through this registry, unique data on the management and outcomes of AF patients on treatment will become available.[13]

Article 38 of the new 2014 constitution ensures preventative and curative health services receive priority, including social protection and free healthcare for low-income populations and the provision of sufficient resources towards quality services.[27] Essential medicines are also available free of charge in the public health sector.[26]

Tunisia, along with Rwanda, South-Africa and Senegal, is one of the few countries in our project with a system to measure the quality of care provided to people who have suffered acute cardiac events.[12] The country has an integrated tobacco programme, also warning people against its dangers through mass media campaigns.[22]

Threats

Tunisia's premature CVD mortality rate (11%) is higher than seven of the 12 countries under investigation but lower than the 12% of Cameroon, Namibia and Nigeria and the 14% of South Africa.[3,6] In 2016, the proportional mortality rate of all deaths was 44% for CVD.[7] The total CVD mortality rate is also much higher than any of the other countries in this project, at 51.5%. The same picture is revealed in the percentage of DALYs as a result of CVD, at almost 22%.

Tunisian men are also the heaviest tobacco users in our study, with more than 65% following this practice. Another CVD indicator that needs attention is Tunisia's high prevalence of raised cholesterol levels. The prevalence of obesity and diabetes is high and driven by environmental factors, nutritional transition and a Westernised lifestyle, which are reasons for concern.[34]

Weaknesses

Clinical guidelines for CVD prevention within the last five years are lacking, and not all of the essential CVD medicines are available in the public sector.[9] Although CVD risk stratification and secondary prevention of rheumatic fever and RHD are available at the primary healthcare level, these data have not yet been recorded on the GHO database.

Although a national strategy exists that addresses CVD and their risk factors, there is no dedicated budget to implement the plan. Tunisia has also not implemented a national surveillance system that includes CVD and their risk factors.[21] No legislation exists mandating health financing for CVD or court orders that protect patients' rights and improved CVD interventions, facilities, health system procedures or resources.

There is an overall lack of information regarding stakeholder action in the advocacy, prevention and management of CVD/NCD or the development and implementation of plans to curb these burdening diseases.

Priorities

Priorities include educating the population through lifestyle modification and improved training of healthcare practitioners to diagnose and treat patients with diabetes and other NCD, which are urgently needed.[34]

Since cardiovascular risk factors such as hypertension are highly prevalent in Tunisia, an urgent need to implement innovative strategies to improve awareness, treatment and control of the resultant conditions are encouraged.[35] Involvement of civil society and NGOs in the national multi-sectoral co-ordination mechanism for NCD/CVD should be advocated.

This publication was reviewed by the PASCAR governing council and approved by the president of the Tunisian Heart Foundation.

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… continued from page 256

The researchers were interested to see that over half of the patients who received the drug did not need a shock to restore their regular heart rhythm. They recommend that physicians try the drug cardioversion first, to avoid unnecessary sedation.

'If I have a patient on a drug infusion, I can see other patients at the same time,' said Dr Jeffrey Perry, study co-author and senior scientist at the Ottawa Hospital and professor at the University of Ottawa. 'To do an electrical cardioversion, I need to find another doctor, a nurse and a respiratory therapist, and it takes time to assemble those people.'

The researchers note that patients often have a strong preference for one kind of cardioversion over the other, especially if they need it done regularly. 'While we believe that there are advantages to trying the drug infusion before the shock, the treatment choice is ultimately a shared decision between the patient and physician,' said Perry. While cardioversion is common in Canada, it isn't as well known in other parts of the world.

'In some countries, patients with acute atrial fibrillation are sent home with pills to slow their heart rate, while others are admitted to hospital,' said Stiell. 'Our study showed that cardioversion in the emergency department is safe and effective. We hope our results convince more physicians around the world to adopt these methods.'

'Given the crowding which exists in the emergency healthcare setting, the Canadian Institutes of Health Research (CIHR) is proud to support this high-quality research that enhances evidence-informed clinical decisions in the transitions of care for patients with atrial fibrillation,' said Dr Brian Rowe, study co-author, scientific director of the CIHR's Institute of Circulatory and Respiratory Health, and professor of emergency medicine at the University of Alberta.

Source: Medical Brief 2020

Case Reports

Idiopathic hypereosinophilic syndrome associated with rapid progression of cardiac, pulmonary and skin infiltration

Yu-Quan He, Jin-Ming Zhu, Ya-Liang Tong, Hong Zeng, Ping Yang

Abstract

Idiopathic hypereosinophilic syndrome (IHES) is a rare myeloproliferative disease characterised by multisystem dysfunction and persistent, extreme eosinophilia of unknown cause. Here we present a 42-year-old patient complaining of moderate to severe chest pain and shortness of breath, and typical ischaemic electrocardiography changes were recorded. He was initially suspected of having acute coronary syndrome, however the coronary angiogram excluded coronary abnormalities. Bone marrow biopsy, left ventriculography, transthoracic echocardiography and cardiac magnetic resonance examinations confirmed the diagnosis of IHES and IHES-mediated cardiac involvement. The patient's illness was alleviated during the first hospitalisation, whereas it had rapidly worsened one month after discharge. In addition, simultaneous pulmonary and skin-infiltrating lesions occurred during the second hospitalisation. The patient's condition improved markedly with combined glucocorticoid, hydroxyurea and warfarin therapy, as well as treatment for heart failure. In this report the diagnostic modalities and treatment strategies for IHES are discussed and reviewed.

Keywords: idiopathic hypereosinophilic syndrome, cardiac involvement, pulmonary, skin, case report

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Department of Cardiology, China–Japan Union Hospital of Jilin University, Cardiovascular Institute of Jilin Province, Changchun 130033, Jilin Province, China
Yu-Quan He, MD, PhD
Jin-Ming Zhu, MD, PhD
Ya-Liang Tong, MD, PhD
Hong Zeng, MD, PhD, zenghong@jlu.edu.cn
Ping Yang, MD, PhD

Idiopathic hypereosinophilic syndrome (IHES) is a rare myeloproliferative disorder with unknown aetiology, characterised by persistent hypereosinophilia accompanied by multiple eosinophil-mediated organ injuries.[1-3] It was initially reported by Anderson and Hardy[4] in 1968, and Clusid *et al*.[1] in 1975 defined the following clinical diagnostic criteria: (1) absolute peripheral eosinophil count > 1.5×10^9 cells/l for at least six months; (2) evidence of one or multiple eosinophil-mediated organ damage; and (3) exclusion of allergic, parasitic, drug and connective tissue disorders, rheumatism, malignancies or any other cause for secondary hypereosinophilia.

It has been reported that eosinophil-mediated cardiac involvement occurs in more than 50% of IHES patients and is a major cause of death.[5-7] In addition, eosinophil-mediated lung and skin damage is occasionally reported in the literature.[8,9]

We present a rare case of IHES that was accompanied by a simultaneous occurrence of left ventricular (LV) myocardial necrosis, endomyocardial fibrosis, intra-cardiac thrombi, as well as pulmonary and skin-infiltrating lesions. The patient was initially suspected of having acute coronary syndrome due to the complaints of chest pain, ischaemic changes on electrocardiogram (ECG), and abnormal biomarkers for blunt cardiac injury. However, a negative coronary angiogram excluded coronary artery anomalies. The patient's condition deteriorated within one month of discharge, whereas it improved markedly with combined therapy of glucocorticoids, hydroxyurea and warfarin, as well as treatment for heart failure. In this report diagnostic modalities and treatment strategies for IHES are discussed and reviewed.

Case report

A 42-year-old male Chinese farmer was admitted to the emergency department of the China–Japan Union Hospital of Jilin University, complaining of intermittent moderate to severe chest pain and shortness of breath of one year duration, associated with intermittent fever (37–39°C) and fatigue over two weeks. He had lost 25 kg weight in the past three months. He had smoked 20 cigarettes per day for more than 20 years. His past medical history was unremarkable with no similar disease found in his family.

On examination, his body temperature was 37.2°C and blood pressure was 103/60 mmHg. He had no other positive findings except for a mild holosystolic blowing murmur with 2/6 degree that was heard at the mitral valve area. The 12-lead ECG showed

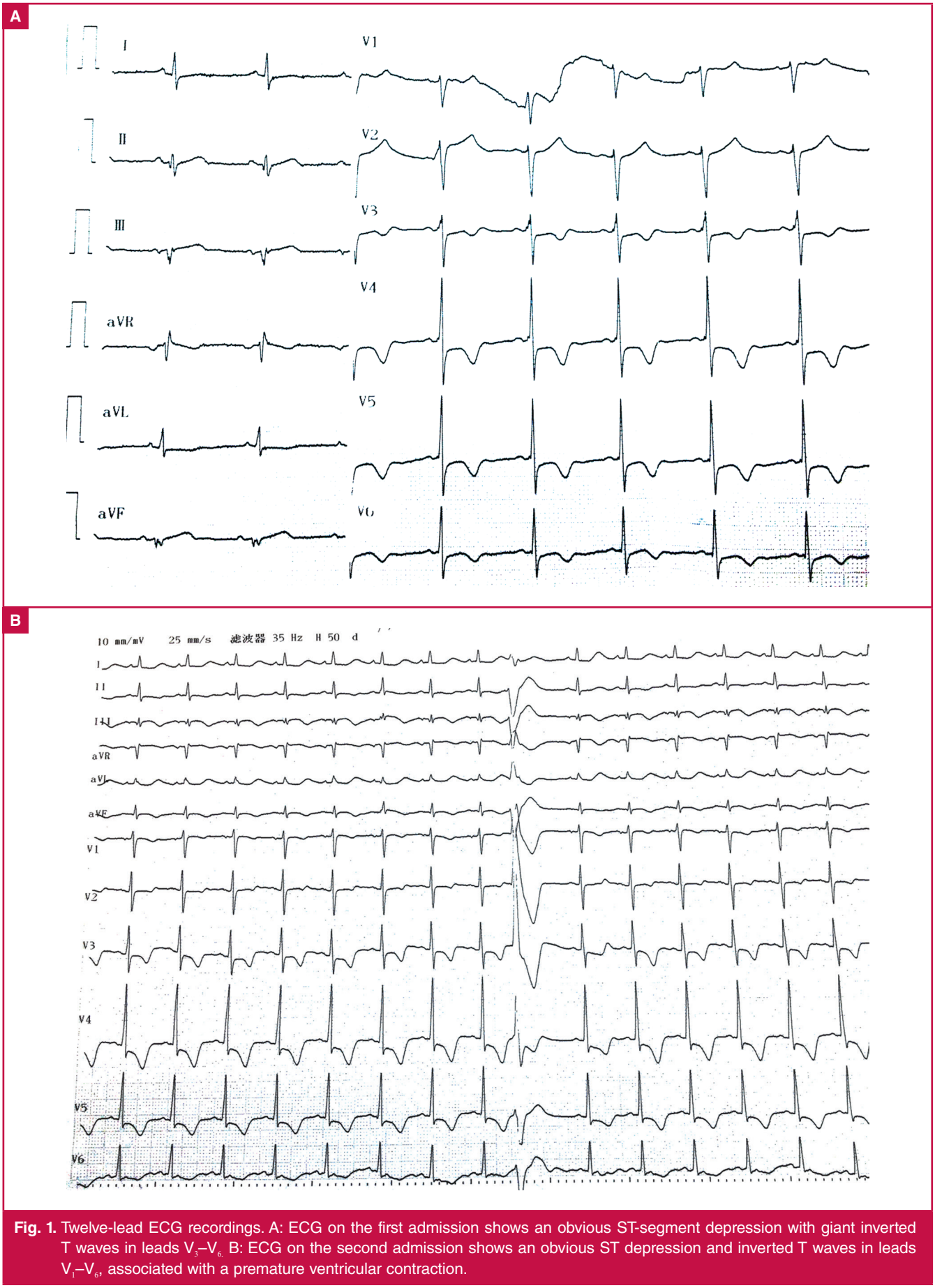

Fig. 1. Twelve-lead ECG recordings. A: ECG on the first admission shows an obvious ST-segment depression with giant inverted T waves in leads V_3–V_6. B: ECG on the second admission shows an obvious ST depression and inverted T waves in leads V_1–V_6, associated with a premature ventricular contraction.

ST-segment depression > 0.3 mV with giant inverted T waves in leads V_3–V_6 (Fig. 1A). An emergency blood test showed a white blood cell (WBC) count of 46.38 × 10^9 cells/l, neutrophils of 17.3% and eosinophils of 73.7%, and a total blood count of 34.18 × 10^9 cells/l. The platelets, red blood cells and haemoglobin were in the normal range. Levels of troponin-I, aspartate aminotransferase, lactate dehydrogenase, C-reactive protein and D-dimer were elevated at 2.24 ng/ml, 76 IU/l, 1173 IU/l, 18.3 mg/l and 845 ng/ml, respectively. Levels of myoglobin, creatine kinase and creatine kinase isoenzyme were normal.

The emergency room doctor suspected the patient of having acute coronary syndrome such as non-ST-elevation myocardial infarction, therefore he transferred him for an emergency coronary evaluation. The coronary angiogram showed no coronary artery abnormalities, and the left ventriculography examination revealed normal myocardial movement associated with a substantial thickening of the LV endomyocardium (Fig. 2).

A further peripheral blood smear showed 20% neutrophilic granulocytes and 68% eosinophilic segmented granulocytes. A bone marrow biopsy indicated that the rates of eosinophilic myelocytes, eosinophilic metamyelocytes, eosinophilic stab granulocytes and eosinophilic segmented granulocytes were 0.5, 12.5, 15.5 and 49%, respectively. No abnormalities were found in glucose, plasma protein, bilirubin, ions, blood lipids, NT-pro brain natriuretic peptide (NT-proBNP) and vitamin B_{12} levels, and renal and coagulation function.

His urine and stool tests were normal. The antibodies to hepatitis B and C viruses, *Treponema pallidum* and human immunodeficiency virus were negative. There were no abnormalities in the tuberculin test, thyroid function, rheumatic, immune and tumour biomarkers, and no parasites were found. Allergen tests showed IgE > 200 IU/ml with short ragweed and artemisia at 2.12 IU/ml, and cashew, peanut and soybean at 3.70 IU/ml. His chromosome pattern was 46, XY [20] with no positivity in fusion genes, including *PDGFRα* (*FIPIL1*/*PDGFRα*), *PDGFRβ*, *FGFRI*, *AMLI*, *CAN*, *MLL*, *BLR*/*ABL* and *JAK2*.

Two-dimensional transthoracic echocardiography (TTE) performed the day after admission revealed a markedly thickened LV wall accompanied by mild mitral regurgitation of 2.5 cm^2 (Fig. 3A). The sizes of the bilateral atrial and ventricular chambers were normal with no evidence of pericardial effusion. The LV systolic function was normal with an ejection fraction (EF) of 67%, but a mild LV diastolic dysfunction was noted with E (0.52 m/s)/A (0.77 m/s) = 0.67, e′ (6.7 cm/s)/a′ (8.5 cm/s) = 0.78, and E/e′ = 7.76.

Chest computed tomography (CT) showed increased bronchovascular shadows at the bilateral lung bases (Fig. 4A). Abdominal ultrasound showed no abnormalities in the liver, spleen, gall bladder, pancreas, kidneys and adrenal glands. Cine-cardiac magnetic resonance (CMR) imaging (Skyra 3.0 T scanner, Siemens, Munich, Germany) with steady-state free precession (True FISP) sequences revealed a substantially thickened LV endomyocardium and low-density thrombotic signals within the LV cavity (Fig. 5). CMR parameters of cardiac function were EF of 50%, LV end-diastolic volume of 149 ml, LV end-systolic volume of 75 ml, stroke volume of 74 ml, cardiac output of 4.5 l/min and cardiac index of 2.3 l/min/m^2.

Secondary hypereosinophilia due to drugs, allergic and connective tissue disorders, parasites, malignancies, rheumatism, as well as haematological neoplasm with clonal eosinophilia was excluded. The patient was diagnosed as IHES and IHES-related cardiac injuries.

The patient received subcutaneous injections of low-molecular weight heparin of 40 mg twice daily for five consecutive days, and oral warfarin and prednisolone at an initial dose of 2.5 and 75 mg/day, respectively. Seven days after hospital admission, the patient's symptoms completely resolved and the eosinophil count dropped significantly. Repeat ECG showed similar changes to those before admission, whereas TTE recheck showed a normal

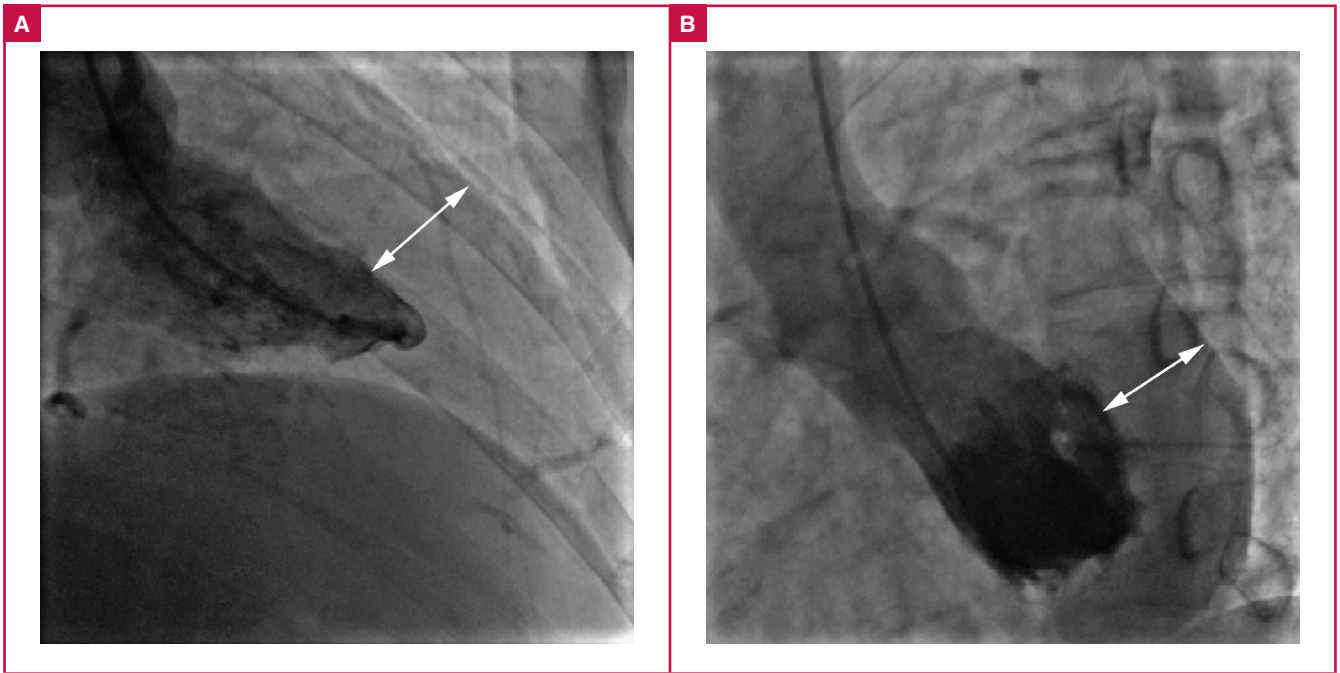

Fig. 2. Left ventriculography at the ventricular end-systolic phase. A: right anterior oblique 30° view. B: left anterior oblique 60° view. The white double arrows indicate the substantially thickened endomyocardium of the LV.

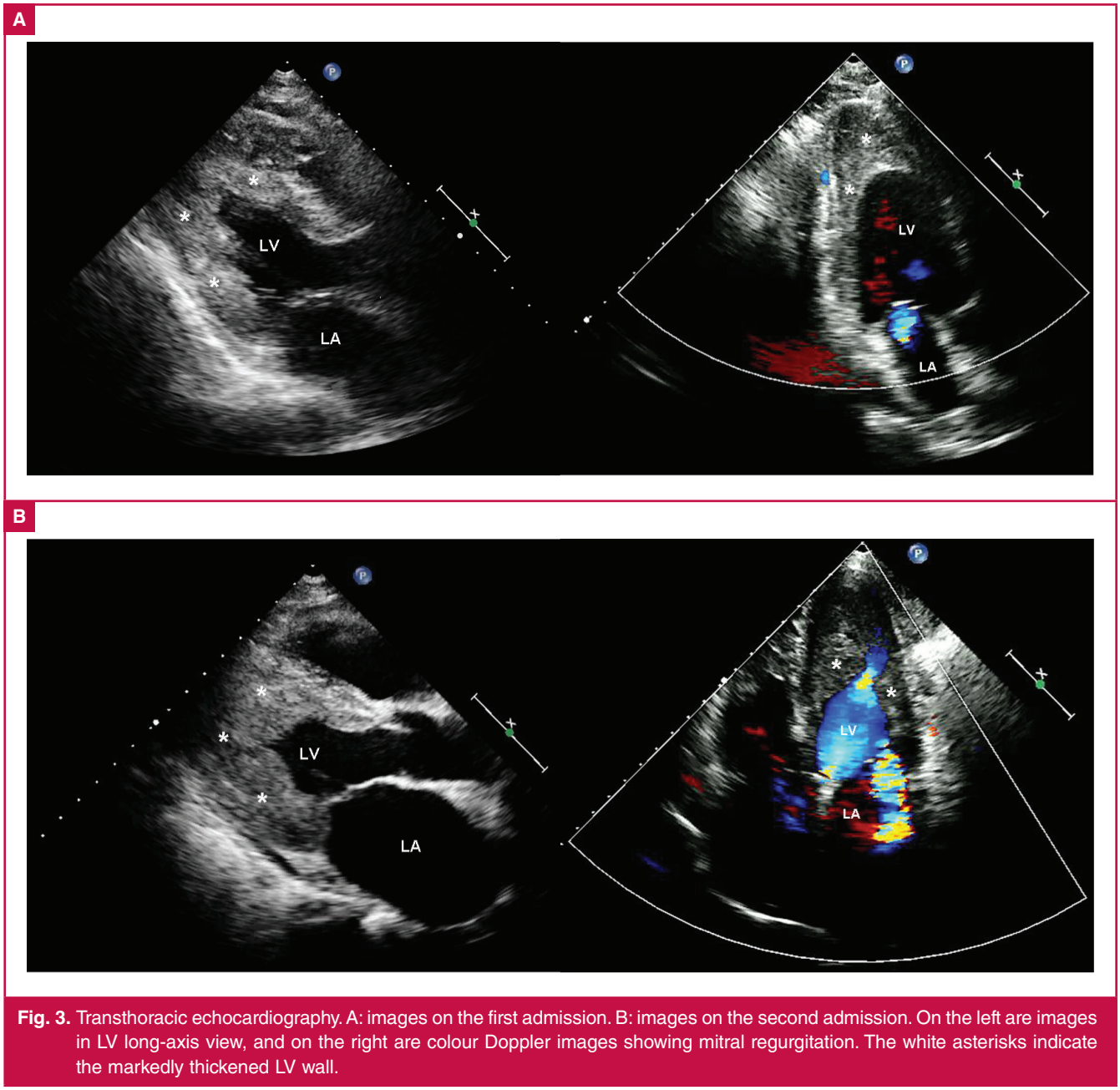

Fig. 3. Transthoracic echocardiography. A: images on the first admission. B: images on the second admission. On the left are images in LV long-axis view, and on the right are colour Doppler images showing mitral regurgitation. The white asterisks indicate the markedly thickened LV wall.

LV diastolic function with E (0.8 m/s)/A (0.6 m/s) = 1.5, e′ (6.9 cm/s)/a′ (6.3 cm/s) = 1.1 and E/e′ = 11.6.

After discharge, the patient discontinued the prednisolone and warfarin treatment for personal reasons. Symptoms of high fever (39°C), chest pain and shortness of breath recurred, associated with a severe cough and nocturnal dyspnoea at one month after discharge. At the second admission, the patient's body temperature was 38.2°C and blood pressure was 90/60 mmHg. He appeared acutely ill with a restricted semi-fowler position; a rash was seen all over his trunk and four limbs (Fig. 6); obvious jugular vein distension was noted on the bilateral neck regions; and moist rales were heard at the bases of both lungs. His heart rate was 110 beats per minute with a regular rhythm. A holosystolic blowing murmur with 4/6 degree was heard at the auscultatory mitral area associated with concomitant S_3 gallop. In addition, a moderate pitting oedema was noted on both legs.

A routine blood test showed a WBC count of 47.75 × 10^9 cells/l, with 67.6% eosinophil and a total blood count of 24.53 × 10^9 cells/l. His international normalised ratio, troponin-I, D-dimer, and NT-proBNP were 1.85, 3.17 ng/ml, 2 273 ng/ml and 9 690 pg/ml, respectively. An ECG showed sinus tachycardia, premature ventricular contractions and ST-segment depression with inverted T waves on V_1–V_6 leads (Fig. 1B). Chest CT showed a bilateral pleural effusion with large flaky high-density infiltrates throughout the right lung and the inferior left lung (Fig. 4B).

A TTE recheck showed a significantly thickened LV wall, accompanied by an enlarged right atrium (48.1 × 55.3 mm) and left atrium (antero-posterior diameter of 41.3 mm). The mitral, aortic and tricuspid regurgitation areas were increased to 8.0, 1.9 and 4.8 cm^2, respectively (Fig. 3B). The pulmonary arterial pressure was increased to 63.0 mmHg. The LV systolic function

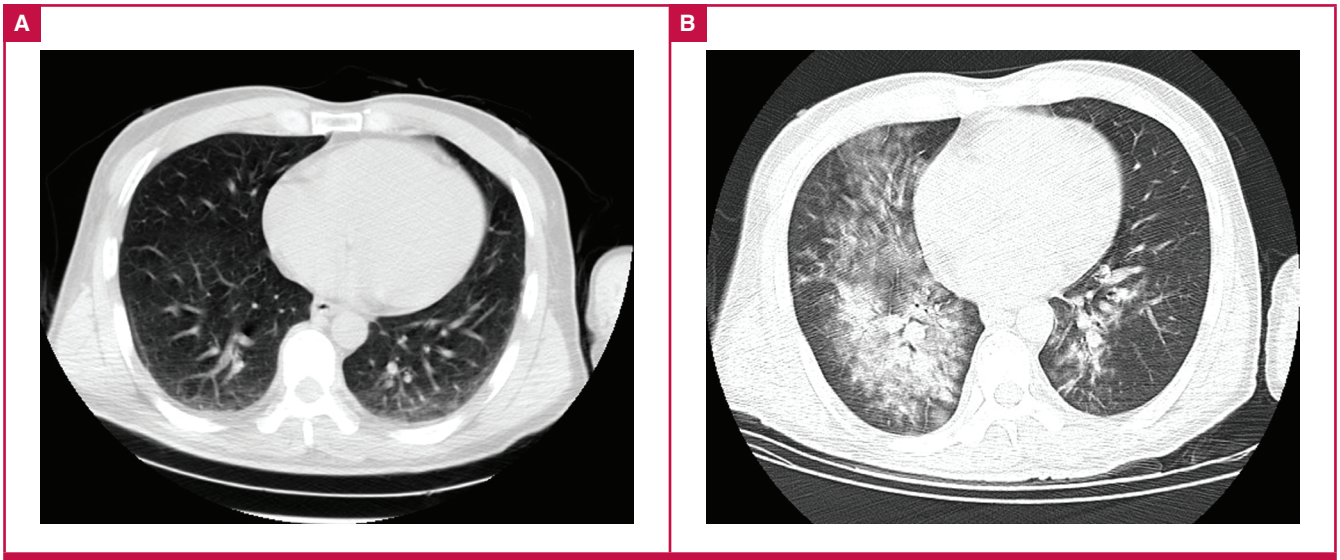

Fig. 4. Chest CT. A: image on the first admission showing slightly increased bilateral bronchovascular shadows on the lungs. B: image on the second admission showing large, flaky, high-density infiltrates throughout the right and inferior left lung.

was normal with an EF of 75%, while the diastolic function was worsened with E (1.0 m/s)/A (0.6 m/s) = 1.7, e′ (3.5 m/s)/a′ (2.8 m/s) = 1.2 and E/e′ = 28.5. A 3.7-mm pericardial effusion was also identified on the roof of the right atrium.

In addition to diuretics and aldosterone receptor antagonists, as well as beta-blockers to control the fast heart rate, the patient received a five-day intravenous dexamethasone infusion at a dosage of 10 mg once per day, and oral prednisone and warfarin at the dosage of 75 and 3.5 mg once per day, respectively. Additionally, cytotoxic hydroxycarbamide, a cytotoxic agent, was added at a dosage of 500 mg twice per day.

The patient's symptoms of cough and dyspnoea were markedly alleviated one week later. His temperature returned to normal, the rash completely disappeared, and the moist rales disappeared on both lungs. Repeat chest X-ray revealed substantially reduced infiltrating shadows with no evidence of pleural effusion. The WBC count was decreased to 18.54 × 10^9 cells/l, with 37.7% eosinophils and a total blood count of 6.99 × 10^9 cells/l. The patient was discharged and closely followed up by his field physicians.

Discussion

IHES is a rare eosinophilic proliferative disease involving multiple vital organs. It more often occurs in men, and the ratio of male-to-female is about 9:1.[4] Studies have reported that cardiac involvement occurs in more than 50% of IHES patients and is the leading cause of death. The in-hospital death rate due to cardiac involvement secondary to IHES was reported in one study to be 12.5%.[7]

Eosinophil-mediated cardiac injury occurs in three stages:[5,6] (1) an early necrotic stage characterised by the formation of myocardial necrosis and micro-abscess due to eosinophil infiltration and toxic cationic protein released from degranulation of the eosinophils; (2) an intermediate thrombotic stage manifesting as the formation of thrombi on the surface of damaged myocardium; and (3) a late fibrotic phase characterised by the formation of endomyocardial fibrosis and scar, which is frequently associated with cardiac diastolic dysfunction and even restrictive cardiomyopathy. Progressive extensive endomyocardial fibrosis may also attack the chordae tendineae and papillary muscles, leading to valvular insufficiency.[10]

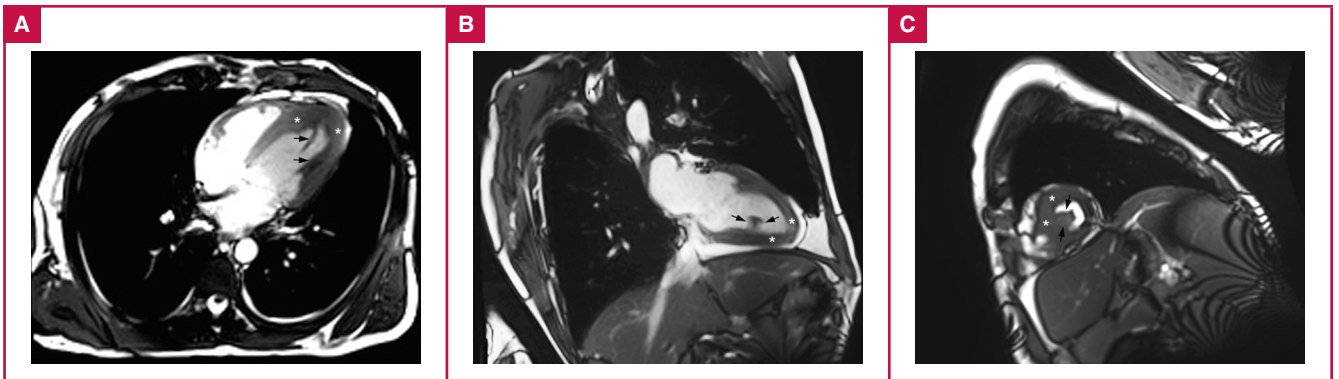

Fig. 5. Frozen images of cine-cardiac magnetic resonance true fast imaging with steady-state free precession sequences. A: four-chamber view. B: two-chamber view. C: short-axis view. The white asterisks indicate the markedly thickened endocardium and black arrows indicate the thrombi within the LV cavity.

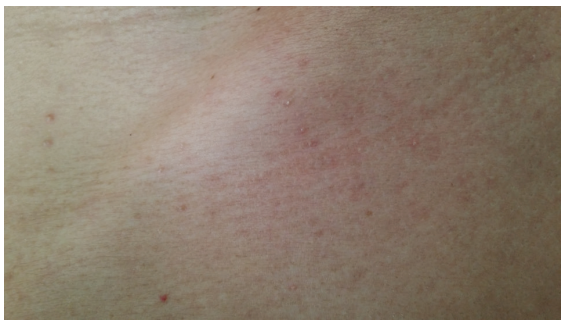

Fig. 6. Rash on the skin of the trunk.

Mimicking acute coronary syndrome (ACS), IHES-mediated myocardial necrosis may manifest as chest pain, abnormal ischaemic ECG changes and elevated troponin-I,[7] which may be neglected by clinical doctors. Our presenting patient was initially misdiagnosed as ACS by the emergency room doctor; however, the negative coronary angiogram excluded coronary artery anomalies. Additionally, it should be noted that normal CK and CK-MB levels with only increased troponin-I and without enzymatic dynamics are not likely to confirm a diagnosis of ACS. Due to the highly elevated peripheral eosinophil numbers and atypical near-mature eosinophils in the bone marrow, as well as finally excluding secondary causes of hypereosinophilia, the patient was diagnosed with IHES and IHES-mediated cardiac injury.

TTE is the most common and convenient modality to identify cardiac injury in clinical practice. Typical findings of IHES-mediated cardiac involvement on TTE include endomyocardial thickening, mural thrombus, valvular insufficiency and restrictive diastolic dysfunction.[11,12] In this report, the findings of thickened endomyocardium, ventricular diastolic dysfunction, enlarged bilateral atria, elevated pulmonary arterial pressure and aggravated valvular regurgitations on TTE were consistent with a diagnosis of IHES-mediated cardiac damage.

The thickened endomyocardium may be explained by the extensive formation of endomyocardial fibrosis and scar, and the multiple valve regurgitations can be ascribed to the adverse involvement of chordae tendineae and/or papillary muscles secondary to IHES. Impaired LV diastolic function may suggest restrictive cardiomyopathy resulting from substantially thickened ventricular endomyocardium and reduced compliance in the LV myocardium. Additionally, the IHES-mediated restrictive LV filling dysfunction limits blood evacuation from the atria into the ventricles, thereby, leading to volumetric dilation of both atria and subsequent elevated pulmonary artery pressure. These abnormalities on TTE strongly indicated that the patient's IHES-mediated cardiac injury had progressed into the final stage.

CMR has been validated as a fairly accurate method of detecting cardiac injury in the clinic.[13,14] In the present case, the LV intra-cavity blood, thickened LV endomyocardium and attached LV mural thrombus showed different intensities of signal on the frozen cine-CMR images, thereby facilitating identification of LV thrombotic lesions from the attached thickened LV endomyocardium.[13,14]

Pulmonary infiltration has seldom been reported in IHES patients.[8] In the present case, no obvious abnormality was found on chest CT during the first admission, whereas large, flaky, high-density infiltrating lesions had developed rapidly within one month after hospital discharge. The fact that the infiltration shadows were markedly resolved after treatment with glucocorticoid and hydroxycarbamide without antibiotics suggests that the pulmonary lesions were related to IHES.

Skin damage resulting from a toxic mediator released from the degranulation of eosinophils has been reported in 12 to 15% of IHES patients.[9] Typical symptoms of skin involvement secondary to IHES may include angioneurotic oedema, urticaria or pruritic papules.[9] In the present case, a rash was apparent throughout the patient's trunk and limbs on the second hospital admission. The rapid disappearance of the rash with combined therapy of glucocorticoid and hydroxycarbamide suggests that the skin lesion was IHES related.

In a review of the literature, the objective of IHES treatment is to reduce the number of eosinophils, as well as to minimise organ injury and thromboembolic complications. Glucocorticoids are the first-line drug for IHES patients. If glucocorticoids are ineffective or a minimum maintenance dose of > 10 mg/d is required, α-interferon or cytotoxic agents, such as hydroxyurea, vincristine, etoposide, chlorambucil, cladribine and cyclosporine may be added. Targeted therapeutic drugs, including imatinib mesylate, anti-IL-5 (mepolizumab) and anti-CD52 (alemtuzumab) monoclonal antibody, as well as allogeneic haematopoietic stem cell transplantation may be options for refractory IHES patients.[15,16]

In this report, glucocorticoids were initially effective for the patient; however, treatment with glucocorticoids was interrupted after hospital discharge for the patient's own reasons, leading to a rapid deterioration in his condition. After the glucocorticoids were resumed and hydroxyurea was added, the patient's condition improved. The markedly decreased peripheral eosinophils and the reduced infiltrating lesions of the lungs and skin demonstrated that the combined therapy of glucocorticoids and hydroxyurea was effective for this IHES patient.

IHES patients generally show a trend toward hypercoagulation. It is unclear whether prophylactic anticoagulants should be given to IHES patients; however, if there is any evidence of cardiac thrombosis, aggressive anticoagulation therapy is warranted.[15] In our case, the LV thrombus was diagnosed by CMR, therefore timely and adequate heparin and warfarin anticoagulants were administered.

In a review of literature, surgical thrombectomy, endocardium resection and valvular replacement are appropriate options for some refractory IHES patients. Heart transplantation may be the last resort for those patients with end-stage cardiac damage.[17,18]

Conclusion

IHES is an eosinophilic proliferative disorder involving multiple vital organs. IHES-mediated cardiac injury mimics ACS, which may be under-recognised by clinicians. Combined therapy with glucocorticoids, hydroxyurea and wafarin was effective for our IHES patient.

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Internal thoracic artery pseudoaneurysm after redo aortic root replacement

Yoshinori Kuroda, Tetsuro Uchida, Azumi Hamasaki, Mitsuaki Sadahiro

Abstract

Pseudoaneurysm of the internal thoracic artery (ITA) or bleeding from the ITA is an extremely rare complication after cardiovascular surgery via a median sternotomy. Early treatment is needed in the case of massive haemorrhage or a rapidly enlarging pseudoaneurysm. Herein, we present a rare case of a delayed large pseudoaneurysm of the right ITA in a 49-year-old woman with Marfan syndrome who underwent redo aortic root replacement via re-median sternotomy and pacemaker implantation. Diagnostic selective angiography revealed the origin of the pseudoaneurysm, and simultaneous transcatheter embolisation of the ITA was successfully performed. Follow-up computed tomography imaging showed no evidence of contrast media extravasation from the ITA and recurrent extra-pleural haemorrhage. Our findings suggest that postoperative management of patients who have undergone median sternotomy, including cardiovascular surgeries, should also focus on the prevention or early detection of pseudoaneurysm of the ITA to avoid life-threatening conditions.

Keywords: Marfan syndrome, post aortic root replacement, pseudoaneurysm of the internal thoracic artery

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Pseudoaneurysm or bleeding of the internal thoracic artery (ITA) is an extremely rare complication after cardiovascular surgery via a median sternotomy, especially during the delayed postoperative phase. Early treatment may be needed in the case of massive haemorrhage or a rapidly enlarging pseudoaneurysm. Herein, we describe a case of pseudoaneurysm of the ITA in a patient with Marfan syndrome after redo aortic root replacement.

Case report

The patient was a 49-year-old woman who underwent valve-sparing aortic root replacement (re-implantation procedure) and total arch replacement for a type A aortic dissection. Although she was asymptomatic, four months after the aortic root replacement, a massive aortic root pseudoaneurysm was detected on routine follow-up computed tomography (CT) scan. Redo aortic root replacement (Bentall procedure) through re-median sternotomy was urgently performed.

After the surgery, complete atrioventricular block occurred, and pacemaker implantation (PMI) was performed via the right axillary vein through a cut-down procedure two days after the redo aortic root replacement. On the following day, chest radiography revealed massive right pleural effusion (Fig. 1A) although chest radiography performed the day before PMI revealed little pleural effusion (Fig. 2). A large amount of blood (1 600 ml) was drained by thoracentesis.

Emergency CT conducted immediately after thoracentesis revealed upper anterior extra-pleural haemorrhage, extravasation of contrast media inside the haemorrhage and pleural effusion (Fig. 1B). Although the extravasation inside the extra-pleural haemorrhage detected on CT looked like a torturous abnormal vessel, pre-operative CT revealed a normal ITA and its branch vessels (Fig. 3). Additionally, the origin of the extravasation was unclear on CT. Selective angiography of the right ITA detected extravasation from a thin branch of the right ITA running to the mediastinum (Fig. 4A). Right ITA embolisation was completed with coils and n-butyl-2-cyanoacrylate, and the bleeding was controlled (Fig. 4B).

The patient had an uneventful postoperative recovery, and follow-up CT showed no evidence of contrast media extravasation from the ITA or recurrent extra-pleural haemorrhage.

Discussion

Injury and pseudoaneurysm or bleeding of the ITA are reported as rare postoperative complications of surgery via a median sternotomy, which are caused by closure wire injury,

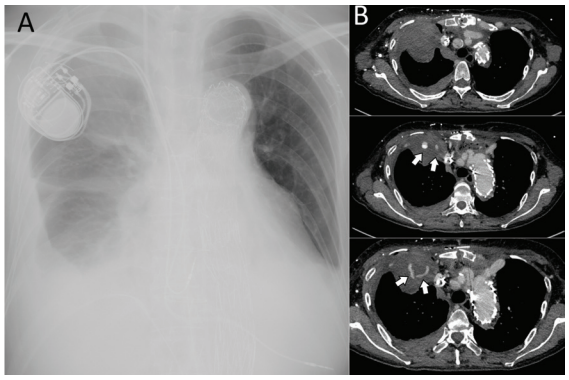

Fig. 1. Chest radiography and computed tomography after pacemaker implantation. A: Chest radiograph shows massive right pleural effusion. B: Emergency computed tomography after thoracentesis shows extravasation of contrast to the extra-pleural haemorrhage of the upper portion of the right pleura (arrow), and pleural effusion.

Division of Cardiovascular Surgery, Department of Surgery II, Faculty of Medicine, Yamagata University, Yamagata, Japan
Yoshinori Kuroda, PhD, y-kuroda@med.id.yamagata-u.ac.jp
Tetsuro Uchida, PhD
Azumi Hamasaki, PhD
Mitsuaki Sadahiro, PhD

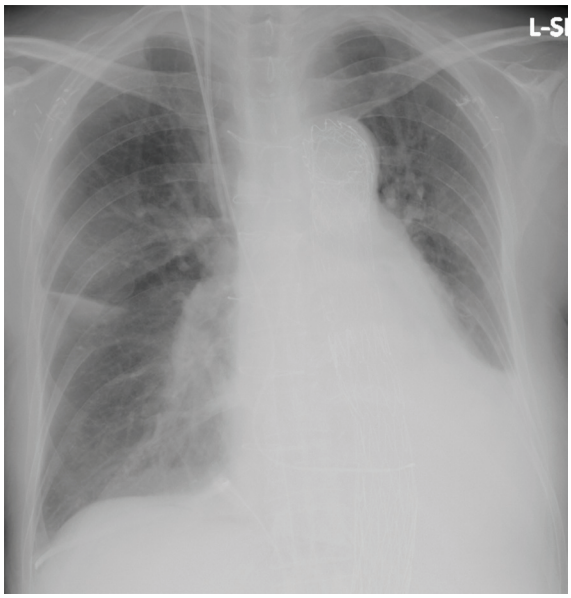

Fig. 2. Chest radiography performed the day before pacemaker implantation reveals minimal right pleural effusion.

sternum retraction and electric cautery injury.[1-3] Other causes of pseudoaneurysm of the ITA are idiopathic, trauma, penetrating injury, infection, PMI and central vein cannulation.[1,4,5] Massive bleeding may result in life-threatening conditions. Pseudoaneurysm of the ITA is commonly diagnosed using medical imaging modalities such as CT and ultrasonography; however, it could also be diagnosed through surgical exploration.[1]

In our case, ITA aneurysm occurred in the delayed phase after surgery and the pathogenesis of the right ITA pseudoaneurysm formation was uncertain. Direct injury during the opening or closure of the sternum or a manoeuvre during PMI was suspected as the cause of the ITA pseudoaneurysm, although it was unlikely that it was caused by PMI because this was performed using a cut-down technique. The fragility of vessels in patients with Marfan syndrome was also considered to contribute to the formation of the ITA pseudoaneurysm.

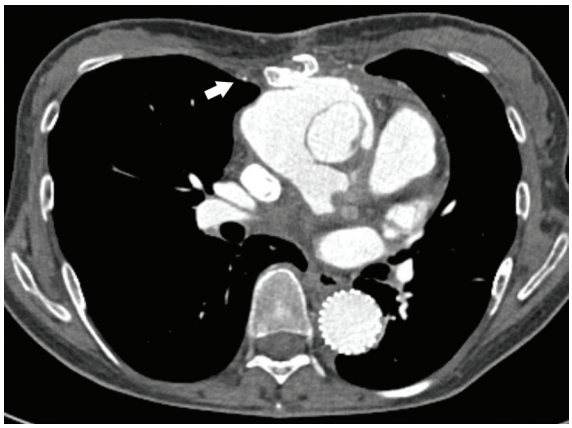

Fig. 3. Computed tomography before redo aortic root surgery reveals a normal internal thoracic artery and its branch vessels.

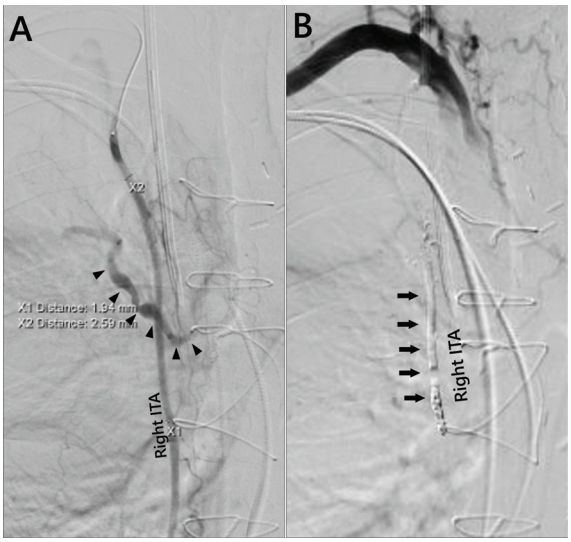

Fig. 4. A: Selective angiography of the right internal thoracic artery reveals that the bleeding originated from a branch of the right internal thoracic artery (arrowhead). B: The right internal thoracic artery was selectively embolised (arrow) and bleeding was controlled.

CT is a useful diagnostic tool; however, detecting the origin of bleeding using this modality is difficult. Selective angiography allowed precise identification of the origin of bleeding. Nanami *et al*. reported that ITA angiography was a useful diagnostic tool for the treatment of ITA pseudoaneurysm.[1] Furthermore, the bleeding could be controlled soon after the diagnosis by simultaneous embolisation of the ITA.

Conclusion

Although the possibility of the occurrence of a delayed pseudoaneurysm or bleeding of the ITA is low after a median sternotomy procedure, postoperative management of patients who have undergone median sternotomy should also focus on the prevention or early detection of pseudoaneurysm of the ITA to avoid life-threatening conditions.

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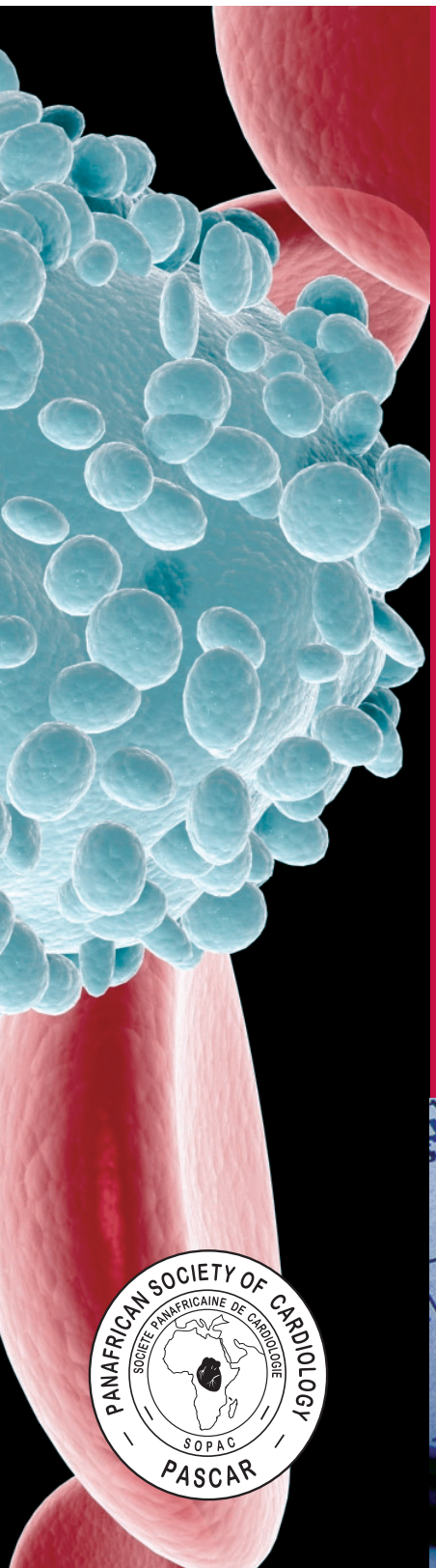

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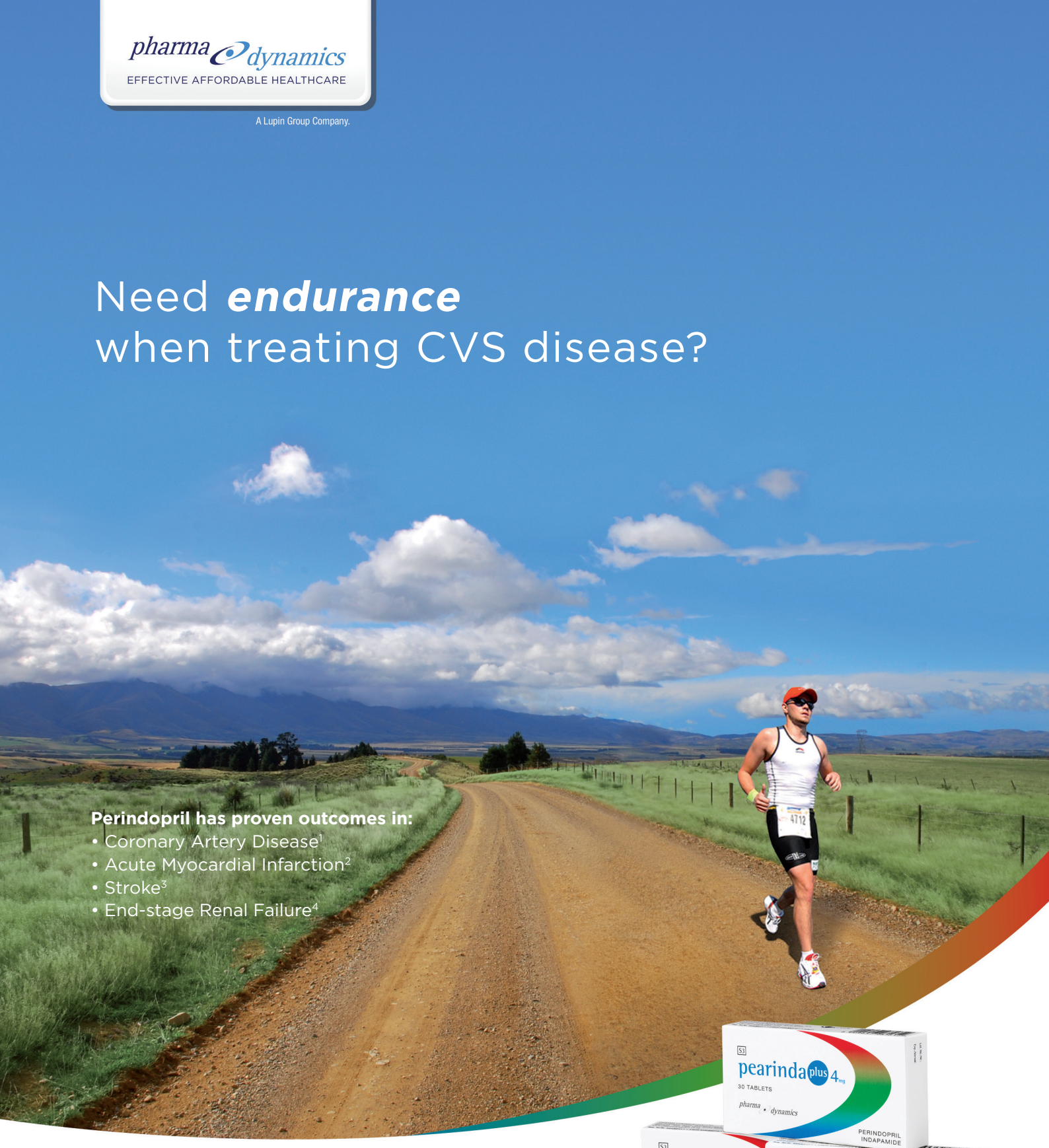

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PEARINDA 4, 8. Each tablet contains 4, 8 mg perindopril *tert*-butylamine respectively. S3 A41/7.1.3/0649, 0650. NAM NS2 10/7.1.3/0476, 0477. For full prescribing information, refer to the professional information approved by SAHPRA, April 2009. **PEARINDA PLUS 4.** Each tablet contains 4 mg perindopril *tert*-butylamine and 1,25 mg indapamide. S3 A41/7.1.3/0633. NAM NS2 10/7.1.3/0611. For full prescribing information, refer to the professional information approved by SAHPRA, April 2010. **1)** The EUROPA study Investigators. "Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study)". *The Lancet* 2003;362:782-788. **2)** The PREAMI study Investigators. "Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodelling and clinical outcome. Results of the randomized perindopril and remodelling in elderly with acute myocardial infarction (PREAMI) study". *Arch Intern Med* 2006;166:659-666. **3)** PROGRESS Collaborative Group. "Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack". *The Lancet* 2001;358:1033-41. **4)** Guerin AP, *et al.* "Impact of Aortic Stiffness Attenuation on Survival of Patients in End-Stage Renal Failure". *Circulation* 2001;103;987-992. **PAI594/04/2019.**