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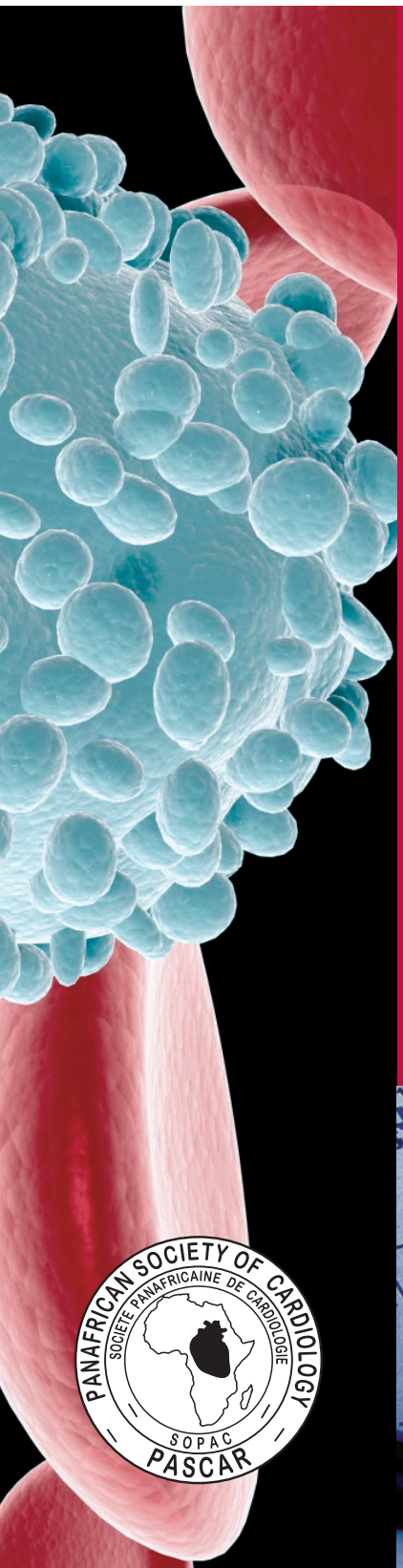

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Editorial

Familial hypercholesterolaemia and its management in South Africa

AD Marais

This issue of the *Cardiovascular Journal of Africa* has published two articles relevant to severe dyslipidaemias. A new therapeutic agent under review by the South African Health Products Regulatory Agency (SAHPRA) has already been used in pharmaceutical trials[1] in South Africa, a country renowned for founder effects in familial hypercholesterolaemia (FH) in the Afrikaner, Jewish and Indian communities (page 279). The workshop on FH provides an update and important local information (page 297).[2]

Twenty years after the World Health Organisation publication,[3] renewed efforts are being made internationally to recognise, detect and treat FH. The FH Foundation in the USA arranged a global call-to-action summit meeting last year.[4] The high risk of atherosclerosis, successful treatment and the high prevalence in all populations are compelling reasons for the recognition of FH worldwide, as well as in our healthcare system, despite the current strains.

Atherosclerosis incubates asymptomatically until an abrupt clinical manifestation at thrombosis, most prominently in the coronary arteries. In the Cape Town experience, the mean age for myocardial infarction in men is 45 years,[5] but has been documented at 23 years. While atherosclerosis is multifactorial in its pathogenesis and its risk is best assessed by taking into account several risk factors for most patients, in FH the process is almost entirely driven by the elevated low-density lipoprotein cholesterol (LDL-C) concentration.

At the time that screening for treatment of hypercholesterolaemia was advised for higher-risk cases in the Sheffield table,[6] testing for hypercholesterolaemia to detect FH at a young age was highlighted owing to its high risk. Persons with FH are excluded from risk calculations that guide treatment in the South African guideline for treatment of dyslipidaemia.[7] LDL hypercholesterolaemia exceeding a concentration of 5 mmol/l, equivalent to a total hypercholesterolaemia exceeding 7.5 mmol/l, is suggestive of FH and requires intervention[8] owing to the exponential function of risk. In FH, the triglyceride concentration is generally normal. Common secondary causes for hypercholesterolaemia that require exclusion are nephrotic syndrome and hypothyroidism. LDL hypercholesterolaemia of > 5 mmol/l together with an Achilles tendon xanthoma clinches the diagnosis. Tendon xanthomata are useful clinical signs that set in after the second decade but are often overlooked.

In FH, impaired clearance of LDL from the circulation into the liver relates to dysfunction of the LDL receptor, poor binding to the receptor of apoliprotein B in LDL, and increased LDL receptor degradation by proprotein convertase subtilisin/kexin type 9 (PCSK9). These disorders are autosomal dominantly inherited. Rarely, recessive disorders cause a FH phenotype and in some cases FH may be polygenic.[9] There is a gradation of severity in FH according to the functional impact of mutations.[8] Fortunately, the severe homozygous FH phenotype is rare but must be considered when both parents have FH.

The target concentration for LDL-C concentration in FH subjects may be similar to that for other cases of primary prevention of atherosclerosis, i.e. 3 mmol/l when detected early. But for those at higher risk at older age, the recommended LDL-C concentration is at least below 2.5 mmol/l.[7] Because the lower border of LDL cholesterol concentration in FH is 5 mmol/l, prescription of maximal doses of atorvastatin or rosuvastatin should achieve the target concentration. Less than 10 and 50% of heterozygous FH, without and with heart disease, respectively, will achieve target on such treatment. Additional ezetimibe will achieve target in 54 and 93%, respectively.[10] A number of more severe cases will require the additional lowering that PCSK9-neutralising antibodies provide.

Based on the prevalence of FH at one in 500 persons, there are more than 1.5 million individuals with FH in sub-Saharan Africa and about 250 000 in South Africa; of whom the majority will be in the black population. Africa is lagging behind in the detection and treatment of FH. Despite early research in FH in South Africa, translation of the diagnosis and treatment of FH into clinical practice has been disappointing in both the public and private healthcare sectors. The discipline of lipidology, or vascular medicine in some countries, has not developed in South Africa. Not only are there few doctors with relevant clinical skills but also the scope of diagnostic investigation for severe dyslipidaemia is limited.

In most cases management is not difficult. Maximal doses of the more powerful statins will suit a large proportion of FH patients, with a majority achieving target with the addition of ezetimibe, with dramatic improvement in the quality and duration of life.

Keywords: familial hypercholesterolaemia, national health insurance, statins, ezetimibe, PCSK9 neutralising agents

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Education of the public about FH is appropriate, given its prevalence and severity, but should be preceded by education of healthcare providers who need to consider the differential diagnosis and tailor management accordingly. Given our limited resources and the treatable high risk of FH, this condition should receive no less support than other conditions with similar risk of morbidity and mortality, expense of symptomatic treatment, and negative impact on families.

While genetic confirmation is desirable and is relatively efficient owing to founder effects, clinical diagnosis suffices in most cases. In a small proportion of severe and problematic cases, referral to specialised clinics is recommended. A national network of clinics should be supported by at least one dedicated laboratory to ensure an accurate diagnosis and appropriate use of treatment, especially if expensive. Since neither the public nor private sector currently provides such an important service, the National Health Insurance system under consideration will do well to consider arrangements for severe lipid disorders.

Compared with the ambitious scale for improving healthcare in general, severe dyslipidaemias affect smaller numbers of patients, require relatively small numbers of staff, require a single laboratory for the country and can serve both the public and private sectors of healthcare at the same referral centres. Expert evaluations will not only improve management and outcome but will also highlight relevant research needs for the future.

Severe dyslipidaemias should be recognised and assessed for judicious use of intervenional strategies, including new therapeutic agents, to ensure best health for the people of South Africa.

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Daily 4-in-1 polypill could cut cardiovascular disease risk in low-income countries

A study has shown that a daily pill containing four medicines can cut the number of heart attacks and strokes by a third. The polypill contains blood-thinning aspirin, a cholesterol-lowering statin and two drugs to lower blood pressure.

The researchers in Iran and the UK said the pill had a huge impact but cost just pennies a day. They suggest giving it to everyone over a certain age in poorer countries, where doctors have fewer options and are less able to assess individuals.

The report says the study was based in more than 100 villages in Iran and about 6 800 people took part. Half the people were given the polypill and advice on how to improve their lifestyle, with the other half just getting the advice.

After five years, there were 202 major cardiovascular events in the 3 421 people getting the polypill and 301 in the 3 417 not getting the pill. At this rate, giving the preventative drug combination to 35 people would prevent one of them developing a serious heart problem over the course of five years.

'We've provided evidence in a developing or middle-income country, and that's a lot of countries, that this is a strategy worth considering,' Professor Tom Marshall, from the University of Birmingham, is quoted in the report as saying.

The drug was given to people over the age of 50 whether they had had a previous heart problem or not. 'Given the polypill's affordability, there is considerable potential to improve cardiovascular health and to prevent the world's leading cause of death,' said Dr Nizal Sarrafzadegan of Isfahan University of Medical Sciences, Iran.

In the UK and other wealthier countries, doctors have the time to assess the needs of individual patients and a wide choice of different drugs, such as statins, to choose from. 'In the UK, the advantages would be more marginal and you would probably want a clinical trial to see any benefits over what is offered at the moment,' said Marshall.

The report says the idea of the polypill has been around since 2001 but this is the first major trial to prove its effectiveness. The drug however is not licensed in the UK and would be tricky to get approved.

Source: Medical Brief 2019

Editorial

Renal denervation: bleak past, brighter future

Brian Rayner

Heradien *et al*. present a timely review of the history and future directions of renal denervation (RD) for the control of hypertension and the prevention of cardiovascular disease (CVD) page 290.[1] In their review they outline the importance of sympathetic overactivity (or autonomic imbalance) in the pathogenesis of hypertension and in CVD in particular; the role of renal sympathetic overactivity; methods of interrupting renal sympathetic fibres; advances in catheters and techniques; results of initial and recent trials; prevention of cardiac arrhythmias; and future directions. This editorial will provide a perspective on the clinical role of RD.

The publication of SYMPLICITY HTN-1, followed shortly thereafter by SYMPLICITY HTN-2, sent shock waves through the hypertension community.[2,3] Both studies showed profound and long-lasting office blood pressure (BP) reduction (approximately 30/15 mmHg) after RD in patients with resistant hypertension (RH). SYMPLICITY HTN-1 was a proof-of-concept study, while SYMPLICITY HTN-2 was a randomised, unblinded study of RD versus no procedure. There was great excitement and there appeared little doubt that the procedure was highly effective.

However, the Federal Drug Administration (FDA) requested a single-blind, randomised trial with sham procedure using ambulatory BP monitoring as an endpoint before registration, so SYMPLICITY HTN-3 was conceived and executed. Unfortunately, the study showed no significant benefit of RD over sham procedure on ambulatory or office BP.[4] This was a great lesson to everyone, and also reinforced the concept that randomised, prospective, blinded studies are the only way to prove efficacy of any intervention to avoid bias and confounding factors. Many now believed that RD had no future in the treatment of hypertension. However, in all three studies, no safety concerns were demonstrated.

As a result, the South African hypertension practice guideline in 2014 (and other hypertension guidelines) did not recommend RD for the treatment of hypertension,[5,6] and it looked as though RD had fallen off the radar and had a bleak future. Furthermore, the PRAGUE-15 study showed that RD, in the setting of true RH with confirmed adherence, was not superior to intensified pharmacological treatment, and the addition of spironolactone (if tolerated) seemed to be more effective in BP reduction.[7]

The results of SYMPLICITY HTN-3 led to a great deal of introspection by investigators involved in RD studies. However, there were several problems with SYMPLICITY HTN-3 that may have explained the negative result. First, it was underpowered because of the impressive results of SYMPLICITY HTN-1 and -2. Second, many operators were extremely inexperienced, only performing one procedure. Third, full bilateral denervation was not achieved in a high percentage of cases, and non-adherence at baseline and adherence in the study reduced differences between sham and active treatment.[8]

Recommendations were mandated for the next generation of sham, randomised, controlled trials. Four-quadrant ablation of both kidneys circumferentially had to be achieved using only experienced interventionalists from experienced centres.[8] This was assisted by the development of a radiofrequency multi-electrode catheter (Spyral, Medtronic, Ireland), designed to enable reliable circumferential four-quadrant ablation. Adherence had to be confirmed by either witnessed intake of medication (if applicable) and/or urine analysis of medication adherence in each patient. BP assessment had to be performed by 24-hour ambulatory BP to avoid bias and super-added white coating. Studying patients in the absence of any medication was also suggested to assess the 'true' BP reduction of RD.

The recent publication of three pivotal studies greatly renewed interest in RD. Two studies were performed in patients off medication (SPYRAL HTN-OFF and RADIANCE-HTN SOLO) and one on medication (SPYRAL HTN-ON).[9-11] The prospective, randomised, double-blind, sham-controlled SPYRAL HTN-OFF study included patients with hypertension with an office systolic BP between 150 and 180 mmHg, office diastolic BP > 90 mmHg, and ambulatory SBP of 140–170 mmHg with no concomitant antihypertensive therapy.

In the first interim analysis at three months of 80 patients treated, a significant reduction in office systolic BP of –7.7 mmHg ($p = 0.0155$) and diastolic BP of –4.9 mmHg ($p = 0.0077$), ambulatory systolic BP of –5.0 mmHg ($p = 0.04$) and 24-hour diastolic BP of –4.4 mmHg ($p = 0.0024$) was documented, compared with sham treatment. RADIANCE HTN-SOLO was a similar study except that a balloon-based catheter (Paradise, Recor, CA, USA) ablated renal sympathetic nerves circumferentially using ultrasound energy. A similar magnitude of BP reduction to SPYRAL HTN-OFF was achieved compared to sham treatment.

The SPYRAL HTN-ON, a prospective, randomised, double-blind, sham-controlled study, used the same BP criteria as for the SPYRAL-OFF study, but included moderate, uncontrolled

Keywords: renal denervation, hypertension

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hypertensive patients on one to three commonly prescribed antihypertensive drugs. The first interim analysis documented a progressive fall in both office and ambulatory BP at three and six months, compared to sham treatment, respectively.

These studies showed the first biological proof that RD was effective in lowering BP in humans with or without concomitant antihypertensive medication, and the pathophysiological contribution of the renal efferent and afferent nerves in hypertension was confirmed. [8] This has given many investigators renewed hope that RD may have a brighter future in the treatment of hypertension, but there may be a major shift away from RH.

One of the important outcomes of the RD programme is that we have come to appreciate the crucial role of non-adherence to medication as a major contributor to apparent treatment resistance. RD only offers the BP-lowering efficacy of little more than one antihypertensive drug,[12] and it can never be the sole answer to patients requiring three or more medications for the treatment of severe hypertension. It could be an adjuvant therapy for true RH, but it must also be appreciated that patients with true resistance with low renin levels respond to spironolactone or amiloride.

In the author's view, indications for RD may be for the treatment of patients with hypertension with intolerance to multiple antihypertensives, difficult-to-treat hypertension or patients with irremediable non-adherence despite extensive counselling, for example, hypertensive patients with forgetfulness due to early dementia, resulting in poor adherence.

There are many unanswered questions about RD. There are no outcome studies showing the benefits of RD on hard CV outcomes and mortality, although the 10/5-mmHg reduction in BP achieved by RD is likely to result in a substantial reduction in CV events and mortality.[13] Afferent and efferent renal nerves also play a crucial role in CV, metabolic and renal diseases beyond hypertension, and RD may offer a new interventional treatment option to prevent heart failure, atrial fibrillation, ventricular arrhythmias, chronic kidney disease, obstructive sleep apnoea and diabetes.[8]

Another unsolved question is to identify those patients who respond most to RD, as analysis of studies suggests there are responders and non-responders to RD.[11] This is a critical question as the estimated cost of RD is in excess of R100 000 and it is really important to ensure success of the procedure. Further research needs to better define the place of RD. The SPYRAL HTN-OFF and HTN-ON have presented only preliminary data and longer-term follow up is required. One needs to proceed cautiously as RD is not a panacea for the treatment of hypertension and may have a place in very carefully selected patients in centres of expertise in the management of hypertension, backed up by experienced interventionists.

Conclusion

Three recent studies showing the BP-lowering efficacy of RD have renewed interest in the procedure. Further research is required to determine an evidence-based role for RD in the treatment of hypertension and the prevention of CVD.

Prof Rayner has served on an advisory board for Medtronics.

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Cardiovascular Topics

The effects of HIV/AIDS on the clinical profile and outcomes post pericardiectomy of patients with constrictive pericarditis: a retrospective review

DP Naidoo, G Laurence, B Sartorius, S Ponnusamy

Abstract

Objective: The clinical profile and surgical outcomes of patients with constrictive pericarditis were compared in HIV-positive and -negative individuals.

Methods: This study was a retrospective analysis of patients diagnosed with constrictive pericarditis at Inkosi Albert Luthuli Central Hospital, Durban, over a 10-year period (2004–2014).

Results: Of 83 patients with constrictive pericarditis, 32 (38.1%) were HIV positive. Except for pericardial calcification, which was more common in HIV-negative subjects (n = 15, 29.4% vs n = 2, 6.3%; p = 0.011), the clinical profile was similar in the two groups. Fourteen patients died pre-operatively (16.9%) and three died peri-operatively (5.8%). On multivariable analysis, age (OR 1.17; 95% CI: 1.03–1.34; p = 0.02), serum albumin level (OR 0.63; 95% CI: 0.43–0.92; p = 0.016), gamma glutamyl transferase level (OR 0.97; 95% CI: 0.94–0.1.0; p = 0.034) and pulmonary artery pressure (OR 1.49; 95% CI: 1.07–2.08; p = 0.018) emerged as independent predictors of pre-operative mortality rate. Peri-operative complications occurred more frequently in HIV-positive patients [9 (45%) vs 6 (17.6%); p = 0.030].

Conclusions: Without surgery, tuberculous constrictive pericarditis was associated with a high mortality rate. Although peri-operative complications occurred more frequently, surgery was not associated with increased mortality rates in HIV-positive subjects.

Keywords: constrictive pericarditis, HIV, pericardiectomy

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Constrictive pericarditis remains an uncommon yet treatable cause of heart failure.[1,2] The hallmark of constrictive pericarditis is impaired ventricular diastolic filling caused by a thickened, fibrosed pericardium, resulting in decreased stroke volume and varying degrees of systemic venous congestion.[2-5] The natural history of this disorder remains unknown.[6]

While medical therapy has been used to successfully treat patients with constriction in its early stages, surgical pericardiectomy remains the only treatment for chronic constrictive pericarditis.[7,8] The surgical mortality rate remains high and has been reported to be between five and 14% in multiple large series.[1,2,6,9-15]

Over the past two decades, there has been a changing spectrum of constrictive pericarditis in the developed world, with a declining incidence of infective aetiologies, in particular tuberculosis.[1,3] In sub-Saharan Africa, tuberculosis remains the dominant cause; about 30 to 60% of patients diagnosed with tuberculous pericarditis progress to constriction despite appropriate anti-tuberculous therapy and adjunctive corticosteroids.[16]

The effect of HIV on the incidence, natural history and surgical outcomes of patients with constrictive pericarditis has not been adequately documented.[2] Recent data suggest that co-existing HIV infection may modify the clinical manifestations and natural history of tuberculous pericarditis and resultant constriction.[17,18] Our study was designed to evaluate the clinical profile and surgical outcomes of HIV-positive and -negative patients with constrictive pericarditis.

Methods

This study was a retrospective chart review of all patients referred to Inkosi Albert Luthuli Central Hospital in Durban, KwaZulu-Natal, for evaluation and management of suspected constrictive pericarditis during the period 2004–2014. Patients eligible for inclusion in the study constituted those in whom the diagnosis of constrictive pericarditis was confirmed using a combination of clinical symptoms and signs associated with typical echocardiographic and computer tomography (CT) scan findings.

Clinical supporting features included peripheral oedema, ascites, pleural effusions, hepatomegaly, elevated jugular venous pressure and pericardial knock. Typical echocardiographic features of constriction were a thickened echogenic pericardium accompanied by paradoxical interventricular septal motion, and dilated non-compressible hepatic veins and inferior vena cava.

Thoracic CT scans were used to confirm pericardial thickening and calcification, and to demonstrate lymph node enlargement.

Tuberculosis (TB) as the cause for constrictive pericarditis was inferred from a history of previous diagnosis of tuberculosis (pulmonary or extrapulmonary), or previous treatment for tuberculosis. Proven tuberculosis was defined by isolation of the organism or typical histological findings. Patients in whom the diagnosis of constrictive pericarditis was incorrect were excluded from the study population.

Informed consent for HIV testing was obtained from all patients with suspected constriction who were referred to Inkosi Albert Luthuli Hospital with a view to surgical pericardiectomy. Relevant data (demographics, HIV status, clinical symptoms, signs and symptoms, and laboratory, echocardiographic, radiological and operative data) and follow-up findings were extracted.

In the subset that underwent pericardiectomy, constrictive pericarditis was confirmed intra-operatively by identifying constrictive features with pericardial thickening and fibrosis. Surgery was performed by median sternotomy without cardiopulmonary bypass in all but one patient. At operation the entire ventricular epicardium, apex and diaphragmatic surface of the heart was freed. The pericardium was removed anteriorly extending laterally to the phrenic nerves and the posterior pericardium was left *in situ* after being freed from the epicardium. Any resection less than this was deemed a partial pericardiectomy. Immediate peri-operative mortality was defined as any death occurring during the index hospitalisation.

The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE 324/15).

Statistical analysis

Data were analysed using Stata 13.0 (StataCorp 2013, Stata Statistical Software: Release 13, College Station, TX: StataCorp LP). Continuous variables were summarised using mean and standard deviation or median and interquartile range. Differences in means of continuous predictors by HIV status (two groups) were assessed using the student's *t*-test. If the data were not normally distributed then the Kruskal–Wallis equality-of-populations rank test was employed instead. Association between HIV status and categorised explanatory variables/risk factors were assessed using a Pearson chi-squared (χ^2) test. Multivariate logistic regression was employed to estimate the

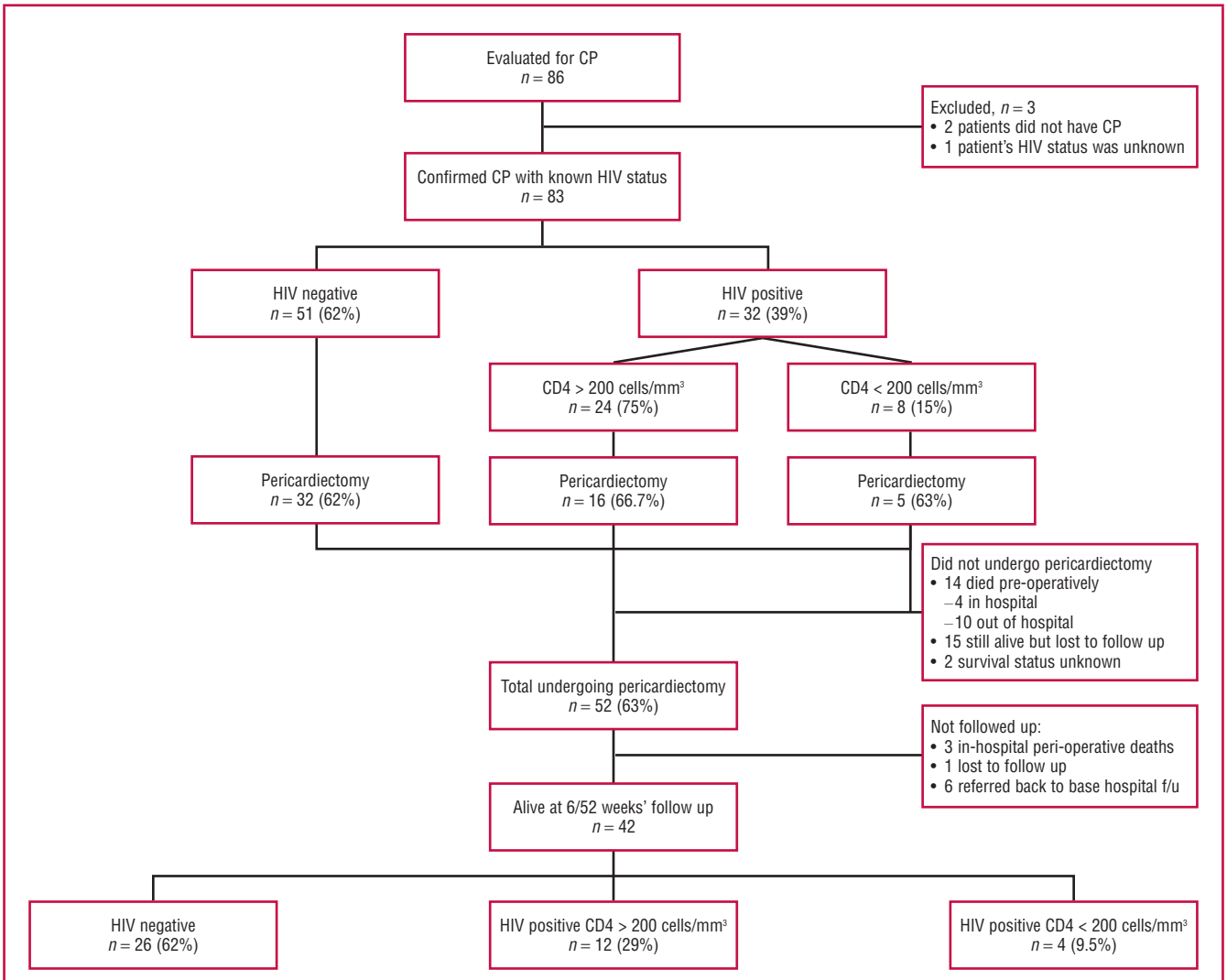

Fig. 1. Early outcome of patients with constrictive pericarditis (CP).

strength of association (odds ratios) between the explanatory predictors and HIV status. A *p*-value of < 0.05 was considered statistically significant.

Results

Pre-operative clinical profile

A total of 86 patients were eligible for inclusion during the study period (Fig. 1). Three patients were excluded, (incorrect diagnosis: $n = 2$, HIV status unknown: $n = 1$) leaving 83 (43 male, 40 female) for analysis. The mean age of the total sample was 37.98 ± 12.91 years (range 19–69). Of these patients, 32 (38.6%) were HIV positive, of whom 21 (65.6%) were on antiretroviral therapy, and of these, 19 (59%) patients were virally suppressed (viral load < 1 000 copies/ml). Three patients who were not on antiretroviral therapy had viral loads < 1 000 copies/ml. In total 8/32 (25.0%) patients had a CD4 count of less than 200 cells/mm^3. The baseline characteristics stratified by HIV status are shown in Table 1.

The aetiology of constriction was tuberculosis in 80/83 (96.3%) patients. Constriction was deemed to have followed viral pericarditis in two patients and the third developed constriction following repeated radio-ablation procedures for tachyarrhythmias. Tuberculosis was proven in 22 (26.5%) patients and was considered the probable aetiology in a further 58 (69.5%) patients. Although proven tuberculosis was identified more frequently in HIV-positive (40%) compared to HIV-negative patients (17.6%), this finding was not statistically significant.

The mean body weight of HIV-positive patients was 5 kg less those who were HIV negative (62.77 ± 12.01 vs 67.69 ± 13.05 kg; $p = 0.09$) but this finding was also not statistically significant. Moderate dyspnoea (NYHA class II) was present in almost two-thirds (63.9%) of the patients and severe symptoms were present in 32.5% (NYHA class III and IV) of patients. Similarly, two-thirds ($n = 57$; 68.7%) of patients had ascites. There was no difference in the clinical characteristics between HIV-positive and -negative patients except for peripheral oedema, which was significantly more frequent in HIV-negative patients (86.2 vs 65.6%; $p = 0.026$). Atrial fibrillation was documented in five patients (all HIV negative), four of whom had extensive pericardial calcification on chest radiography.

All patients (n=83) had chest radiographs and echocardiograms and 77 (94%) had thoracic CT scans. A total of 17 patients (20.5%) had pericardial calcification on the chest radiograph and one additional patient had pericardial calcification identified on CT scan only. Extensive pericardial calcification was more common on the chest radiograph in HIV-negative compared to HIV-positive patients ($n = 15$, 29.4 vs $n = 2$, 6.3%; $p = 0.011$). Mediastinal lymphadenopathy was identified in 47 (61%) patients and there was no difference between HIV-positive and -negative patients ($p = 0.642$)

On echocardiography, effusive constrictive pericarditis was found in seven (8.4%) patients, of whom four were HIV negative and three HIV positive. There was no significant difference in the ejection fraction (51.88 ± 7.5 vs 52.69 ± 4.96%; $p = 0.593$) and pulmonary arterial pressure (33.88 ± 8.86 vs 34.96 ± 7.76 mmHg; $p = 0.571$) between HIV-negative and -positive patients, respectively.

Laboratory data showed no significant differences in haemoglobin, white cell count, urea, creatinine and albumin

Table 1. Baseline characteristics of study patients stratified by HIV status

Characteristics	*All (n = 83)*	*HIV negative (n = 51)*	*HIV positive (n = 32)*	p-*valve*
Age (years)	37.98 ± 12.91	38.82 ± 14.56	36.63 ± 14.56	0.454
Weight (kg)	65.75 ± 12.81	67.69 ± 13.05	62.77 ± 12.01	0.91
Gender				4.24
Male	43(51.8)	29 (56.9)	14 (43.75)	
Female	40 (78.2	22 (43.1)	18 (56.35)	
Aetiology of pericarditis				0.140
Probable tuberculosis	58 (69.9)	39 (76.5)	19 (59.4)	
Proven tuberculosis	22 (26.5)	9 (17.6)	13 (40.6)	
Other	3 (3.6)	3 (5.9)	0	
NYHA functional class				0.481
I	3 (3.6)	2 (3.9)	1 (3.1)	
II	53 (63.9)	33 (64.7)	20 (62.5)	
III	22 (26.5)	4 (7.8)	1 (3.1)	
IV	5 (6.0)	4 (7.8)	1 (3.1)	
Examination				
SBP (mmHg)	110.83 ± 11.85	110.78 ± 11.67	110.91 ± 12.32	0.963
DBP (mmHg)	70.57 ± 10.63	71.43 ± 9.86	69.19 ± 11.78	0.352
Pulse rate (beats/min)	88.76 ± 14.72	86.35 ± 14.74	92.59 ± 14.05	0.060
Jugular vv pressure	77 (92.8)	48 (94.1)	29 (90.6)	0.358
Pericardial knock	43 (51.8)	24 (47.1)	19 (59.4)	0.274
Hepatomegaly	76 (91.6)	46 (90.2)	30 (93.8)	0.767
Ascites	57 (68.7)	35 (68.3	22 (68.8)	0.991
Oedema	65 (78.3)	44 (86.2)	21 (65.6)	0.026
Chest X-ray				
Pericardial calcification	17 (20.5)	15 (29.2)	2 (6.3)	0.011
Pleural effusion	67 (80.7)	43 (84.3)	24 (75.0)	0.295
Echocardiography				
Ejection fraction (%)	52.19 ± 6.61	51.88 ± 7.50	52.69 ± 4.96	0.593
End-diastolic dimension	47.95 ± 7.793	47.4 ± 7.92	48.81 ± 8.01	0.435
Left atrial size (mm)	43.85 ± 8.57	44.86 ± 9.5	42.28 ± 6.70	0.185
Septal bounce	81 (97.6)	49 (96.1)	32 (100.0)	0.257
PA pressure (mmHg)	34.31 ± 8.41	33.88 ± 8.86	34.96 ± 7.76	0.571
Dilated IVC/hepatic vv	73 (97.3)	45 (100.0)	28 (93.3)	0.157
CT chest				
Pleural effusion	58 (75.3)	37 (80.4)	21 (67.7)	0.282
Pericardial thickening	73 (94.8)	45 (97.8)	28 (90.3)	0.297
Pericardial calcification	18 (23.4)	15 (32.6)	3 (9.7)	0.032
Lymphadenopathy	47 (61.0)	27 (58.7)	20 (64.5)	0.64
Laboratory results: mean ± SD				
Haemoglobin (g/dl)	12.78 ± 1.75	12.91 ± 1.76	12.58 ± 1.74	0.418
White cell count (10^9 cells/l)	5.15 ± 1.47	5.25 ± 1.48	4.99 ± 1.46	0.444
Platelets (10^{12} cells/l)	251.86 ± 84.37	244.20 ± 79.82	264.06 ± 91.11	0.299
Sodium (mmol/l)	136.96 ± 3.33	137.27 ± 3.50	136.47 ± 3.03	0.286
Urea (mmol/l)	60.58 ± 2.57	6.40 ± 2.79	6.86 ± 2.20	0.286
Creatinine (µmol/l)	81.70 ± 20.57	81.76 ± 20.05	81.59 ± 21.55	0.971
Albumin (g/l)	37.60 ± 6.33	38.04 ± 5.99	36.91 ± 6.89	0.431
AST (U/l)	39.35 ± 13.59	37.22 ± 10.51	42.28 ± 16.69	0.110
ALT (U/l)	25.21 ± 16.94	20.71 ± 10.70	32 ± 22.06	0.002
Alkaline PO_4 (U/l)	167.40 ± 89.50	146.02 ± 67.70	201 ± 108.82	0.005
Gamma GT (U/l)	249.16 ± 224.09	172.96 ± 104.76	370 ± 300.59	< 0.001

Data presented as mean ± standard deviation for continuous variables and *n* (%) for categorical variables. NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; PA pressure, pulmonary artery pressure; IVC, inferior vena cava; CT, computed tomography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; alkaline PO_4, alkaline phosphatase; gamma GT, gamma glutamyl transferase.
CT scanning was not undertaken in six subjects (five HIV-negative and one HIV-positive subject).
No results for dilated IVC and hepatic veins for eight subjects (six HIV-negative and two HIV-positive subjects).

levels between HIV-negative and -positive patients. Of note, alkaline phosphatase (146.0 ± 67.7 vs 201.0 ± 108.8 U/l; p = 0.005) and gamma glutamyl transferase (172.96 ± 104.76 vs 370 ± 300 U/l; $p \leq 0.001$) levels were significantly elevated in HIV-positive patients.

Pre-operative mortality rate

Of the initial study cohort of 83 patients with constrictive pericarditis, 31 (37.3%) patients did not undergo immediate pericardiectomy. Of these 31 subjects, four died in hospital shortly after admission (all HIV negative) from a low-cardiac-output state, and the remaining 27 who were offered surgery did not return for the operation. Survival status of those lost to follow up was established telephonically as well as by checking the national registry of deaths. In this way it was established that a further 10 had died out of hospital (HIV positive: n = 4), yielding a total pre-operative mortality rate of 16.7% (14/83) (95% CI: 9.5–26.6%).

Bivariate logistic regression analysis identified seven predictors of pre-operative mortality (Table 2). These were age (OR 1.11; 95% CI: 1.04–1.18; $p \leq 0.001$), levels of haemoglobin (OR 0.67; 95% CI: 0.45–0.99; p = 0.031), albumin (OR 0.90; 95% CI: 0.82–0.99; p = 0.019) and aspartate aminotransferase (OR 0.91; 95% CI: 0.85–0.98; p = 0.003), and pulmonary artery pressure (OR 1.13; 95% CI: 1.05–1.22; $p \leq 0.001$). HIV status had no influence on the pre-operative mortality rate (p = 0.693).

On multivariable analysis, age (OR 1.17; 95% CI: 1.03–1.34; p = 0.02), serum albumin level (OR 0.63; 95% CI: 0.43–0.92; p = 0.016), gamma glutamyl transferase level (OR 0.97; 95% CI: 0.94–0.1.0; p = 0.034) and pulmonary artery pressure (OR 1.49; 95% CI: 1.07–2.08; p = 0.018) emerged as independent predictors of pre-operative mortality rate.

Table 2. Bivariate logistic regression model of associated pre-operative mortality

Characteristics	*Alive (n = 69)*	*Pre-operative death (n = 14)*	*Odds ratio (95% CI)*	p-*value*
Gender				
Female	33 (47.8)	7 (50.0)	0.92 (0.29–2.89)	0.882
Male	36 (52.2)	7 (50.0)		
HIV positive				0.693
CD4 > 200 cells/mm^3	21 (30.4)	3 (21.4)	0.59 (0.15–2.36)	
CD4 < 200 cells/mm^3	7 (10.1)	1 (7.1)	0.59 (0.65–5.32)	
NYHA class	69 (100)	14 (100)	1.50 (0.65–3.48)	0.351
Haemoglobin (g/dl)	12.96 ± 1.70	11.91 ± 1.78	0.67 (0.45–0.99)	0.031
White cell count (10^9 cells/l)	5.17 ± 1.45	4.99 ± 1.58	0.91 (0.61–1.37)	0.660
Platelets (10^{12} cells/l)	257 ± 89.01	224.64 ± 49.96	0.99 (0.99–1.00)	0.160
Sodium (mmol/l)	137 ± 3.33	136 ± 3.28	0.91 (0.77–1.07)	0.243
Urea (mmol/l)	6.37± 2.17	7.6 ± 3.96	1.17 (0.96–1.42)	0.131
Creatinine (umol/l)	80.37 ± 20.87	88.21 ± 17.94	1.02 (0.99–1.04)	0.192
Albumin (g/l)	38.35 ± 6.29	33.93 ± 5.37	0.90 (0.82–0.99)	0.019
AST (U/l)	41.16 ± 13.71	31.36 ± 9.97	0.91 (0.85–0.98)	0.003
ALT (U/l)	25.87 ± 16.88	22 ± 17.52	0.98 (0.94–1.03)	0.403
Alkaline PO_4 (U/l)	175.94 ± 93.06	125.29 ± 54.11	0.99 (0.98–1.00)	0.061
Gamma GT (U/l)	269.39 ± 235.30	149.43 ± 119.43	1.00 (0.99–1.00)	0.071
Ejection fraction (%)	51.97 ± 6.75	53.29 ± 6.06	1.03 (0.94–1.13)	0.491
PA pressure (mmHg)	32.80 ± 6.88	43 ± 11.19	1.13 (1.05–1.22)	< 0.001

Data presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. NYHA, New York Heart Association; CI, confidence interval; AST aspartate aminotransferase; ALT alanine aminotransferase; alkaline PO_4, alkaline phosphatase; gamma GT, gamma glutamyl transferase; PA pressure, pulmonary artery pressure.

Operative outcome of patients undergoing pericardiectomy

A total of 52 patients (62.7%) underwent pericardiectomy, which included 32 HIV-negative (61.54%) and 20 HIV-positive patients (38.5%). Of the 20 HIV-positive patients, 15 (75%) were on antiretroviral therapy with successful viral load suppression (< 1 000 copies/ml). Pericardial biopsy specimens taken at the time of surgery showed histological evidence of tuberculosis in the form of granulomas and/or acid-fast bacilli in 12/49 (24.5%) patients.

Complete pericardiectomy was achieved in 38 patients (73.1%) and there was no significant difference between HIV-positive and -negative patients (26%; 81.3 vs 12; 60%; p = 0.093). There were three in-hospital peri-operative deaths, yielding a peri-operative mortality rate of 5.7% (95% CI: 9.5–26.7%). One patient (HIV positive) died of intra-operative haemorrhage in theatre and two (HIV negative), who were both severely symptomatic pre-operatively (NYHA IV) with impaired ejection fraction, died in the intensive care unit (ICU) as a result of a low-cardiac-output state in the ICU. There was no significant difference in the length of ICU stay between HIV-negative and -positive patients (4.28 ± 2.74 vs 5.11 ± 2.84 days; p = 0.321).

Postoperative complications occurred in seven patients (9.6%), three of whom had also suffered intra-operative complications. These postoperative complications were: sternal wound sepsis (one), re-intubation for respiratory failure and tachyarrhythmia (one), thoracotomy for postoperative haemorrhage (one), postoperative renal impairment (one) and low-output cardiac failure (three). In total, peri-operative (intra- and post-operative) complications occurred more frequently in HIV-positive patients (HIV positive: 9, 45% vs HIV negative: 6, 17.6%; p = 0.030). The higher complication rate in HIV-positive patients could not be explained by left ventricular function since the left ventricular function was similarly preserved in both groups (HIV negative 53.33 ± 6.7% vs HIV positive 53.93 ± 6.79%; p = 0.783).

Of the 49 patients who were discharged (three died in hospital) after undergoing pericardiectomy, 41 (26 HIV positive) returned for the six-week postoperative follow up at our hospital. Six patients were followed up at their referral hospital and two were lost to follow up. Most patients improved their NYHA class by one or two levels ($p < 0.001$) (Fig. 2). The majority of patients had improved from NYHA class II to class I (n = 21, 50%) and NYHA class III to class I (n = 10, 23.8%). Eight patients showed no improvement in functional class. There was no significant difference in symptoms of dyspnoea (p = 1.000) or ejection fraction (p = 0.785) between HIV-positive and -negative patients.

Discussion

This study shows a relatively high rate of HIV infection (32/83, 38.6%) among patients with constrictive pericarditis compared to the 14.6% reported by Mutyaba *et al.*[2] in a recent South African study, but less than the 12/19 (63%) reported by Abubaker and colleagues[17] in a Nigerian study. These data for developing countries are in contrast to the very low rate reported by Gopaldas *et al.*[18] in the USA, who found only 10 HIV-positive

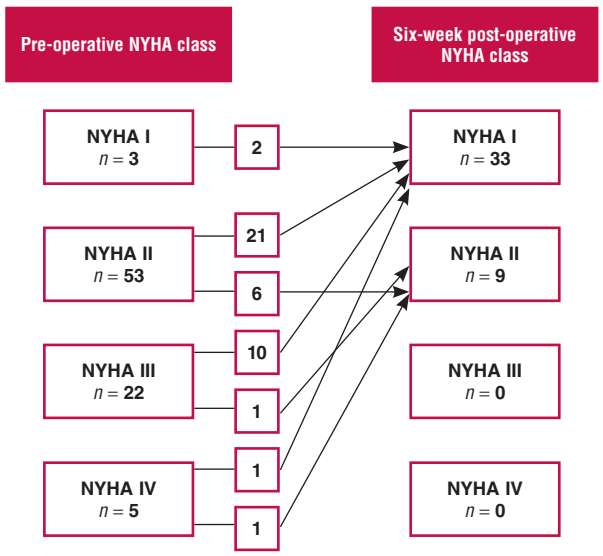

Fig. 2. Comparison of pre-operative and six-week postoperative New York Heart Association functional class status in 41 patients ($p < 0.0001$). Most subjects improved by at least one functional class. NYHA, New York Heart Association.

patients with constrictive pericarditis out of a sample size of 3 847 undergoing pericardiectomy.

In keeping with other studies from developing countries,[2,11,12,19-21] and in contrast to Western series,[22,23] tuberculosis was the major aetiology of constrictive pericarditis in our study and highlights the impact of the HIV/AIDS epidemic in refuelling a resurgence of tuberculosis infections.[24,25] Similar to other series,[2,15] proven tuberculosis (pericardial histology, culture of AFB from sputum, lymph nodes) was documented in 22 (26.5%) of the patients. In contrast to Reuter's findings in TB pericarditis,[26] we found histological evidence of definite tuberculosis in only nine operative pericardial biopsy specimens and could not determine from these small numbers whether histological evidence of tuberculosis is more common in HIV-positive subjects. The natural history of tuberculous pericarditis has been previously described, including treatment options to prevent progression to constriction.[16,27-30]

In this study we found few differences in the clinical profile between HIV-positive and -negative patients. The higher levels of alkaline phosphatase and gamma glutamyl transferase among HIV-positive patients might have been due to hepatic tuberculosis or more likely to more severe hepatic congestion in these subjects. Importantly, there was no difference in the pre-operative and follow-up ejection fraction between HIV-positive and -negative patients. This finding differs from studies in patients with tuberculous pericarditis co-infected with HIV who have been found to have a higher prevalence of myopericarditis.[27,31]

Preservation of ejection fraction might explain why we found no significant differences in peri-operative mortality rate observed between HIV-positive and -negative patients. It is also likely that antiretroviral therapy in our patients may have helped to preserve left ventricular function by preventing the development of opportunistic infections or HIV-associated myocardial dysfunction.

Pericardial calcification was identified on chest radiography in 17 (20.5%) of our study patients, which is much higher than the 5% reported by Strang *et al.* in the pre-HIV era.[19] While equivalent rates of pericardial calcification in HIV-positive and -negative patients (21.4 vs 20.7%; $p = 0.953$) have been described in the study by Mutyaba *et al.*,[2] we found that calcification was an uncommon finding in HIV-positive compared with HIV-negative patients (6.3 vs 29.4%; $p = 0.011$). Furthermore none of the eight patients with CD4 counts < 200 cells/mm^3 developed pericardial calcification.

We attributed the higher prevalence of pericardial calcification among HIV-negative patients to longer survival in these patients with a more prolonged duration of infection, progressing to fibrosis and calcification. Alternatively it could be explained by the suppression of CD4 helper by the HI virus, leading to less fibrogenesis and calcification in these subjects.[26]

Among the 31 subjects who did not undergo early surgery, 15 patients on telephonic contact were still alive, and of these, five reported improvement in their symptoms (survival status unknown in two) on anti-tuberculous therapy. Strang *et al.*[32] have shown that a significant number of patients diagnosed with tuberculous constrictive pericarditis may undergo resolution of their symptoms on anti-tuberculous therapy. The high pre-operative mortality rate of 16.78% in our study emphasises the importance of pericardiectomy in ensuring a successful outcome in subjects who do not respond to anti-tuberculous therapy.

Our analysis of the pre-operative outcome showed that HIV status had no effect on the pre-operative mortality rate in constrictive pericarditis in subjects on antiretroviral therapy. Instead, our analysis showed that older age, unsuppressed viral load, lower serum haemoglobin and albumin levels, as well as

Table 3. Operative characteristics of study patients stratified by HIV status

Characteristic	*All* (n = *52*)	*HIV negative* (n = *32*)	*HIV positive* (n = *20*)	p-*value*
Pericardiectomy				0.093
Total	38 (73.1)	26 (81.3)	12 (60.0)	
Sub-total	9 (17.3)	2 (6.3)	7 (35.0)	
Not known	5 (9.6)	4 (12.5)	1 (5.0)	
Inotrope usage	48 (94.1)	31 (96.9)	17(85.0)	0.547
Days in ICU	4.59 ± 2.84	4.28 ± 2.74	5.11 ± 2.84	0.321
Postoperative complications	15 (28.9)	6 (18.8)	9 (45.0)	0.030
Pericardial histology				
Granulomas	9 (18.4)	4 (12.9)	5 (27.8)	0.259
Acid-fast bacilli	3 (6.1)	1 (3.2)	2 (11.1)	0.546
Calcification	12 (24.4)	10 (32.3)	2/18 (11.1)	0.168
Postoperative ejection fraction	53.55 ± 6.65	53.33 ± 6.70	53.93 ± 6.79	0.783
Postoperative six-week follow up				0.687
NYHA I	33 (80.4)	20 (76.9)	13 (86.7)	
NYHA II	9 (21.4)	6 (23.1)	2 (18.8)	
Ejection fraction	53 ± 9.16	52.44 ± 11.50	53.83 ± 4.67	0.785

Data presented as mean ± standard deviation for continuous variables and *n* (%) for categorical variables.
ICU, intensive care unit; NYHA, New York Heart Association.
Details of inotrope usage was not available for one subject; three subjects' histology results were not found (one HIV negative, two HIV positive); nine subjects did not have postoperative measurement of ejection fraction (four HIV-negative subjects and five HIV-positive subjects); 41 patients attended six-week follow up (26 HIV negative, 15 HIV positive). Follow up ejection fraction (10 HIV-negative, five HIV-positive patients).

elevated pulmonary pressure were shown to predict pre-operative mortality rate.

Similarly, we found no difference in the peri-operative and postoperative outcomes between HIV-positive and -negative patients. At the six-week follow-up visit, most patients in our series showed significant improvement in NYHA class ($p \leq 0.001$) (Table 3), with improvement of at least one functional class to NYHA I (78.6%) and II (21%). This finding is consistent with reports by Mutyaba *et al*.[2] and Tetty *et al*.[20] Furthermore, ejection fraction was preserved in both HIV-positive and -negative subjects.

Although our in-hospital peri-operative mortality rate of 5.7% is higher than the 3.7% reported by Fennel *et al*.[12] in the pre-HIV era, it is consistent with the majority of series worldwide.[6,9,11-14,18] It is much lower than the 14% mortality rate found by Mutyaba *et al*.[2] in their series, possibly because our HIV-positive patients were virally suppressed on treatment.

Peri-operative complications in our study appeared to be more common in HIV-positive patients undergoing pericardiectomy. Furthermore, complete pericardiectomy was less likely to be achieved in HIV-positive (n = 9, 50%) compared to -negative patients (n = 37, 71%). Whether this was due to the inflammatory process, with greater anatomical distortion making surgery more difficult, is not clear.

Study limitations

Our study has limitations related to its retrospective design, including a number of patients who were lost to follow up while awaiting surgical pericardiectomy. We were able to obtain survival status in most patients and were able to show that a number of subjects died while awaiting surgery. Furthermore, long-term patient follow up was often not possible because many patients were from rural areas and had difficulty in accessing the clinic. Based on the available patient records we could only accurately comment on in-patient peri-operative mortality rate and the early six-week follow-up visit after surgery. Furthermore, in this study the diagnosis of constriction was made clinically and supported by echocardiographic findings. Although Doppler echocardiographic parameters (restrictive pattern) to confirm pericardial constriction were not measured, the diagnosis was confirmed in all subjects who underwent surgery for pericardial constriction.

Conclusion

The findings of this study have important clinical implications. Without surgery, constrictive pericarditis is associated with a high mortality rate. Our study emphasises the benefits of surgery in patients who do not respond to anti-tuberculous therapy. Over a third of patients with constriction are HIV-positive in a developing country. Although HIV infection is associated with a higher in-hospital complication rate, peri-operative mortality rate is unaffected in subjects who are on antiretroviral treatment and are virologically suppressed.

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Healthy food more important than type of diet to cut heart disease risk

Everyone knows that achieving or maintaining a healthy body weight is one key to preventing cardiovascular disease. But even experts don't agree on the best way to achieve that goal, with some recommending eliminating carbohydrates and others emphasising reducing fats to lose weight. Few studies have investigated the effects of these specific macronutrients on cardiovascular health.

In a study, researchers at Beth Israel Deaconess Medical Centre (BIDMC) examined the effects of three healthy diets emphasising different macronutrients – carbohydrates, proteins, or unsaturated fats – on a biomarker that directly reflects heart injury. Using highly specific tests, the team found that all three diets reduced heart cell damage and inflammation, consistent with improved heart health.

'It's possible that macronutrients matter less than simply eating healthy foods,' said corresponding author Dr Stephen Juraschek, assistant professor of medicine at BIDMC and Harvard Medical School. 'Our findings support flexibility in food selection for people attempting to eat a healthier diet and should make it easier. With the average American eating fewer than two servings of fruit and vegetables a day, the typical American diet is quite different from any of these diets, which all included at least four to six servings of fruits and vegetables a day.'

Juraschek and colleagues analysed stored blood samples from 150 participants of the Optimal Macro-Nutrient Intake Trial to Prevent Heart Disease (OmniHeart) trial, a two-centre, in-patient feeding study conducted in Boston and Baltimore between April 2003 and June 2005. The average age among the study participants was 53.6 years, and 55% were African American and 45% were women. The participants, all of whom had elevated blood pressure, but were not yet taking medications to control hypertension or cholesterol, were fed each of three diets – emphasising carbohydrates, protein, or unsaturated fat – for six weeks with feeding periods separated by a wash-out period.

The diets were: a carbohydrate-rich diet similar to the well-known DASH diet, with sugars, grains and starches accounting for more than half of its calories; a protein-rich diet with 10% of calories from carbohydrates replaced by protein; and an unsaturated fat-rich diet with 10% of calories from carbohydrates replaced by the healthy fats found in avocados, fish and nuts. All three diets were low in unhealthy saturated fat, cholesterol and sodium, while providing other nutrients at recommended dietary levels.

The research team looked at the effects of each diet on biomarkers measured at the end of each dietary period compared to baseline and compared between diets.

All three healthy diets reduced heart injury and inflammation and acted quickly within a six-week period. However, changing the macronutrients of the diet did not provide extra benefits. This is important for two reasons. First, the effects of diet on heart injury are rapid and cardiac injury can be reduced soon after adopting a healthy diet. Second, it is not the type of diet that matters for cardiac injury (high or low fat, high or low carb), but rather the overall healthfulness of the diet.

'There are multiple debates about dietary carbs and fat, but the message from our data is clear: eating a balanced diet rich in fruits and vegetables, lean meats, and high in fibre that is restricted in red meats, sugary beverages, and sweets, will not only improve cardiovascular risk factors, but also reduce direct injury to the heart,' said Juraschek. 'Hopefully, these findings will resonate with adults as they shop in grocery stores and with health practitioners providing counsel in clinics throughout the country.'

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Ellisras Longitudinal Study 2017: association of hypertension with increasing levels of adiposity in 10- to 14-year-old boys and girls in the Eastern Cape (ELS 31)

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Abstract

Objectives: Previous studies suggest a strong relationship between obesity and hypertension. This study aimed at evaluating the prevalence of hypertension and pre-hypertension in 10- to 14-year-old boys and girls in the Eastern Cape Province of South Africa and to determine the association between blood pressure parameters and selected measures of adiposity.
Methods: A cross-sectional, school-based study of 540 10- to14-year-old children from seven schools in the Eastern Cape Province was carried out. Anthropometry and blood pressure parameters were determined.
Results: All measures of adiposity and blood pressure were significantly higher in the girls ($p < 0.05$). The prevalence of hypertension and pre-hypertension was over 20 and 12%, respectively. Systolic blood pressure and pulse pressure were associated ($r > 0.27$; $p < 0.05$) with increasing levels of adiposity.
Conclusion: This study highlights the importance of weight-control strategies for the prevention of hypertension in these adolescents and later on in life.

Keywords: adolescent, school, hypertension, pre-hypertension, adiposity, obesity

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An increasing number of studies are reporting hypertension and pre-hypertension in the paediatric population.[1-3] Once considered rare or secondary only to known causes, essential hypertension is now a reality among children.[4] Lifestyle risk factors for hypertension are generally very subtle to find since most children in this phase of life do not smoke or drink and are mostly active. Hypertension in children has been associated with family history and low birth weight.[5] However, as in the adult population, the prevalence of obesity and overweight have reached pandemic levels in children in rural and urban communities in developing and industrialised countries.[6] Consequently, complications of overweight and obesity such as hypertension and diabetes have also become commonplace in children.[7]

Indeed, studies in the USA suggest that blood pressure increases correlate with body mass index in children and adolescents.[8] Kemp *et al*.[9] showed an eight and 20% prevalence of pre-hypertension and hypertension, respectively, in grade 1 children in a rural South African community. Furthermore, we previously showed that the prevalences of pre-hypertension and hypertension in adolescents in Mthatha were 13.6 and 22% in males and 16.5 and 20.9% in females, respectively.[3]

Although studies have demonstrated hypertension in children, it remains under-diagnosed or not diagnosed at all since blood pressure measurement is not routine in paediatric patients. Importantly, adult criteria for the diagnosis of hypertension are often applied to children and adolescents. Consensus guidelines for defining pre-hypertension and hypertension in children require the systolic and diastolic blood pressure values to be converted to percentiles for age, gender and height,[10] which is often a challenge for the already overworked physicians in developing countries. This has therefore led to the perception that children do not suffer from hypertension, with the consequent under-diagnosis of the problem.[11] Nevertheless hypertension in childhood had been shown to track to adulthood, when it progresses to established hypertension.[12]

Overweight and obesity in childhood are risk factors for hypertension in children.[13] Overweight and obesity, as expressed by various measurements of adiposity, have shown relationships with hypertension. In this study we explored the impact of increasing adiposity on blood pressure and consequently hypertension.

Methods

A cross-sectional study was carried out in seven selected middle schools in the Eastern Cape Province, South Africa, from May to September 2016. Data were collected once during this period from participating children. Ten- to 14-year-old boys and girls were recruited into the study in order to determine gender differences on adiposity and blood pressure.

Ethical clearance was obtained from the University of Fort Hare (CH1011SCHU01) and consent was obtained from parents and children involved in the study and from the schools' authorities. All consenting children who were not pregnant or lactating or suffering from any debilitating condition were included in the study. Data were collected on the school premises where the children were comfortable and had a sense of security.

Boys and girls were required to rest in a seated position for 10 minutes, after which their right upper arms were fitted with

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appropriate arm-size cuffs and blood pressure was measured at three-minute intervals using the Omron (Hem 7120) automated blood pressure machine. The mean of three recordings of systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) were computed. SBP and DBP were converted to percentiles for age, gender and height for each child, based on the Paediatric Task Force standards.[14]

Both waist (WC) and hip circumference (HC) were measured using the World Health Organisation guidelines.[15] Participating children were requested to stand upright with feet together and arms hanging freely at the sides. WC was measured at the smallest circumference of the waistline with a non-stretch tape. Boys and girls were requested to dress lightly on days of data collection. HC was measured at the largest circumference around the greater trochanter of the femur.[15]

Height was measured using a stadiometer. Boys and girls were requested to take off their shoes and to step on the stadiometer platform with feet together and close to the stadiometer rod. The movable bar was lowered to just touch the head. Height was read off to the nearest cm.

Personal data such as height, age and gender were entered into the Omron body composition monitor (BF511). Then each child was requested to step onto the electrode pads of the body composition monitor and hold the arm piece tightly in both hands, with arms held out at right angles to the body, until the equipment stopped scanning. The equipment displayed weight, body mass index (BMI) and total fat mass (TFM). BMI was converted to percentiles for age and gender.

Statistical analysis

Data were analysed using Stata version 14. Data were checked for normality, and differences between the means of normally distributed data were assessed using the *t*-test or ANOVA with Dunnet's test, while the Kruskal–Wallis test with Friedman's *post hoc* test was used for skewed data. Spearman's correlation coefficient (*r*) was used to determine the relationships between blood pressure parameters and selected measures of adiposity. Adiposity was categorised as lean with BMI < 85th percentile or ≤ 75th percentile for WC, HC or TFM for gender, and overweight/obesity as BMI ≥ 85th percentile or > 75th percentile of WC, HC and TFM for gender. Fisher's exact test was used to determine the relative risk for hypertension associated with overweight/obesity as determined for the four selected measures of adiposity. Statistical significance was set at $p \leq 0.05$.

Results

A total of 540 10- to 14-year-old boys and girls were recruited into this study. Male and female participants were of similar ages. Females had significantly ($p < 0.05$) higher BMI, WC, HC, TFM, waist-to-height ratio (WHtR), SBP and DBP (Table 1). On the other hand pulse pressure (PP) was similar for males and females.

The prevalence of overweight was 10.9% in the total cohort and was higher in the girls (13.5%) compared to boys (8.0%). The prevalence of obesity was 14.0% in the total cohort, 12.8% in the boys and 15.2% in the girls (Table 2). Similarly, the prevalence of pre-hypertension and hypertension were higher in girls compared to boys.

In order to better understand the relationship between blood pressure and measures of adiposity (BMI, WC, TFM, WHtR), Spearman's rank correlations were performed. Pairwise correlations between SBP, DBP, PP, BMI, WC, TFM and WHtR were positive in both boys and girls. BMI, WC, TFM and WHtR correlated modestly with SBP and PP in females (Table 3). Only BMI had a weak correlation with SBP and PP in males. On the other hand there was no correlation between DBP and all measures of adiposity in boys or girls.

In order to determine the effect of selected measures of adiposity on blood pressure values, boys and girls were classified according to their adiposity (BMI, WC, TFM, WHtR) quartiles. SBP, DB and PP [PP = (SBP – DBP)] for each quartile were computed and the prevalence of hypertension and pre-hypertension in each quartile was determined. SBP, DBP and PP increased progressively from the first quartile (lowest adiposity) to the fourth quartile (highest adiposity). The prevalence of hypertension and pre-hypertension were highest in the fourth quartile for all measures of adiposity. The first quartiles for all measures of adiposity had the lowest levels of SBP, DBP, HR and PP. It also had the lowest prevalence of hypertension and pre-hypertension (Table 4).

Table 1. Characteristics of the learners by gender

Characteristics	*Boys*	*Girls*
Number	250	290
Age (years)	11.9 ± 0.6	11.9 ± 0.5
BMI (kg/m²)	18.9 ± 0.2	20.2 ± 0.3*
WC (cm)	65.4 ± 0.7	69.2 ± 0.7**
TFM (%)	22.5 ± 0.01	24.1 ± 0.01**
HC (cm)	80.1 ± 0.6	85.6 ± 0.7**
WHtR	0.44 ± 0.01	0.46 ± 0.00**
SBP (mm Hg)	110.1 ± 0.7	112.7 ± 0.6*
DBP (mm Hg)	70.6 ± 0.5	73.1 ± 0.4*
PP (mm Hg)	39.5 ± 0.5	39.5 ± 0.0.4

Calculated percentages were cohort specific.
BMI: body mass index, WC: waist circumference, TFM: total fat mass, HC: hip circumference; WHtR: waist-to-height ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure.
*$p < 0.05$, **$p < 0.01$.

Table 2. Prevalence of overweight, obesity, pre-hypertension and hypertension

Variables	*Overweight*	*Obesity*	*Pre-hypertension*	*Hypertension*
Total cohort, *n* (%)	59 (10.9)	76 (14.0)	66 (12.2)	112 (20.7)
Boys, *n* (%)	20 (8.0)	32 (12.8)	28 (11.2)	39 (15.6)
Girls, *n* (%)	39 (13.5)	44 (15.2)	45 (15.5)	76 (26.2)

Table 3. Spearman's rank correlation coefficients between blood pressure parameters and selected measures of adiposity

	Spearman's rank correlation coefficients			
Variables	*BMI (kg/m²)*	*WC (cm)*	*TFM (%)*	*WHtR*
SBP (mmHg)				
Boys	0.24*	0.12	0.10	0.11
Girls	0.39*	0.37*	0.33*	0.27*
DBP (mmHg)				
Boys	0.07	0.09	0.07	0.09
Girls	0.08	0.07	0.08	0.06
PP (mmHg)				
Boys	0.22	0.05	0.05	0.05
Girls	0.41*	0.38*	0.35*	0.32*

BMI: body mass index, WC: waist circumference, TFM: total fat mass, WHtR: waist-to-height ratio, SBP: systolic blood pressure; DBP: diastolic blood pressure, PP: pulse pressure. *$p < 0.05$.

Boys and girls were separated into lean and overweight/obese groups using selected measures of adiposity. BMI < 85th percentile was classified as lean and BMI ≥ 85th percentile as overweight/obese. WC, TFM and WHtR were separated into two groups: ≤ 75th percentile for gender was classified as lean while > 75th percentile was classified as overweight/obese. A greater WC conferred a 1.7-times greater risk of developing hypertension ($p = 0.008$) in the cohort. The relative risk of having hypertension conferred by high BMI, WC, WHtR and TFM was absent in boys but weak and not significant in girls (Table 5).

Discussion

In this study we showed that the prevalence of overweight and obesity in 10- to 14-year-old children in the Eastern Cape was over 10 and 14%, respectively, while the prevalence of pre-hypertension and hypertension were 12 and 20%, respectively. Gender-specific analysis showed that the girls were more obese and also had a higher prevalence of hypertension and pre-hypertension. Although the relative risk of having hypertension with increasing adiposity was small, children whose BMI, WC, TFM and WHtR were higher than the third quartile had significantly ($p < 0.05$) higher blood pressure than those in the lower quartiles.

Table 4. Components of blood pressure in the four quartiles of BMI, WC, TFM and WHtR

Parameters	*1st quartile*	*2nd quartile*	*3rd quartile*	*4th quartile*	*p-value*
BMI					
SBP (mmHg)	107.1 ± 1.5	110.4 ± 0.5	113.9 ± 1.0**	117.3 ± 1.1**##	0.0001
DBP (mmHg)	69.1 ± 1.1	71.8 ± 0.4	73.4 ± 0.8*	73.3 ± 0.9*	0.03
HR (beats/min)	87.9 ± 1.9	87.3 ± 0.7	84.9 ± 1.6	89.3 ± 1.3	0.14
PP (mmHg)	38.1 ± 1.3	38.7 ± 0.4	40.4 ± 0.9##	44.1 ± 0.9##	0.0001
HT, *n* (%)	3 (8.8)	59 (16.1)	14 (23.7)	13 (16.5)	
preHT, *n* (%)	9 (26.5)	125 (34.2)	23 (39.0)	34 (44.7)	
TFM					
SBP (mmHg)	108.8 ± 0.9	110.2 ± 0.9	112.2 ± 0.9**	114.9 ± 0.8**##	0.0001
DBP (mmHg)	70.6 ± 0.7	71.7 ± 0.7	72.4 ± 0.9	73.0 ± 0.6	0.14
HR (beats/min)	87.5 ± 1.1	86.1 ± 1.1	88.5 ± 1.2	87.7 ± 1.0	0.50
PP (mmHg)	38.2 ± 0.7	38.5 ± 0.7	39.8 ± 0.7	42.0 ± 0.7**##	0.0001
HT, *n* (%)	17 (12.8)	20 (14.8)	23 (11.8)	28 (20.1)	
preHT, *n* (%)	37 (27.8)	46 (34.1)	48 (24.6)	58 (43.6)	
WC					
SBP (mmHg)	108.1 ± 0.8	109.8 ± 0.9	112.3 ± 1.1**	115.8 ± 0.7**##	0.0001
DBP (mmHg)	70.9 ± 0.6	71.2 ± 0.7	71.7 ± 0.7*	73.7 ± 0.6*	0.05
HR (beats/min)	86.8 ± 1.1	87.6 ± 1.1	87.1 ± 1.2	89.3 ± 1.3	0.78
PP (mmHg)	37.2 ± 0.6	38.6 ± 0.7	40.7 ± 0.9##	42.1 ± 0.6##	0.001
HT, *n* (%)	25 (16.7)	27 (18.9)	19 (20.4)	46 (29.7)	
preHT, *n* (%)	49 (32.9)	44 (30.8)	31 (33.3)	69 (44.5)	
WHtR					
SBP (mmHg)	109.0 ± 0.9	111.1 ± 0.9	110.6 ± 0.9	115.4 ± 0.8**###$$$	0.0001
DBP (mmHg)	71.0 ± 0.7	72.3 ± 0.7	71.0 ± 0.6	73.3 ± 0.6*$	0.05
HR (beats/min)	86.9 ± 1.1	87.1 ± 1.2	88.1 ± 1.1	87.3 ± 1.0	0.75
PP (mmHg)	37.9 ± 0.6	38.8 ± 0.7	39.6 ± 0.7	42.1±0.7**###$	0.0001
HT, *n* (%)	19 (14.1)	26 (19.3)	28 (20.6)	40 (30.1)	
preHT, *n* (%)	37 (27.4)	54 (40)	42 (30.9)	59 (44.4)	

BMI: body mass index, WC: waist circumference, TFM: total fat mass, WHtR: waist-to-height ratio, HT: hypertension; preHT: pre-hypertension, SBP: systolic blood pressure; DBP: diastolic blood pressure, HR: heart rate, PP: pulse pressure. *Compared to first quartile (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$), #compared to second quartile (#$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$) and $comparing quartile 4 to quartile 3 ($p < 0.05$, $$p < 0.01$; $$$p < 0.001$).

Using all four selected measures of adiposity (BMI, WC, TFM and WHtR) our study showed that girls were larger and had a higher prevalence of overweight and obesity. Participants in this study were 10 to 14 years old, which is a period of much hormonal activity. Puberty begins in girls from eight to 12 years old, while in boys it begins from nine to 14 years old. This period in girls corresponds with an increase in BMI, and changes in body fat composition and distribution, while in boys it is a period of fat loss and muscle development,[16] thus explaining the differences in BMI, WC, TFM and WHtR between boys and girls.

Several studies have shown an association between BMI and blood pressure.[17,18] A Brazilian study showed that overweight and obese children had a 3.6-fold greater risk of having higher SBP and 2.7-times increased risk for higher DBP.[19] Both SBP and DBP as well as PP were higher in the girls than boys. The growth spurt of puberty, which is often accompanied by a rise in blood pressure,[20] occurs earlier in girls than in boys, thus explaining the higher blood pressure in girls.

The current study showed a difference in the prevalence of hypertension and pre-hypertension when overweight/obesity was classified as the fourth quartile of WC, TFM and WHtR. An increased WC is a known risk for metabolic diseases in both children[21] and adults. We have previously shown that BMI, TFM, WC and WHtR correlated similarly with SBP and PP in females, although these relationships were different in males. These results further strengthen the suggestion that the 10- to 14-year-old girls involved in the study were mostly pubertal and therefore increased adiposity contributed to higher blood pressure in the girls. Furthermore, another study showed that children who had low BMI but high WC were at great risk of developing hypertension.[22,18]

Our results show that children with WC and HC greater than the 75th percentile had an increased relative risk (1.7 and 1.5, respectively) of being hypertensive. This finding was confirmed by the fact that both pre-hypertension and hypertension were over 1.5 times more prevalent in 10- to 14-year-old girls compared to age-matched boys. On the other hand, higher BMI did not confer a significant risk of higher BP. However when subjects were separated into quartiles for BMI, WC, TFM and WHtR, it was noted that SPB, DBP and PP were significantly higher in boys and girls in the fourth quartile, indicating that adiposity contributes to blood pressure levels.

Table 5. Relative risk of having hypertension with high measures of adiposity

	Relative risk		
Variables	*Cohort*	*Males*	*Females*
BMI	1.04	1.05	1.28
95% CI	0.544–1.975	0.652–1.716	0.974–1.675
p-value	0.86	0.862	0.090
WC	1.71	1.203	1.328
95% CI	1.284–2.279	0.774–1.870	1.003–1.758
p-value	0.0008	0.418	0.06
TFM	1.42	0.859	1.384
95% CI	0.891–2.00	0.539–1.370	0.877–1.558
p-value	0.183	0.542	0.189
WHtR	1.27	1.245	1.26
95% CI	0.766–2.119	0.790–1.961	0.956–1.671
p-value	0.351	0.385	0.133

BMI: body mass index, WC: waist circumference, TFM: total fat mass, WHtR: waist-to-height ratio, CI: confidence interval.

Although the fourth quartile of all measures of adiposity had significantly higher SBP, DBP and PP, only WC conferred a significantly ($p < 0.001$) greater risk (1.7 times) for hypertension. This finding is in agreement with Dong *et al*.,[17] who highlighted the importance of increased WC on the risk of hypertension in children. The retrospective study of data from the NHANES study showed that WC was associated with higher blood pressure in children and adolescents.[23]

Conclusion

This study demonstrates that the prevalence of hypertension and pre-hypertension was higher in 10- to 14-year-old girls than boys. The relative risk of having hypertension in this study cohort was greater in children who had larger WC. The linear relationship between blood pressure and BMI, WC, TFM and WHtR in children was weak. However, SBP, DBP, PP and mean arterial pressure increased with increasing quartiles of BMI, WC, TFM and WHtR. Consequently, the greatest prevalence of hypertension and pre-hypertension was in overweight and obese children, therefore confirming the role of increasing levels of adiposity in the prevalence of hypertension and pre-hypertension in 10- to 14-year-old children in the Eastern Cape.

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Ellisras Longitudinal Study 2017: patterns of physical activity in an urban and rural setting among black South African adults (ELS 23)

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Abstract

Background: Understanding patterns of physical activity among adults can lead to targeted approaches to improve activity levels in the African population. This study aimed to determine whether age, gender, location and employment status could predict physical activity among rural and urban South African adults, and to determine the participants' risk of developing cardiovascular disease (CVD).

Methods: A cross-sectional design was conducted on 319 participants of mean age 57 ± 10.43 years. Participants were sampled using a stratified random-sampling procedure from an urban township in Langa, Western Cape Province, and a rural township in Mt Frere, Eastern Cape Province, South Africa. A researcher-generated questionnaire was used to collect sociodemographic and physical activity data. Linear regression analysis was used to test predictive relationships.

Results: Gender and geographical location were significant predictors ($p = 0.001$) of physical activity. Rural participants engaged more in physical activity (91.5%) than urban participants (84.2%) and were more likely to meet the physical activity recommendations to promote cardiovascular fitness ($p = 0.000$). The most frequent physical activities in rural participants were walking (15.4%), household chores (18.8%) and household chores + gardening (15.4%). The most frequent physical activities in urban participants were household chores (34.2%), and household chores + walking (33.7%). In terms of duration of physical activity, rural participants spent longer periods engaging in activities lasting up to two hours (21.4%), compared to 5.9% in urban participants ($p = 0.000$).

Conclusions: Gender and geographical location were significant predictors of physical activity among black South African adults. Overall, rural adults engaged in more physical activity than urban-dwelling adults. Males also engaged in more physical activity and at a higher intensity than females. Most rural participants met the American College of Sports Medicine recommendations for cardiovascular fitness and therefore were at minimal risk for developing CVD compared to their urban counterparts.

Keywords: black South African adults, physical activity

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Ecological models of health behaviour emphasise the importance of sociodemographic and psychological factors, as well as the physical environment in explaining the behavioural patterns of physical activity (PA).[1] In most cases, urban neighbourhoods are built in such a way that they are pedestrian orientated, with high walkability that encourages physical activity and active transportation.[2] On the other hand, rural neighbourhoods are said to be more automobile dependent with poor street connectivity.[3] Therefore, given the differences in environmental characteristics, physical activity levels may be lower in rural environments compared to urban environments.[4] Indeed, geographical location may play a role in the physical activity of individuals.

A Belgian study showed that urban adults took more steps per day, walked and cycled more often as a means of transport, and engaged in more recreational walking compared to rural adults.[5] Similarly, some studies in the USA have investigated differences in physical activity between urban and rural adults.[4] As in the van Dyck *et al.*[1] study, the results showed that urban adults were more active than rural adults. In Africa, a similar trend was noted. Rural South African adults were reported to lead sedentary lifestyles compared to their counterparts residing in urban areas.[5]

However, contrasting results have been reported in some studies. In India, Tripathy *et al.*[6] assessed the differences in dietary habits, physical activity levels and obesity among urban and rural adults. They found no significant differences in work-, transport- and recreation-related physical activity between urban and rural participants.[6] An interesting finding of the Tripathy *et al.*[6] study was that females residing in a rural area were reported to engage in more vigorous-intensity physical activity than those residing in an urban area.

There are important gender differences in the motives for engaging in physical activity in males and females.[7] Males have been found to be motivated by intrinsic factors (strength, competition and challenge), whereas females by extrinsic factors (body weight management and physical appearance).[8,9] Khan *et al.*[10] found that gender was a significant predictor of health-

compromising and health-enhancing behaviours among the youth. The male gender was reported to be an important predictor of health-compromising behaviours.[10] On the other hand, the female gender served both as a control and as an instigator of healthy behaviour.[11] These findings have been supported in the literature in terms of a female gender preoccupation with body weight management and body image.[11] For example, Fan *et al.*[12] reported that among women, as body mass index increased, so too did the level of participation in physical activity.

South African females have been reported to be overweight and physically inactive compared to males.[13] A recent South African study reported that women were less likely to engage in physical activity than men.[14] The same study also reported that gender, age, educational level, occupation and geographical location were significantly associated with physical activity.

It is important to assess differences in physical activity between urban and rural populations because it assists researchers in the contextualisation of interventions in physical activity in both rural and urban settings, especially in African populations. This is because most deaths that are attributable to physical inactivity have been reported in low- and middle-income countries (LMICs).[15,16] Furthermore, research on physical activity in LMICs is of importance to assist in understanding the prevalence of physical inactivity globally.[17,18]

Since South Africa, like most developing countries, is experiencing nutritional, lifestyle and socio-economic changes, which are complemented by an increase in the prevalence of non-communicable diseases,[19] it is important to understand the patterns of physical activity in South Africa. Understanding the risk for physical inactivity related to urban–rural sociodemographics may aid in identifying the pertinent areas of focus in local environments, where change in physical activity behaviour warrants attention.[20]

Therefore, this study aimed to determine whether age, gender, location and employment status could predict physical activity among a sample of rural and urban South African adults. Specifically, the aim was to inform physical activity interventions aimed at reducing the risk for cardiovascular disease (CVD) among adults by characterising the physical activity patterns of behaviour among rural and urban South African adults. A secondary aim was to determine the participants' risk of developing CVD, based on their physical activity patterns by geographical location.

Methods

The study was carried out in a peri-urban community of black South Africans in Langa, a predominantly sub-economic urban African township near Cape Town in the Western Cape Province, as well as in Mount Frere, a predominantly sub-economic rural African township in the Eastern Cape Province. These sites were purposely selected because of an existing cohort study, titled the Prospective Rural Urban Epidemiological (PURE) study that was undertaken in these communities by the School of Public Health at the University of the Western Cape.

Participants in the current study were randomly sampled from these townships, i.e. from the 'zones' and 'hostels'. The intention was to implement an intervention based on lifestyle modification in this population, while not upsetting the longitudinal cohort study in the process.

For the urban community (Langa), households were stratified into three development areas, demarcated by the City of Cape Town, which reflected the socio-economic status of the residents. Using a street map obtained from the City of Cape Town, streets were then randomly selected in each of the three areas. Once a street was chosen, a systematic sample of every second house was done for possible inclusion in the study.

For a household to be eligible, at least one member had to be between the ages of 35 and 70 years, and this member also had to continue living in the current home for the next four years. Trained field workers approached all households for recruiting eligible participants. All individuals, who were defined as one 'who eats and sleeps in the household on most days of the week and in [sic] most weeks of the year and [who] considered the household as his/her primary place of habitation', were eligible for the study.

For the rural community (Mount Frere), the lack of delineated streets disallowed the same sampling approach as for the urban township. Therefore, a cluster sample of houses in the community was undertaken according to the division of areas by the clan heads. All households within the clusters were included if there was a household member aged 30 to 70 years.

The Research Ethics Committee of the University of the Western Cape approved the study with registration number 15/7/99. Participants gave their written informed consent after the purpose of the study was explained to them.

Statistical analysis

Data were collected through face-to-face interviews using a short researcher-generated questionnaire that obtained data on the sociodemographic characteristics of the participants, such as age, gender, educational level, employment status, total household income and participation patterns in physical activity. Physical activity was ascertained by asking the following questions: (1) do you engage in physical activities; (2) if yes, what are these activities, and (3) how much time do you spend doing these activities. Data were collected from August to November 2016.

Data were analysed using the Statistical Package for Social Science (SPSS) version 25 (IBM, New York, USA). Frequency distributions were calculated for sociodemographic and physical activity data. Descriptive statistics were performed to show the means and standard deviations for age, physical activity metabolic equivalent of task (MET) and predicted maximal oxygen consumption ($\dot{V}O_2$ max) for both rural and urban participants.

In this study, the METS for physical activity were obtained by converting the participant responses to the question 'What are these activities?' into specific activities based on the Compendium of Physical Activities by Ainsworth *et al.*[21] This compendium quantifies the energy cost of a variety of physical activities determined through self-report.[21] The METS were then converted into $\dot{V}O_2$ max values by multiplying by 3.5 and expressing in millilitres of oxygen per kilogram body weight per minute.[22] Percentages were calculated for gender, educational level, employment status, total household income, engaging in physical activity, MET categories for intensity of physical activity, duration of physical activity and for the types of activities.

Cross-tabulation procedures and Fisher's exact tests were used to check for statistically significant differences between rural and urban groups. Linear regression analysis was used to test predictive relationships for age, gender, employment status and geographical location (rural and urban). The regression was computed using PA METS as the continuous outcome variable.

Results

A total of 319 adult males and females aged 30 to 70 years (females = 78.4%, males = 21.6%) participated in the study. The mean age of the participants was 57 ± 10.43 years, with rural participants being 58 ± 10.71 years and urban participants being 56 ± 10.18 years. Among the rural and urban participants, most were female (82.1% female vs 17.9% male, 76.2% female vs 23.8% male, respectively).The mean PA METs for rural participants was 6.33 ± 3.77 METs and for urban participants 5.57 ± 3.95 METs. $\dot{V}O_2$ max for rural participants was 22.17 ± 13.19 ml/kg/min and for urban participants 19.50 ± 13.83 ml/kg/min. Overall, rural participants engaged in more physical activity than urban participants.

Regarding gender and physical activity, females had a mean of 5.62 ± 3.74 PA METs and $\dot{V}O_2$ max of 19.67 ± 13.08 ml/kg/min. Males, on the other hand, had a mean of 6.69 ± 4.35 PA METs and a $\dot{V}O_2$ max of 23.43 ± 15.22 ml/kg/min. Overall, men engaged in more physical activity than women and at a higher intensity. However, PA METs values between genders ($p = 0.248$) and between rural and urban participants ($p = 0.013$) were not significantly different.

The majority of the rural participants engaged in more than 30 minutes of exercise per day, with most engaging in vigorous-intensity physical activity. However, most of the urban participants engaged in less than 30 minutes of physical activity per day, but most engaged in vigorous-intensity physical activity. Significant differences were found ($p = 0.000$) for the duration of physical activity per day between rural and urban participants. Rural participants were more likely to meet the physical activity recommendations to promote cardiovascular fitness than the urban participants.

Table 1 shows the frequency distributions of the socio-demographic variables for both rural and urban participants. Table 2 shows the frequency distributions of physical activity behaviours for both rural and urban participants

The means and standard deviations for all predictors and outcome variables were assessed for normality. Tests for skewness and kurtosis were not significant. Therefore the assumptions for regression analysis were met. Table 3 shows the results of the regression analysis.

The model combining age, gender, geographical location and employment status tested significantly at a 0.03 alpha level. The model explained 3.4% of the variance in physical activity. Gender was a significant predictor of physical activity when controlling for geographical location, age and employment status. Physical activity increased by 0.118 METs from female to male gender. Geographical location was a significant predictor of physical activity, when controlling for gender, age and employment status. Although the overall effect size was very modest, it provided empirical support for the role of gender and geographical location in predicting overall physical activity. Physical activity decreased by 0.112 METs from rural to urban location.

Discussion

The results of the study reveal that the majority of rural participants engaged in more than 30 minutes of exercise per day, with most engaging in vigorous-intensity physical activity. Although most of the urban participants engaged in less than 30 minutes of physical activity per day, most engaged in vigorous-intensity physical activity. In terms of duration and intensity of physical activity, it appears that the rural participants were more likely to meet the physical activity recommendations to promote cardiovascular fitness than the urban participants.[23]

A study investigating the prevalence of sociodemographic correlates of physical activity among rural and urban adults in South Africa found that women engaged less in physical activity compared to men.[14] An earlier study also indicated that men were more likely to engage in physical activity than women, especially in leisure time and occupational activities.[24] Similar findings were also reported by Guthold and colleagues.[25] A Rwandan study[26] also reported that women engaged less in physical activity compared to men.

In the present study, gender was found to be a significant predictor of physical activity, with men engaging in more physical activity than women in both urban and rural environments. The findings of the current study could be linked to the fact that South Africa is a country in transition, with marked infrastructural development where men are usually employed to perform activities that are associated with moderate-to-vigorous intensity physical activity.[14] On the other hand, the influence of African culture may mean that women are employed in domestic work, which is typically associated with minimal and light-to-moderate intensity physical activity, which is especially so in black township communities in South Africa.[27] Therefore within low-income communities, where most men are usually involved in unskilled manual labour, it is expected that they would have higher levels of physical activity than the women.

Table 1 Frequency distributions of the sociodemographic variables

	Sociodemographic details				
	Rural (n = 117)		*Urban (n = 202)*		*Fisher's exact test (p-value)*
Category	n	*%*	n	*%*	
Gender					
Male	21	17.9	48	23.8	0.000**
Female	96	82.1	154	76.2	
Education					
None	3	2.6	1	0.5	0.000**
Primary	51	43.6	71	35.1	
Secondary	59	50.4	118	58.4	
Vocational/trade school	2	1.7	2	1.0	
Tertiary	2	1.7	5.0	10	
Employment					
Full time	5	4.3	29	14.4	0.000**
Part time	8	6.8	16	7.9	
Self-employed	9	7.7	14	6.9	
Unemployed	59	50.4	89	44.1	
Retired	36	30.8	54	26.7	
Total household income/month					
< R2 000	85	72.6	124	61.4	0.001**
R2 000 – R5 000	29	24.8	62	30.7	
R5 001 – R10 000	2	1.7	14	6.9	
> R10 000	1	0.9	2	1.0	

*Statistically significant at the 95% confidence level;
**statistically significant at the 99% confidence level.

Table 2. Frequency distributions of physical activity for both rural and urban participants

	Physical activity					*Fisher's exact test (p-value)*
Rural (n = 117)	n	%	*Urban (n = 202)*	n	%	
Do you engage in physical activity			Do you engage in physical activity			
Yes	107	91.5	Yes	170	84.2	0.000**
No	10	8.5	No	32	15.8	
What are these physical activities (most frequent physical activities > 10%)			What are these physical activities (most frequent physical activities > 10%)			
Walking	18	15.4	Household chores	69	34.2	#
Household chores	22	18.8	Household chores + walking	68	33.7	
Household chores + gardening	18	15.4				
What are these physical activities (least frequent physical activities < 5%)			What are these physical activities (least frequent physical activities < 5%)			
Home repair	3	2.6	Walking	7	3.5	#
Home repair + gardening + conditioning exercise	1	0.9	Gardening	2	1	
Home repair + household chores	1	0.9	Occupation	4	2	
Household chores + conditioning exercise	1	0.9	Walking + gardening	1	0.5	
Religious exercise + gardening	1	0.9	Household chores + gardening	2	1	
Home repair + gardening	2	1.7	Walking + household chores + gardening	2	1	
Walking + conditioning exercise + household chores + gardening	1	0.9	Household chores + conditioning exercise	2	1	
Household chores + occupation	1	0.9	Household chores + occupation	2	1	
			Household chores + conditioning exercise + walking	6	3	
			Walking + occupation	2	1	
			Household chores + home repair + walking + conditioning exercise	1	0.5	
			Gardening + walking + conditioning exercise	1	0.5	
			Home repair + walking	1	0.5	
How much time do you spend on these activities			How much time do you spend on these activities			
1–30 min	14	12	1–30 min	91	45.0	0.000**
31–60 min	18	15.4	31–60 min	36	17.8	
1–1:30	21	17.9	1–1:30	15	7.4	
1:30–2 h	25	21.4	1:30–2 h	12	5.9	
> 2 h	28	23.9	> 2 h	16	7.9	
PA METs			PA METs			
1.6–2.9 METs (light activity)	0	0	1.6–2.9 METs (light activity)	0	0	0.013
3–5.9 METs (moderate activity)	49	41.9	3–5.9 METs (moderate activity)	78	38.6	
≥ 6 METs (vigorous activity)	57	48.7	≥ 6 METs (vigorous activity)	92	45.5	

METs = metabolic equivalent of task; PA = physical activity; min = minutes; h = hours. For the section 'What are these physical activities' within the table under 'Physical activity', only the most frequent (> 10% of participants) and least frequent activities (< 5% of participants) are reported, therefore it is to be expected that the total number of participants that engage in these activities is less than the total number of both rural and urban participants. For rural participants, 11 (9.4%) had missing data on the questions 'What are these activities' and 'How much time do you spend on these activities', and therefore data on PA METs. For urban participants, 32 (15.8%) had missing data on the questions 'What are these activities' and 'How much time do you spend on these activities', and therefore data on PA METs. *Statistically significant at the 95% confidence level; **statistically significant at the 99% confidence level. #Fisher's exact test could not be calculated because of the differences in the most-frequent and least-frequent physical activities between rural and urban participants.

Another reason for this finding could be related to the parental and marriage status of the adult participants in this study. Bellows-Rieken[28] noted that gender may have a moderating influence on physical activity during parenthood, with nascent mothers experiencing a substantial decline in physical activity, since African women are traditionally the primary caregivers. Moreover, Verhoef and Love[29] reported that for women who are mothers, the amount of leisure time available to them was one of the most important predictors of participation in physical activity. The implication is that South African adult women may not have adequate time to engage in meaningful physical activity because they may spend more time engaged in parenting responsibilities. Therefore physical inactivity might be a major health risk factor for African women, and increases in rates of morbidity and mortality may be expected.[14] Women could gain from gender-sensitive physical activity interventions that have the potential to promote participation in physical activity and thus develop a healthier population.

Table 3. Multiple regression analysis (n = 858)

Model	*Predictors*	*Outcome*	R^2	β
1	Age	PA METs	0.034*	–0.060
	Gender			0.118*
	Location			–0.112*
	Employment status			–0.049

**p < 0.001. PA METs = physical activity metabolic equivalent of task; β: standardised coefficient; R^2: coefficient of determination.

Geographical location was also found to be a significant predictor of physical activity, with rural participants engaging in more physical activity than their urban counterparts. As in the current study, a study that examined differences in sedentary lifestyle of rural and urban participants in Nigeria showed that urban participants were more sedentary than their rural counterparts.[30] Similarly, in Cameroon, it was found that urban dwellers reported low physical activity levels and had a higher prevalence of the metabolic syndrome than their rural counterparts.[31] Furthermore, Jayamani *et al.*[32] also reported that

urban women in India had unhealthy physical activity levels compared to rural women. Conversely, in the USA, a study that examined urban–rural differences in physical activity found that the differences that exist in physical activity behaviours between rural and urban communities are largely to be expected. Adesina,[34] and Mensik *et al*.[35] reported that the environment impacts on the health and well-being of an individual. Alemu and Lindjorn[36] reported that rural populations walked more often as a means of transportation, and engaged in intense agricultural activities and manual work as part of their employment. This could also be said of rural-dwelling South Africans, who also use walking as a means of transportation, and usually rely on farming for their livelihoods.

In contrast to rural dwellers, the high prevalence and usage of automobiles, telephones, mobile phones and household gadgets, such as washing machines, significantly decreases the levels of physical activity among urban dwellers.[30] Like most developing countries, the rapid urbanisation of South Africa is associated with physical inactivity, leading to the clustering of metabolic risk factors, such as diabetes, high blood pressure and obesity.[37] In this regard, urban environments are associated with high risks for obesity, diabetes and CVD,[38] the so-called chronic diseases of lifestyle. Consequently, urban populations should be targeted for interventions in CVD prevention,[31] especially those that promote physical activity.

Study limitations

A relatively small study sample size and the lack of objective measures of physical activity contribute to the limitations of the study. The lack of data on frequency of physical activity (i.e. the number of days in which the participants engaged in physical activity per week) limits us in determining whether the participants met the recommended requirements of physical activity to promote cardiovascular fitness. This study was conducted in two specific settings in South Africa (Langa and Mount Frere townships). Due to specific cultural, social and psychological factors, extrapolation of the findings to other geographical locations is limited.

Conclusion

Gender and geographical location were significant predictors of physical activity. Overall, rural adults engaged more in physical activity than urban participants. Males also engaged in more physical activity than females and at higher intensities. Black South African adults also engaged in a variety of physical activities, including household chores, walking and gardening. Furthermore, in terms of duration of physical activity per day and intensity of physical activity, most rural participants met the American College of Sports Medicine[23] recommendations for adults and therefore were at minimal risk for developing CVD compared to their urban counterparts. Designers of physical activity interventions should consider gender and geographical location when promoting physical activity through activities of daily living. Physical activity interventions should particularly target women and urban dwellers, as they were at an increased risk for CVD. Physical activity interventions should also aim to promote physical activity through engaging in activities of daily living.

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Effects of atorvastatin on time-dependent change of fast sodium current in simulated acute ischaemic ventricular myocytes

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Abstract

Introduction: Our previous experiments showed that the transient sodium current (I_{Na}) was abnormally increased in early ischaemia and atorvastatin could inhibit I_{Na}. The aim of this study was to observe the time-dependent effects of simulated ischaemia on I_{Na} and characterise the direct effects of atorvastatin on ischaemic I_{Na}.

Methods: Left ventricular myocytes were isolated from Wistar rats and randomly divided into two groups: a control group (normal to simulated ischaemia) and a statin group (normal to simulated ischaemia with 5 μmol/l atorvastatin). The I_{Na} was recorded under normal conditions (as baseline) by whole-cell patch clamp and recorded from three to 21 minutes in the next phase of simulated ischaemic conditions.

Results: In the control group, normalised I_{Na} (at –40 mV) was increased to the peak (1.15 ± 0.08 mA) at three minutes of ischaemia compared with baseline (0.95 ± 0.04 mA, $p < 0.01$), it subsequently returned to baseline levels at nine and 11 minutes of ischaemia (0.98 ± 0.12 and 0.92 ± 0.12 mA, respectively), and persistently decreased with prolonged ischaemic time. In the statin group, there were no differences between baseline and the early stages of ischaemia (0.97 ± 0.04 mA at baseline vs 0.92 ± 0.12 mA in ischaemia for three minutes, $p > 0.05$).

Conclusion: Our results suggest that, in the early stages of ischaemia, changes in I_{Na} in ventricular myocytes are time-dependent, showing an initial increase followed by a decrease, while atorvastatin inhibited the transient increase in I_{Na} and made the change more gradual.

Keywords: ventricular myocytes, sodium, ventricular arrhythmia, membrane potential, statin

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Clinically, acute ischaemia is one of the common causes of malignant ventricular arrhythmias.[1] A retrospective study showed that 7.5% of patients with acute myocardial infarction developed ventricular arrhythmias, most of which (78%) occurred within the first 48 hours of ischaemic symptoms,[2] suggesting that electrical activities are very unstable in the early stage of ventricular ischaemia.

Sodium current (I_{Na}) is the starting current of the action potential and affects the shape and conduction of the action potential.[3] It is one of the most common targets to cause and treat arrhythmias. Animal experiments found that in an aconitine-induced arrhythmia model,[4] increased I_{Na} could lead to pre-contraction and even ventricular arrhythmias. Therefore I_{Na} plays an important role in arrhythmogenesis.

Previous studies have shown that I_{Na} would be decreased or Nav1.5, which is the ion channel protein of I_{Na}, would be downregulated in the ischaemic condition.[5,6] However in our pre-experiment of simulated ischaemia, peak I_{Na} was transiently increased in the very early stage of ischaemia (three to five minutes), suggesting unstable early ischaemic electrical activity. As the decreased I_{Na} demonstrated in ischaemia or simulated ischaemia usually needs myocyte exposure for more than 10 minutes,[5] this indicates that time is a key factor affecting I_{Na} in the ischaemic state.

On the other hand, as the basic therapeutic agents of acute coronary syndrome, statins may reduce the incidence of ischaemic ventricular arrhythmias[7,8] and can prevent sudden cardiac death,[9] as well as other cardiovascular events. However, the mechanisms are controversial. One view is that electrical protection from the statin is secondary to a decrease in low-density lipoprotein cholesterol, whereas another view is that statins act as an upstream protection on the basis of pleiotropic effects.[10] In addition, Vaquero *et al.*[11] confirmed that atorvastatin and simvastatin had an inhibitory effect on atrial plateau currents [hKv1.5 and Kv4.3 channels, while $I_{Ca,L}$ (L-type calcium current) could also be blocked by simvastatin acid] at the cellular level. Similarly, there is a direct electrical effect on the I_{Na} of ventricular myocytes in the early stage of ischaemia only.

We assumed that the effect of ischaemia on I_{Na} was time-dependent, that I_{Na} may be transiently increased during the first 10 minutes of ischaemia, and that atorvastatin could inhibit this phenomenon. Therefore we used a patch-clamp technique to observe the time-dependent effects of simulated ischaemia on I_{Na} in ventricular myocytes by setting the observation interval to two minutes. In addition, we also applied atorvastatin on the above basis, in order to observe its direct effect on I_{Na} in the early ischaemic condition.

Methods

Thirty Wistar rats (300 ± 50 g, male and female) were purchased from the Chinese Academy of Medical Sciences Institute of

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Radiation Medicine Experimental Animal Centre. All study protocols and use of rats were approved by the Institutional Animal Care and Use Committee of Tianjin Medical University (Tianjin, China).

Ca^{2+}-free Tyrode solution contained (mM): NaCl 137, KCl 5.4, $MgCl_2$ 1, NaH_2PO_4 0.33, HEPES 10, and glucose 10 (pH 7.4 with NaOH). KB solution contained (mM): L-glutamic acid 50, KCl 40, $MgCl_2$ 3, KH_2PO_4 20, taurine 20, KOH 70, EGTA 0.5, HEPES 10, and glucose 10 (pH 7.4 with KOH). The pipette solution contained (mM): CsCl 140, NaCl 10, EGTA 5, HEPES 5, Na_2ATP_5 (pH 7.3 with CsOH). The normal extracellular solution contained (mM): choline-Cl 120, NaCl 25, CsOH 4, $CaCl_2$ 0.1, $CoCl_2$ 2, $MgCl_2$ 1, HEPES 10, and glucose 10 (pH 7.4 with CsOH). The simulated ischaemic extracellular solution contained (mM): choline-Cl 120, NaCl 25, CsOH 4, $CaCl_2$ 0.1, $CoCl_2$ 2, $MgCl_2$ 1, HEPES 10, and natrium lacticum 20 (adjusted to pH 6.8 and filled with nitrogen for more than five minutes before using). Atorvastatin calcium (USP Corporation, Lot 344423-98-9) was dissolved in the ischaemic extracellular solution to prepare the drug solution containing 5 μM atorvastatin (usually 3.02 mg of atorvastatin calcium was dissolved in 500 ml of extracellular solution).

For isolation of the myocytes, single ventricular myocytes were dissociated from hearts of Wistar rats using type II collagenase (Gibco). Rats were weighted, heparinised (5 000 UI/kg), anaesthetised with chloral hydrate (40 mg/kg), the chest was opened and the hearts were removed, and then the rats were euthanised. The heart was immersed in Ca^{2+}-free Tyrode solution (4°C) and immediately clipped.

The heart was cannulated through the aorta and mounted on a Langendorff perfusion apparatus (100% O_2, 37°C, perfusion pressure 70 cm H_2O). It was retrogradely perfused with Ca^{2+}-free Tyrode solution until the blood was washed out, followed by perfusion with the same Ca^{2+}-free Tyrode solution supplemented with 0.6 mg/ml collagenase II and 0.5 mg/ml albumin bovine serum (68 kD, Roche). As the drip rate reached 20 ml/min and the colour of the heart changed to orange and transparent, the perfusion was complete.

The heart was then removed into KB solution (37°C). The free left ventricular wall was cut into approximately 8 × 2-mm sections with a fine scissors and the endocardium and epicardium were removed in the KB solution. The mid-myocardial section was cut up and agitated with a dropper in order to obtain isolated cells. The cell suspension was then filtered with a strainer (200 mesh). Before recording, the myocytes were placed in filtered KB solution for more than two hours.

I_{Na} was recorded at room temperature (25°C) using the whole-cell configuration of the patch-clamp with Axopatch 700B amplifiers and pClamp 10.1 software (Axon Instruments, USA). Pipettes were pulled from borosilicate capillary tubes using a programmable horizontal micro-electrode puller (P-97, Sutter Instruments, USA) and heat polished with a microforge (MF-830, Narishige). Micropipette resistance was kept at 2–5 MΩ when filled with pipette solution and immersed in the extracellular solution.

The cells were placed in normal extracellular solution for rupture of the membrane, compensation for membrane capacitance and series resistor (75%), and the currents were recorded for baseline. Then the cell bath was perfused with the simulated ischaemic solution (control group) or drug solution (statin group) for three minutes (3 ml/min). At this time, the extracellular solution was replaced completely and we considered the time after one minute of perfusion as the zero point for the start of ischaemia. The cells were then left standing for one minute to avoid interference from mechanical vibration. Thereafter I_{Na} was recorded every two minutes from three minutes after the start of ischaemia to 21 minutes, in both the statin and the control groups.

The holding potential was maintained at –90 mV and the protocol for recording I_{Na} was composed of 50-ms pulses that were imposed in 5-mV increments between –80 and +50 mV, and pulse frequency was 2.5 Hz, which was matched with the rat's natural heart rate. In order to trace the inactivation curves, a double-pulse protocol was set up: the first 50-ms conditioning pulses were imposed in 5-mV increments between –80 and +50 mV, each of which was followed by a test pulse to +10 mV. Finally, to describe the recovery curves after inactivation, another double-pulse protocol was used: the first conditional pulses were imposed at –40 mV for 50 ms, each of which was followed by a fixed 80-ms test pulse from –90 to –40 mV, and the interval between the two pulses was increased in 2-ms increments from 2 to 76 ms.

Statistical analysis

In order to eliminate the effect of cell size on I_{Na}, the I_{Na} from different myocytes should be standardised. As atorvastatin may also affect the membrane capacitance, which may become a confounding factor in the current density, we used the relative current value as the normalised I_{Na} in order to evaluate the effects of atorvastatin on the peak value of the I_{Na}.

The Boltzmann equation was used to fit the activation and inactivation curves, and the recovery curve after inactivation was fitted with an exponential equation. We observed the normalised I_{Na}, membrane potential at 50% maximal activation ($V_{1/2,a}$), offsetting of the activation curve (K_a), membrane potential at 50% maximal inactivation ($V_{1/2,i}$), offsetting of the inactivation curve (K_i) and recovery constant (τ). The data were analysed by means of variance analysis of repeated measurement data, and the gating characteristics were analysed with the allogeneic paired *t*-test; $p < 0.05$ indicated that the difference was statistically significant.

Results

Effect of ischaemia on I_{Na} in the early stage after perfusion: Previous experiments showed that ischaemia suppressed the amplitude of I_{Na}, but we observed the normalised I_{Na} was transiently increased in the very early stage of ischaemia in the pre-experiment. In order to verify the increased current was not associated with the mechanical effect of perfusion, we compared the effect of ischaemic and normal extracellular solutions on I_{Na} in the same way. We found compared with normal extracellular solution, normalised I_{Na} was transiently increased after perfusion with ischaemic extracellular solution, while simulated ischaemia was for three minutes (0.92 ± 0.04 vs 1.42 ± 0.34 mA, $p < 0.01$; Fig. 1).

Effect of atorvastatin on I_{Na} in the early stage of ischaemia: When entering the simulated ischaemic state, the whole-cell currents of control and statin groups both changed over time (Fig. 2). Because of the voltage-dependent characteristics, the

maximum currents appeared at –40-mV test potential (Fig. 3), which was used to analyse the time-dependent effects of ischaemia and atorvastatin on I_{Na}.

In the control group, the normalised I_{Na} increased above baseline in the first three to seven minutes of simulated ischaemia, and peaked at three minutes (Figs 3A, 4). Compared with the three-minute point, the normalised I_{Na} decreased at seven minutes ($p = 0.0321$). At the nine- and 11-minute points, the normalised I_{Na} returned to baseline ($p = 0.3209$ and 0.5505, respectively). With the recording time extended, the normalised I_{Na} was lower than baseline ($p < 0.05$) and gradually decreased from 13 to 21 minutes (13 vs 15 minutes, $p = 0.0270$; 15 vs 17 minutes, $p = 0.0146$; 19 vs 21 minutes, $p = 0.0014$, respectively; Fig. 4).

In the statin group, the normalised I_{Na} gradually decreased during the whole time of simulated ischaemia. It decreased by 0.09 ± 0.03 mA at five minutes compared with baseline ($p = 0.0163$), decreased by 0.08 ± 0.03 mA at 13 minutes compared with five minutes ($p = 0.0256$), and continued decreasing by 0.09 ± 0.02 mA ($p = 0.0040$) at 21 minutes compared with 13 minutes (Fig. 4).

Comparing normalised I_{Na} between the two groups (Fig. 4), there were no differences at baseline and 11 to 19 minutes of ischaemia ($p > 0.05$). Normalised I_{Na} in the statin group was lower than in the control group at three to nine minutes of ischaemia ($p < 0.05$), while at 21 minutes, I_{Na} in the statin group was higher than in the control group ($p < 0.05$).

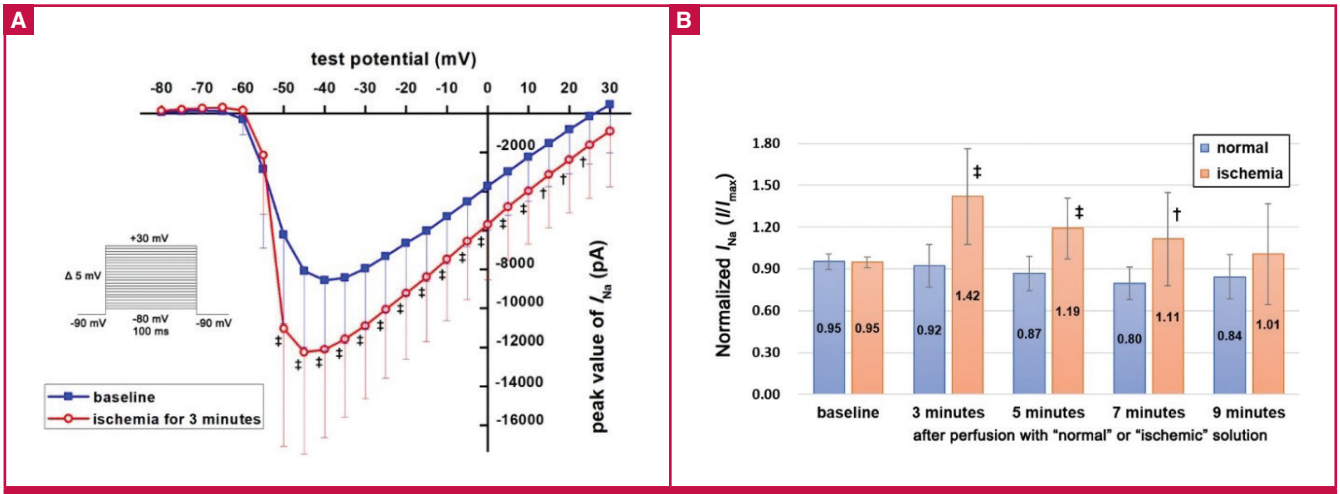

Fig. 1. Effects of ischaemia on I_{Na} in the very early stage after perfusion. (A) Current–voltage (I–V) curves between baseline and ischaemia. When ventricular myocytes were perfused with ischaemic solution, the peak value of I_{Na} was voltage-dependently increased in the stage of ischaemia after three minutes. Compared with baseline, $^{\dagger}p < 0.05$, $^{\ddagger}p < 0.01$. (B) Normalised I_{Na} after perfusion with normal and ischaemic extracellular solution. In the first 10 minutes after perfusion, normalised I_{Na} was transiently increased when perfused with ischaemic solution, whereas there was little change when perfused with normal solution, which excluded the effects of mechanical action on I_{Na}. Compared with normal solution, $^{\dagger}p < 0.05$, $^{\ddagger}p < 0.01$.

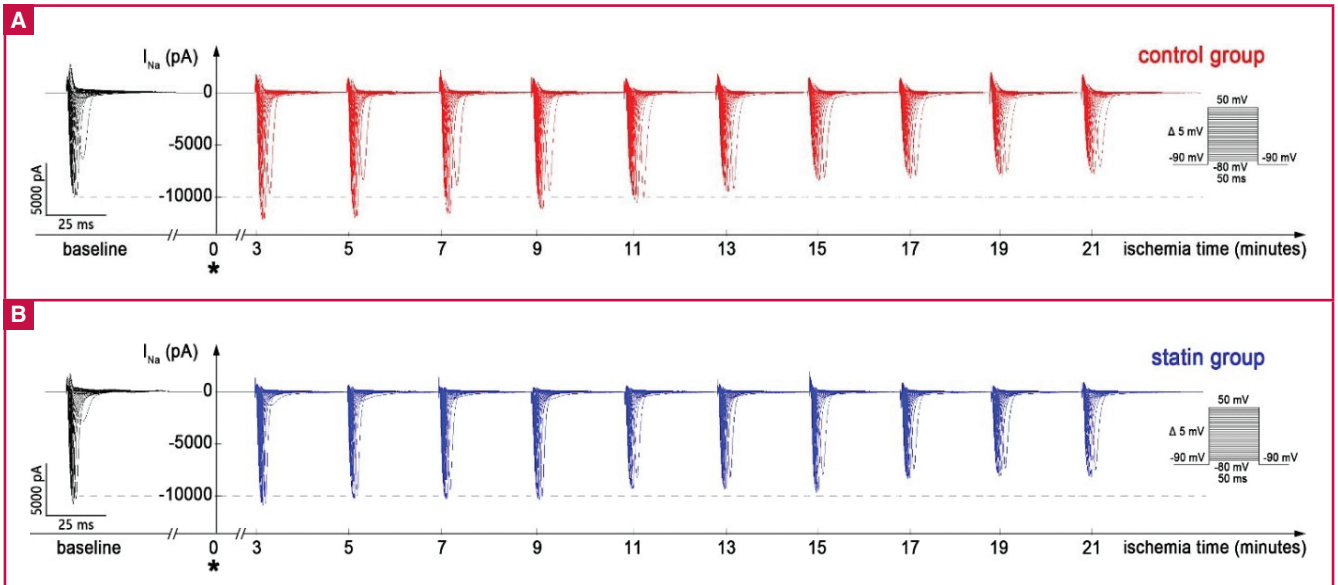

Fig. 2. Trend of whole-cell currents of I_{Na} over time. (A) Whole-cell currents in the control group. (B) Whole-cell currents in the statin group. *zero point of simulated ischaemia.

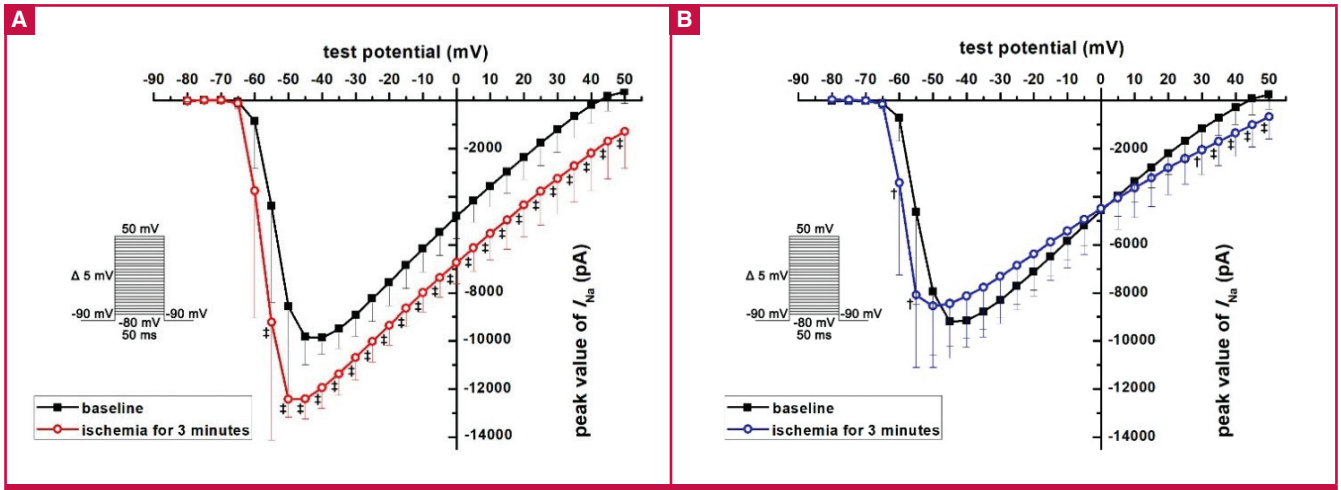

Fig. 3. Current–voltage (I–V) curves between baseline and ischaemia for three minutes. (A) I–V curve of control group, which was down-shifted in the very early stage of ischaemia, and represented the increase of I_{Na} at the test potential from –55 to 50 mV. (B) I–V curve of statin group, which was little changed in the early ischaemic condition, compared to the baseline.

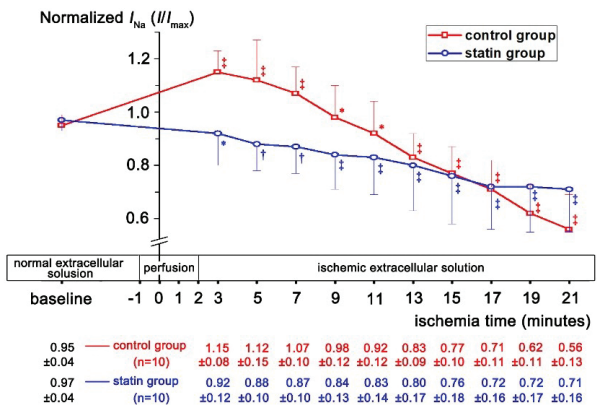

Fig. 4. Time trend of normalised I_{Na} at –40-mV test potential. When entering the simulated ischaemic stage, the normalised I_{Na} in the control group was transiently increased during the first three to seven minutes, and then attenuated rapidly, while in the statin group, the normalised I_{Na} gradually decreased during the whole of the simulated ischaemia.

Table 1. Gating characteristics at three minutes of simulated ischaemia ($\bar{x} \pm s$)

	Activation (n = 8)		*Inactivation* (n = 8)		*Resurrection* (n = 9)
	$V_{1/2,a}$ (*mV*)	K_a (*mV*)	$V_{1/2,i}$ (*mV*)	K_i (*mV*)	τ (*ms*)
Control group					
Baseline (A_1)	–54.91 ± 4.22	1.45 ± 0.48	–62.84 ± 2.50	4.52 ± 0.97	34.23 ± 4.40
Ischaemia (B_1)	–58.82 ± 3.65	0.90 ± 0.31	–65.19 ± 3.33	4.28 ± 1.11	25.54 ± 6.41
Value of B_1–A_1	–3.90 ± 2.16	–0.55 ± 0.44	–2.35 ± 1.71	–0.23 ± 0.38	–8.69 ± 4.75
p (A_1:B_1)	0.0014	0.0090	0.0061	0.1238	0.0006
Statin group					
Baseline (A_2)	–54.70 ± 3.54*	1.41 ± 0.65*	–63.33 ± 2.24*	4.92 ± 0.55*	34.58 ± 8.55*
Ischemia (B_2)	–59.16 ± 3.53	1.03 ± 0.58	–66.45 ± 1.91	4.12 ± 0.56	30.22 ± 9.65
Value of B_2–A_2	–4.47 ± 1.97	–0.38 ± 0.35	–3.12 ± 1.00	–0.81 ± 0.35†	–4.36 ± 4.82†
p (A_2:B_2)	0.0004	0.0169	0.0000	0.0004	0.0263

Compared with the baseline of the control group, *$p > 0.2$, and compared with the value of B_1–A_1, †$p < 0.05$.

Table 1 shows the gating characteristics of the two groups. Compared with baseline, in the three minutes of simulated ischaemia, the curves of activation and inactivation were shifted negatively (Fig. 5A–D), and K_a and τ were decreased in both groups (Table 1, Fig. 5A, B, E, F). At three minutes of simulated ischaemia, K_i in the statin group was lower than in the control group ($p < 0.05$), and τ in the statin group was higher than in the control group ($p < 0.05$; Table 1, Fig. 5C–F).

Discussion

Sodium current plays an important role in ischaemic ventricular arrhythmias, which may affect cardiac conductivity and irritation.[3] Previous studies have shown that sodium current may decrease in the ischaemic state,[5] but in our study, the current transiently increased in the early stage of ischaemia. Ventricular arrhythmias mainly appear in acute myocardial ischaemia in two time periods after birth (0–0.5 and 1.5–9 hours).[12]

In view of the relationship between ischaemic time and the degree of injury, we hypothesised that the change of I_{Na} in simulated ischaemia may be time-dependent. To observe the instantaneous change in I_{Na}, the measurement time interval was shortened to two minutes. The results showed that I_{Na} was transiently increased and peaked at three minutes after simulated ischaemia. At this time, the $V_{1/2,a}$ and $V_{1/2,i}$ were both decreased, which represented the activation and inactivation thresholds, respectively, and meant that both the activation and inactivation processes would be much easier at the early stage of ischaemia. In addition, decreased K_a and τ indicated that the processes of channel activation and recovery had been changed much faster (Fig. 5).

In summary, these changed gating characteristics indicated that channel transition between open and closed states became more frequent, and the open probability of sodium channels per unit time had been increased. Since $I_m = i\ P_0\ N$ (where I_m is the whole-cell current, i is the single-channel current, P_0 is the open probability, and N is the number of channels),[13] the whole-cell I_{Na} had been consequently increased at three minutes of simulated ischaemia. However, this experiment also showed

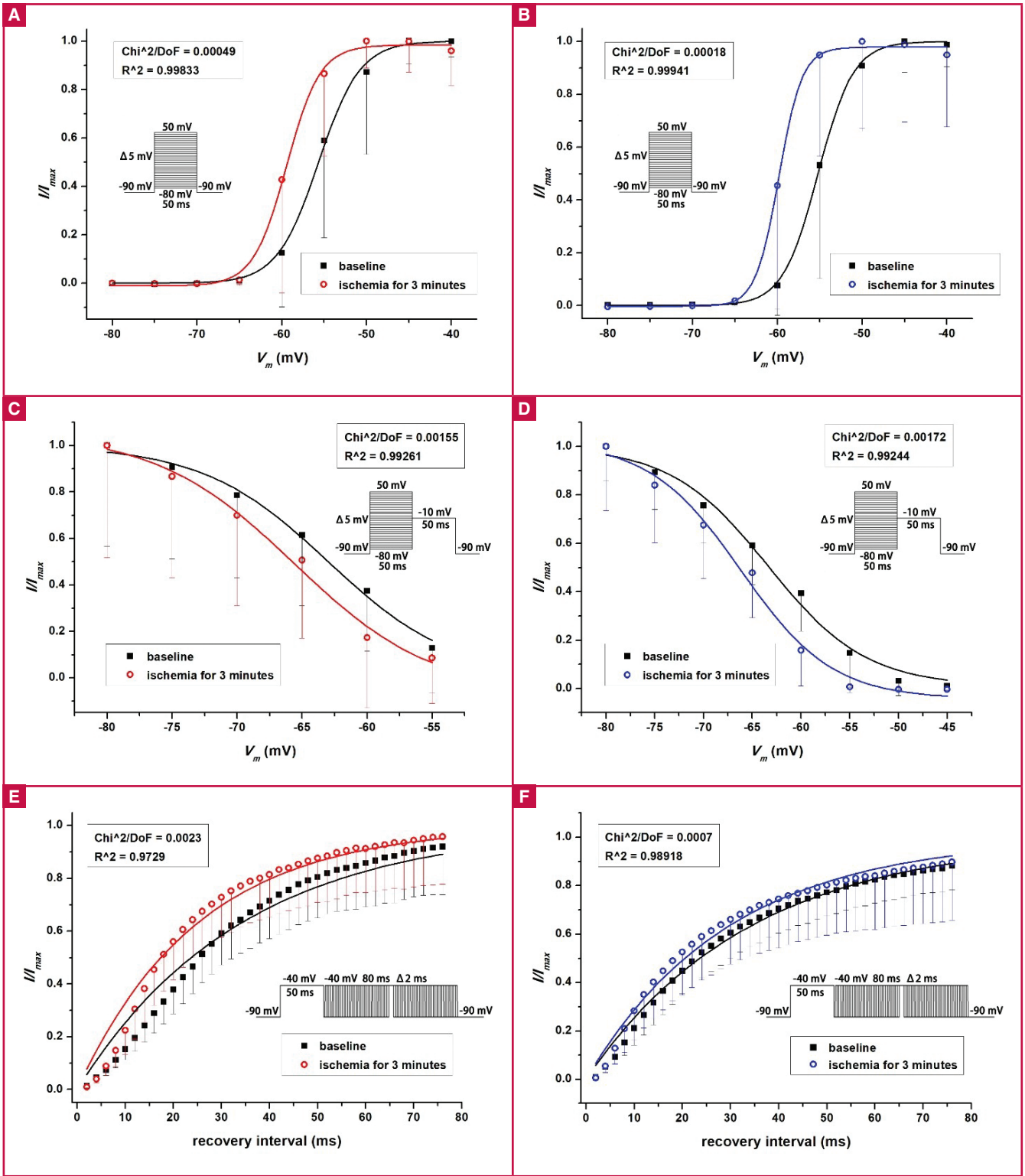

Fig. 5. Gating characteristic curves between baseline and ischaemia for three minutes. (A) Activation curve in the control group. (B) Activation curve in the statin group. (C) Inactivation curve in the control group. (D) Inactivation curve in the statin group. (E) Recovery curve in the control group. (F) Recovery curve in the statin group.

that I_{Na} was gradually attenuated over time after 10 minutes of simulated ischaemia, which was consistent with previous reports.[14] A possible reason may be the secondary damage to cells by secondary calcium overload related to increased intracellular sodium concentration.[15]

The aconitine model has shown[16,17] that the abnormally increased I_{Na} may result in the increase of 0 phase amplitude of the action potential. As the increased action potentials pass into the adjacent tissue in the relative refractory period, it will cause threshold stimulation, which may lead to premature

contraction. In our study, it was observed that I_{Na} had first been increased and then decreased in the simulated ischaemic state. Therefore, in the early stage of ischaemia, cardiomyocytes were in a heterogeneous ischaemic state, and the dispersion of I_{Na} in ischaemic tissue would be increased with the prolongation of ischaemia, which may be one of the bases for the formation of local abnormal current.

As a basic drug of acute coronary syndrome, statins have been shown to reduce the morbidity of ventricular arrhythmias and the mortality rate.[18,19] Therefore we observed the effect of atorvastatin on I_{Na}, which was in the early stage of ischaemia, and found that the increased current was inhibited. As we know, before producing pleiotropic effects, statins should inhibit HMG-CoA reductase and then block the important mevalonate pathway.[20,21] However, Gerber *et al*. showed that atorvastatin decreased the HMG-CoA reductase activity in L cells only after incubation with the drug for 18 hours.[22] In addition, Vaquero *et al*. demonstrated the membrane capacitance was not changed by atorvastatin.[11] Therefore, non-specific perturbation of the membrane seems a very unlikely mechanism for atorvastatin to be responsible for, otherwise the capacitance would be changed as the dielectric constant had been modified.

As a fat-soluble statin, atorvastatin calcium is slightly soluble in pH 7.4 phosphate buffer, which means that the theoretical maximum range of atorvastatin is 82.68 to 826.8 μmol/l. We used a concentration of 5 μmol/l, which was equivalent to the clinical dose of 20–80 mg/d.[23] This could avoid the use of a fat-soluble solvent, which may also influence the membrane currents.

Conclusions

In this study we observed the time-dependent effect of atorvastatin on I_{Na} in a simulated ischaemic condition and found that the phenomenon of transiently increased I_{Na} disappeared. The gated characteristics showed that atorvastatin reduced K_i and weakened the decline of τ value caused by ischaemia. Therefore the channel inactivation was faster and the recovery was slower, which caused the number of open channels per unit time to decrease, finally resulting in a decrease in whole-cell current.

Atorvastatin inhibited the abnormal increase of I_{Na} during the early stage of simulated ischaemia by acting on the processes of inactivation and recovery. As statins can block the activity of a voltage-gated calcium channel,[24] atorvastatin could also transiently block the sodium channel when entering the cell during the first three to seven minutes of ischaemia. Interestingly, atorvastatin appeared to prevent a further decrease in I_{Na} as the ischaemic time extended to more than 19 minutes, indicating another cardioprotective effect of atorvastatin, in preventing further ischaemic injury (such as ischaemic postconditioning of statins[25]). Therefore atorvastatin played a role only as a buffer in abating rapid changes in I_{Na} over time during early ischaemia, which helped to reduce the electrical heterogeneity of the ischaemic myocardium[26,27] and improve the cardiac arrhythmia matrix effect.

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Walnuts may help lower blood pressure for those at risk of heart disease

In a randomised, controlled trial, researchers examined the effects of replacing some of the saturated fats in participants' diets with walnuts. They found that when participants ate whole walnuts daily in combination with lower overall amounts of saturated fat, they had lower central blood pressure.

According to the researchers, central pressure is the pressure that is exerted on organs such as the heart. This measure, like blood pressure measured in the arm in the traditional way, provides information about a person's risk of developing cardiovascular disease (CVD).

Dr Penny Kris-Etherton, distinguished professor of nutrition at Penn State, said the study suggests that because walnuts lowered central pressure, their risk of CVD may have also decreased. 'When participants ate whole walnuts, they saw greater benefits than when they consumed a diet with a similar fatty acid profile as walnuts without eating the nut itself,' Kris-Etherton said. 'So, it seems like there's a little something extra in walnuts that are beneficial – maybe their bioactive compounds, maybe the fibre, maybe something else – that you don't get in the fatty acids alone."

Alyssa Tindall, recent student in Dr Kris-Etherton's lab and a new PhD graduate in nutrition, said the study was one of the first to try to uncover which parts of the walnuts help to support heart health.

'Walnuts contain alpha-linolenic acid (ALA) a plant-based omega-3 that may positively affect blood pressure,' Tindall said. 'We wanted to see if ALA was the major contributor to these heart-healthy benefits, or if it was other bioactive component of walnuts, like polyphenols. We designed the study to test if these components had additive benefits.'

For the study, the researchers recruited 45 participants with overweight or obesity who were between the ages of 30 and 65 years. Before the study began, participants were placed on a 'run-in' diet for two weeks.

'Putting everyone on the same diet for two weeks prior to the start of the study helped put everyone on the same starting plane,' Tindall said. 'The run-in diet included 12% of their calories from saturated fat, which mimics an average US diet. This way, when the participants started on the study diets, we knew for sure that the walnuts or other oils replaced saturated fats.'

After the run-in diet, the participants were randomly assigned to one of three study diets, all of which included less saturated fat than the run-in diet. The diets included one that incorporated whole walnuts, one that included the same amount of ALA and polyunsaturated fatty acids without walnuts, and one that partially substituted oleic acid for the same amount of ALA found in walnuts, without any walnuts.

All three diets substituted walnuts or vegetable oils for 5% of the saturated fat content of the run-in diet. All participants followed each diet for six weeks, with a break between diet periods.

Following each diet period, the researchers assessed the participants for several cardiovascular risk factors, including central systolic and diastolic blood pressure, brachial pressure, cholesterol level and arterial stiffness.

The researchers found that while all treatment diets had a positive effect on cardiovascular outcomes, the diet with whole walnuts provided the greatest benefits, including lower central diastolic blood pressure. In contrast to brachial pressure, which is the pressure moving away from your heart and measured with an arm cuff in the doctor's office, central pressure is the pressure moving toward your heart.

Tindall said that the results underline the importance of replacing saturated fat with healthier alternatives. 'An average American diet has about 12% calories from saturated fat, and all our treatment diets all had about 7%, using walnuts or vegetable oils as a replacement,' Tindall said. 'So, seeing the positive benefits from all three diets sends a message that regardless of whether you replace saturated fats with unsaturated fats from walnuts or vegetable oils, you should see cardiovascular benefits.'

Kris-Etherton added that the study supports including walnuts as part of a heart-healthy diet. 'Instead of reaching for fatty red meat or full-fat dairy products for a snack, consider having some skim milk and walnuts,' Kris-Etherton said. 'I think it boils down to how we can get the most out of the food we're eating, specifically, how to get a little more bang out of your food buck. In that respect, walnuts are a good substitute for saturated fat.'

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Effects of cardiopulmonary bypass on dialysis-dependent patients

Nursen Tanrıkulu, Baburhan Ozbek

Abstract

Background: End-stage renal disease is considered an independent risk factor for early and late survival after coronary artery bypass grafting.

Methods: We retrospectively analysed patients with dialysis-dependent renal insufficiency who had undergone coronary artery bypass surgery between 2010 and 2017. Patients who were operated with the assistance of cardiopulmonary bypass (ONCAB) were in group 1 and those operated with off-pump coronary artery bypass surgery (OPCAB) were in group 2. We compared peri-operative morbidity and mortality rates and short-term results of the two groups.

Results: There were 74 patients in group 1 and 36 in group 2. Blood transfusion requirement, drainage, need for intra-aortic balloon pump and duration of stay in intensive care unit was statistically significantly higher in group 1 ($p < 0.05$). Also, postoperative creatine kinase (CK) and creatine kinase-muscle/brain (CKMB) values were statistically significantly higher in group 1 ($p = 0.003$).

Conclusion: Coronary artery bypass grafting under ONCAB was a potential risk for morbidity and mortality in patients with end-stage renal disease. Performing OPCAB surgery may improve postoperative outcomes and should be kept in mind as a surgical option.

Keywords: cardiac surgery, cardiopulmonary bypass, dialysis, renal insufficiency

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Coronary artery disease is a common cause of mortality in patients requiring dialysis, with a rate higher than 40%.[1] On the other hand, end-stage renal disease (ESRD) is considered an independent risk factor for early and late survival after coronary artery bypass grafting (CABG).[2] Peri-operative mortality risk increases from five to 20% in ESRD patients, which is almost three-fold higher than in non-ESRD patients.[3]

Off-pump coronary artery bypass grafting (OPCAB) is a well-established and feasible procedure with reduced morbidity and mortality rates in high-risk patients.[4,5] By contrast, some authors reported that long-term survival rates after OPCAB were worse than those of on-pump coronary artery bypass grafting (ONCAB) because of lower rates of complete revascularisation.[6] However, it was reported that OPCAB had better short-term outcomes than conventional CABG in ESRD patients.[6]

There are limited data on myocardial revascularisation procedures in patients with ESRD. In this study, we retrospectively analysed peri-operative and short-term outcomes of dialysis-dependent patients after CABG and analysed the effect of cardiopulmonary bypass on the outcomes.

Methods

Patients who had undergone coronary artery surgery from 1 January 2010 to 31 December 2017 in our department were retrospectively analysed. We included patients with selective CABG surgery and dialysis-dependent ESRD. We excluded patients who had undergone a concomitant surgical procedure, had dialysis-independent renal disease and patients younger than 18 years old. All demographics and peri-operative variables were obtained from medical records.

Regarding the surgical procedure, patients were evaluated in two groups. Group 1 consisted of patients who had undergone ONCAB, and those who were operated with OPCAB were in group 2.

All operations were performed via a median sternotomy. Arterial conduits were harvested in a skeletonised fashion. In group 1, heparin was given to achieve an activated clotting time of 480 seconds. Standard cardiopulmonary bypass (CPB) was achieved via cannulating the ascending aorta and right atrium. Cold blood cardioplegia was delivered through the aortic root (antegrade flow) and through the coronary sinus (retrograde delivery). All patients were ultra-filtrated during CPB with a mean volume removal of 1 500 ml.

In group 2, heparin was given to achieve an activated clotting time greater than 300 seconds. Deep pericardial stitches were placed to manipulate the heart and expose the coronary arteries. An Octopus coronary stabiliser (Medtronic Inc, Minneapolis, MN) was used. Distal anastomoses were done first and the operation was ended after a proximal anastomosis. We compared pre-operative demographics and peri-operative and short-term outcomes between the two groups.

Statistical analysis

Statistical analyses were performed with the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) program for Windows. Besides standard descriptive statistical calculations, the Mann–Whitney *U*-test was used for comparison of the groups. The Wilcoxon test was employed in the assessment of pre- and postoperative values. Chi-squared

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Table 1. Baseline demographic characteristics of patients

Variable	*Group 1 (n = 74)*	*Group 2 (n = 36)*	p-*value*
Age (years)	60 ± 7	61.5 ± 7.5	0.781
Gender (male/female)	65/35	67/33	0.895
BMI (kg/m²)	26.9 ± 3	27 ± 2.56	0.979
Ejection fraction	55 ± 15	52.5 ± 14.5	0.422
LVH (*n*)	16 (21.6%)	6 (16.7%)	0.266
Ejection fraction	61.5 ± 7.5	60 ± 7	0.701
Hypertension (*n*)	68	78	0.434
Hyperlipidaemia (*n*)	27	44	0.196
Diabetes mellitus (*n*)	51	72	0.141
Smoking (*n*)	35	44	0.505
COPD (*n*)	31	39	0.540
PAH (*n*)	19	22	0.774
Creatinine (mg/dl)	4.8 ± 1.32	5 ± 1.35	0.802
Previous MI (*n*)	70	56	0.282
EuroSCORE	8 ± 2	7 ± 2.25	0.421

BMI = body mass index, LVH = left ventricular hypertrophy, COPD = chronic obstructive pulmonary disease, PAH = pulmonary arterial pressure, MI = myocardial infarction.

and McNemar's tests were performed during the evaluation of qualitative data. Multiple regression analyses were performed to explain the relationship between group 1 and group 2. The results were evaluated within a 95% confidence interval. Statistical significance level was established at $p < 0.05$.

Results

The study population consisted of 110 patients with dialysis-dependent ESRD among a total of 1 886 patients who underwent CABG surgery between 2010 and 2017. There were 74 patients (26 female, 48 male) in group 1 with a mean age of 60 ± 7 years; 36 patients (12 female, 24 male) were in group 2 and the mean age was 61.5 ± 7.5 years.

There were no statistically significant differences between the two groups with regard to age, gender, old myocardial infarction and other demographic variables (Table 1). Drainage (800 ± 350 vs 600 ± 325 ml, $p = 0.044$), blood transfusion (3 ± 1 vs 2 ± 0.5 units, $p = 0.020$) and length of stay in intensive care unit (ICU) (6 ± 5.3 vs 4 ± 4.5 days, $p = 0.033$) were statistically significantly higher in group 1 (Table 2).

Although pre-operative levels of creatine kinase (CK) and creatine kinase-muscle/brain (CK-MB) were similar, postoperative CK (1076.45 ± 2411.97 vs 208.45 ± 171.94 mg/dl, $p = 0.003$) and CK-MB levels (102.32 ± 115.5 vs 53.15 ± 66.53 mg/dl, $p = 0.044$) were statistically significantly higher in group 1. In the comparison of pre-operative and postoperative CK levels, it was observed that postoperative CK (111.94 ± 139.63 vs 1076.45 ± 2411.97 mg/dl, $p = 0.0001$) and CK-MB levels (102.32 ± 115.5 vs 44.47 ± 124.9 mg/dl, $p = 0.0001$) of group 1 were statistically significantly increased.

Similarly, postoperative troponin values of group 1 were statistically significantly higher than those in the pre-operative period (0.07 ± 0.09 vs 9.15 ± 22.54 mg/dl, $p = 0.043$). Postoperative requirement for inotropic agents (22.2 vs 29.70%, $p = 0.557$) and intra-aortic balloon pump (IABP) (16.7 vs 21.6%, $p = 0.666$) were similar in both groups (Table 3).

Univariate tests were significantly higher in group 1 in terms of blood transfusion, drainage, length of stay in ICU, and postoperative CK and CK-MB values. In the logistic regression analysis, only post-operative CK levels remained statistically significantly higher ($p = 0.038$) (Table 4).

Table 2. Operative and postoperative outcomes

Variable	*Group 1 (n = 74)*	*Group 2 (n = 36)*	p-*value*
Number of the grafts (*n*)	3 ± 1.5	2 ± 0.5	0.114
Use of IMA (*n*)	74	36	1.00
Urgent operation (*n*)	3 (4%)	11 (30%)	0.198
Blood transfusions (units)	3 ± 1	2 ± 0.5	0.02
Drainage (ml)	800 ± 350	600 ± 325	0.044
Entubation time (hours)	16	14	0.723
ICU stay (days)	6 ± 5.3	4 ± 4.5	0.033
Sternal wound infection (*n*)	2 (2.7%)	4 (11.1%)	0.051
Pneumonia (*n*)	3 (4.1%)	11 (30.1%)	0.198
Hospital mortality (*n*)	16 (21.6%)	11 (30.1)	0.716

IMA = internal mammary artery, ICU = intensive care unit.

Table 3. Comparison of laboratory results and need for inotropic support

Variable	*Group 1 (n = 74)*	p_1	*Group 2 (n = 36)*	p_2	p_3
Pre-operative CK (mg/dl)	11.9 ± 139.6	0.001	115.9 ± 11.6	0.07	0.382
Postoperative CK (mg/dl)	1076.5 ± 2412		208.5 ± 171.9		0.003
Pre-operative CK-MB (mg/dl)	44.5 ± 124.9	0.001	23.6 ± 16.84	0.055	0.677
Postoperative CK-MB (mg/dl)	102.3 ± 115.5		53.2 ± 66.5		0.044
Pre-operative troponin (mg/dl)	0.45 ± 0.69	0.011	0.07 ± 0.09	0.043	0.108
Postoperative troponin (mg/dl)	27.8 ± 73.9		15.1 ± 22.5		0.409
Pre-operative inotropic support (*n*)	1	0.002	1	0.25	0.596
Postoperative inotropic support (*n*)	11		4		0.557
Pre-operative IABP (*n*)	1	0.016	1	0.5	0.596
Postoperative IABP (*n*)	8		3		0.666

CK = creatine kinase, CK-MD = creatine kinase-muscle/brain, IABP = intra-aortic balloon pump, p_1 = comparison of pre-operative and postoperative data in group 1. p_2 = comparison of pre-operative and postoperative data in group 2. p_3 = comparison of group 1 and group 2.

Discussion

This study demonstrates that OPCAB had the advantage of decreased incidence of bleeding, lower rates of requirement for transfusion, shorter length of stay in ICU, decreased CK and CK-MB elevation and lower rates of need for IABP when compared to ONCAB in dialysis-dependent patients.

Patients with ESRD have significantly higher risk for cardiovascular morbidity and mortality.[7,8] Most patients with ESRD have left ventricular hypertrophy secondary to systemic arterial hypertension, hyperparathyroidism secondary to chronic renal disease, and several systemic co-morbidities such as cerebrovascular disease or diabetes mellitus. All these factors can lead to accelerated atherosclerosis of the coronary arteries.[9]

Table 4. Results of logistic regression analysis

					95% CI for Exp(B)	
Variable	*B*	*SE*	p-*value*	*Exp(B)*	*Lower*	*Upper*
Blood transfusions	1.33	0.8	0.94	3.8	0.8	18.11
Drainage	0.00	0.00	0.345	1.00	1.00	1.01
ICU stay	0.09	0.11	0.441	1.09	0.88	1.35
CK	0.01	0.00	0.038	1.01	1.00	1.01
CK-MB	0.00	0.01	0.773	1.00	0.98	1.01

ICU = intensive care unit, CK = creatinine kinase, CK-MD = creatine kinase-muscle/brain, SE = standard error, CI = confidence interval, Exp(B) = odds ratio.

Based on the present study and our clinical experience, coronary lesions of dialysis-dependent patients are mostly characterised by extensive, long, diffuse disease with calcification.[10] Peri-operative mortality rate may be increased in patients with diffuse arterial disease. Also, long-term survival may be decreased with the OPCAB procedure due to incomplete revascularisation in these patients.

According to our clinical observation, dialysis-dependent patients may present with two different patterns of coronary artery disease. Some present with typical proximal obstructions and relatively good distal vessels. However a second group presents with severe distal disease in addition to proximal obstruction. The second group has increased surgical risk and decreased chance of benefiting from the operation. In most cases, receiving medical therapy or angioplasty may produce better results in these patients.

Contemporary treatment models for renal replacement have improved survival rates in ESRD patients. This condition, considering the high number of elderly patients on dialysis, increases the incidence of coronary artery disease (CAD) and the need for myocardial revascularisation in such patients. Recent reports have shown that patients with ESRD have improved long-term outcomes when treated surgically compared to percutaneous procedures.[11,12] Cardiac surgery can be performed with acceptable results in dialysis-dependent patients.[5-7,13] In our study, the in-hospital mortality rate was 24.5%, and it was acceptable for patients with a high EuroSCORE.

After CABG, complications develop more often in patients with ESRD.[14] Sternal wound infection and pneumonia are common complications that increase the risk of mortality. In ESRD patients, the in-hospital mortality rate of cardiac surgery varies from zero to 36.7%.[9,13] In chronic renal disease, Herzog *et al.*[9] declared an in-hospital mortality rate of 8.6% and two-year mortality rate of 44% after surgery.

Interestingly, postoperative pneumonia was higher in OPCAB patients in our study. This may have been because of our patient selection, since we performed the OPCAB procedure particularly in patients with severe lung disease. Although patients had severe pulmonary disease in group 2, the in-hospital mortality rate was lower. In this regard, we highlight that, from the randomised-groups statistical analysis, the OPCAB procedure may be more favourable.

Several studies have shown that an increased risk of complications were associated with the use of CPB, decreased leukocyte chemotaxis and leukopaenia, and difficulty in maintaining fluid–electrolyte balance.[15,16] OPCAB is an alternative method that could improve surgical morbidity and mortality rates in dialysis-dependent patients with CAD. The OPCAB procedure prevents the inflammatory and destructive effects of CPB and improves short-term cardiac haemodynamics.[17-19]

Improvements in technology for cardiac stabilisation and increased experience with heart positioning have allowed surgeons to perform routine complete off-pump revascularisation in three-vessel coronary artery disease, especially in patients with multiple co-morbidities. OPCAB surgery improves short-term mortality rates in patients with ESRD.[8,20] While the in-hospital mortality rate of OPCAB was between zero and 1.7% in some studies, the rate for the ONCAB procedure was reported as 14.7–17.2%.[8,21] Potential benefits of off-pump surgery include less postoperative cognitive impairment, lower incidence of renal failure, decreased blood loss, shorter mechanical ventilation, shorter length of ICU and hospital stay, and lower mortality rates in high-risk groups.[22-25] Shrooff *et al.*[24] found an 8% risk reduction of all-cause mortality in dialysis-dependent patients with the OPCAB procedure.

Re-operation for bleeding is also a common problem in ESRD patients.[18,19] Homeostasis disturbances, platelet dysfunction, coagulation defects depending on uraemia, and the mechanical stress of dialysis may be reasons for increased postoperative bleeding. In our study, the rate of re-operation due to bleeding was 10.5% and this may have been caused by dialysis and its complications. In our study, 12 (10.5%) patients needed re-operation caused by bleeding, which was higher than in patients without renal disease.

A limitation of this study includes the disadvantages of retrospective studies, therefore any conclusions are limited in applicability. In this study we report on a single-centre experience with a relatively small number of patients and short follow-up period. Additionally, we have no definitive data for the cause of death after hospital discharge.

Conclusion

In dialysis-dependent patients, CPB has additional risk factors such as inflammatory effects and longer surgical times. The inflammatory response and increased surgery and ventilation times may cause systemic problems, particularly pulmonary dysfunction in high-risk patients. These systemic problems lengthen the hospitalisation period and increase mortality and morbidity rates. The OPCAB procedure is a safe alternative with acceptable outcomes and avoids the side effects of CPB. After detailed investigation with coronary angiography, complete revascularisation with the OPCAB procedure is possible in centres with experienced surgeons. It may be the treatment of choice in high-risk patients, using skilled surgeons.

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Statins with Mediterranean diet reduces cardiovascular mortality risk

For those who have already had a heart attack or a stroke, the combination of statins and a Mediterranean diet appears to be the most effective choice to reduce the risk of mortality, especially from cardiovascular causes. It is the result of an Italian study conducted at the IRCCS Neuromed, Pozzilli, Italy on over 1 000 adults recruited in the Moli-sani study.

The traditional Mediterranean diet is rich in fruit, vegetables, legumes, cereals, olive oil, wine in moderation, fish and low in meat and dairy products.

'We found,' Marialaura Bonaccio, epidemiologist at the Department of Epidemiology and Prevention and first author of the study says, 'that statins and a Mediterranean diet together were more effective, compared to one or the other considered separately, in reducing the risk of cardiovascular mortality. Likely, a Mediterranean diet facilitated the beneficial effect of statins, which in our real-life study were generally used at low doses.'

Researchers also analysed the potential underlying mechanisms of this positive interaction, so far poorly explored, between drugs and eating habits.

'The favourable combination of statins and a Mediterranean diet,' explains Licia Iacoviello, head of the Laboratory of Molecular and Nutritional Epidemiology of the same department and professor of hygiene at the University of Insubria, 'appeared to act, rather than on cholesterol levels, by reducing sub-clinical inflammation, a condition that predisposes to a higher risk of illness and mortality. This finding is of particular interest, especially in the light of our observation that a high level of sub-clinical inflammation doubled the risk of mortality in patients who already had had a heart attack or stroke.'

'Our data,' says Giovanni de Gaetano, director of the Department of Epidemiology and Prevention, 'suggest that we should focus more on the possible interactions between food and drugs, an aspect largely neglected in epidemiological research. Of course, controlled clinical trials will be needed to clarify these findings. If our data are confirmed, new therapeutic possibilities could be designed for those who have already had a cardiovascular event, allowing a better modulation of the pharmacological intervention in relation to life habits. This is a new aspect of personalised medicine.'

Source: Medical Brief 2019

Long-term safety and efficacy of alirocumab in South African patients with heterozygous familial hypercholesterolaemia: the ODYSSEY Open-Label Extension study

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Abstract

Background: Alirocumab reduces low-density lipoprotein cholesterol (LDL-C) levels by up to 61%. The ODYSSEY Open-Label Extension study investigated the effect of alirocumab in patients with heterozygous familial hypercholesterolaemia (HeFH) over 144 weeks.

Methods: Eligible patients with HeFH had completed an earlier double-blind, randomised, placebo-controlled parent study. Patients were initiated on 75 mg alirocumab Q2W subcutaneous (SC) unless baseline LDL-C was > 8.9 mmol/l, in which case they received 150 mg alirocumab Q2W. Dose titration to 150 mg Q2W was at the investigator's discretion.

Results: The study enrolled 167 patients and the parent study mean (± SD) baseline LDL-C level was 3.65 ± 1.9 mmol/l. Mean LDL-C level was reduced by 48.7% at week 144; mean on-treatment LDL-C was 2.30 ± 1.24 mmol/l. Eight patients reported injection-site reactions, with one treatment discontinuation. Treatment emergent anti-drug antibodies were identified in five patients but these did not affect the efficacy.

Conclusion: Alirocumab effectively and safely reduced LDL-C in these patients.

Keywords: alirocumab, PCSK9 inhibitors, familial hypercholesterolaemia, LDL-C goal, lipid-lowering therapy, cardiovascular risk, statin

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Familial hypercholesterolaemia is a genetic disorder of lipid metabolism characterised by low-density lipoprotein cholesterol (LDL-C) hypercholesterolaemia, tendon xanthomata in some but not all patients, and premature severe cardiovascular disease.[1] Founder effects are seen in multiple ethnicities in South Africa, including Afrikaners (one in 72),[2] the Ashkenazy Jewish population of Lithuanian origin (one in 67),[3] and the Indian population of Gujarati origin (more than one in 100).[4] Because heterozygous familial hypercholesterolaemia (HeFH) is characterised by severe baseline LDL-C hypercholesterolaemia, most patients are not able to reach LDL-C targets with current lipid-modifying therapies.[5]

Proprotein convertase/subtilisin kexin type 9 (PCSK9) is an important regulator of LDL-C homeostasis. It is an enzymatically inactive serine protease that is predominantly secreted by the liver. Circulating PCSK9 binds to LDL receptors on the hepatocyte surface. LDL receptors with bound PCSK9 are still internalised normally but cannot recycle to the cell surface and are degraded in the hepatocyte. Reducing the concentration of free PCSK9 reduces degradation of LDL receptors and ultimately enhances LDL-C clearance due to the increased number of LDL receptors available on the hepatocyte cell surface.[6] Alirocumab is a subcutaneously administered (SC)

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fully human monoclonal antibody directed against PCSK9, which reduces LDL-C by up to 61%.[7]

The safety and efficacy of alirocumab in various populations have been assessed in the phase 3 ODYSSEY programme. Three of these studies investigated the effect of alirocumab in patients with HeFH and confirmed the significant reduction in LDL-C levels of alirocumab-treated patients over a period of 78 weeks.[8-10]

The ODYSSEY Open-Label Extension study (OLE; LTS13463) was a 144-week open-label extension study of alirocumab in HeFH patients who had previously participated in the ODYSSEY FH studies [replicate studies FH I (NCT01623115) and FH II (NCT01709500)], High FH (NCT01617655) or Long-Term study (NCT01507831, the HeFH stratum of patients). The objective of the ODYSSEY OLE study was to describe additional long-term safety, efficacy and tolerability of alirocumab in HeFH patients.

This report focuses specifically on the South African patients who participated in this study. Because familial hypercholesterolaemia is so common in South African founder populations, it is important to confirm that the safety and efficacy of alirocumab in South African patients are no different from that observed in the rest of the world.

Methods

The ODYSSEY OLE study was a phase 3, single-arm, open-label extension, multicentre, 144-week study evaluating the long-term safety of alirocumab when added to currently available lipid-modifying drug therapy in patients with HeFH. Detailed inclusion and exclusion criteria for these studies have been published,[8-10] and are included in Table 1. For entry into the parent study, diagnosis of HeFH could be substantiated either by genotyping or using one of the following diagnostic algorithms: Simon Broome (Scientific Steering Committee on behalf of the Simon Broome Register Group, 1991)[11] or the Dutch Lipid Network criteria with a score > 8.[12]

In FH I and FH II, patients were randomised to either alirocumab 75 mg Q2W SC or placebo. Subsequently the dose of 75 mg Q2W could be up-titrated in a blinded fashion at week 12 to 150 mg Q2W in the active-treatment arm if the LDL-C level at week 8 was > 1.8 mmol/l. In the High FH and Long-Term studies, patients were randomised to either alirocumab 150 mg Q2W or placebo. In the High FH study, the LDL-C threshold for entry was ≥ 4.14 mmol/l, whereas for Long-Term, the LDL-C threshold for entry was ≥ 1.81 mmol/l. The study flow is indicated in Fig. 1.

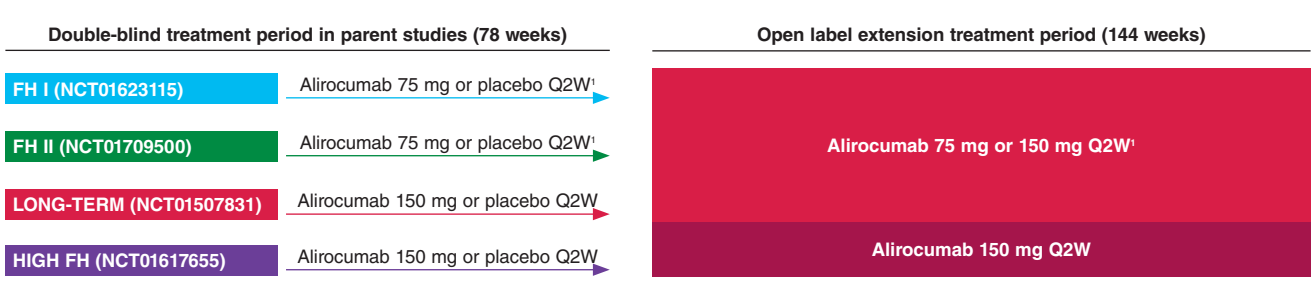
Table 1. Description of the parent studies

Variables	*ODYSSEY FH I (EFC12492)*	*ODYSSEY FH II (R727-CL-1112)*	*ODYSSEY High FH (EFC12732)*	*ODYSSEY Long-Term (LTS11717)*
Patient population enrolled	Patients diagnosed with HeFH, not adequately controlled with a maximally tolerated daily dose (MTD) of statin, stable for at least 4 weeks prior to the screening visit, with or without other lipid-modifying therapy (LMT)			
Screening LDL-C level at entry	≥ 1.80 mmol/l with a history of documented cardiovascular disease ≥ 2.59 mmol/l without a history of documented cardiovascular disease		4.14 mmol/l	2.59 mmol/l with or without documented cardiovascular disease
Sample size (HeFH patients actually randomised in the parent study)	486	249	107	385
Placebo or alirocumab dose at entry in the parent study	75 mg Q2W		150 mg Q2W	
Double-blind treatment period duration (weeks)	78			
Background LMT	MTD* statin (atorvastatin, rosuvastatin, simvastatin) ± other LMT			
% LDL-C reduction from baseline to week 24	−57.9	−51.4	−39.1	−62.0

*Maximum tolerated dose defined as:
- Rosuvastatin 20 or 40 mg daily
- Atorvastatin 40 or 80 mg daily
- Simvastatin 80 mg daily (if already on this dose for > one year)
- Patients not able to be on any of the above statin doses should be treated with the daily dose of atorvastatin, rosuvastatin or simvastatin that is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to, adverse effects on higher doses, advanced age, low body mass index, regional practices, local prescribing information, concomitant medications, co-morbid conditions such as impaired glucose tolerance or impaired fasting glucose.

The start of the OLE study corresponded with the end of the treatment visit of the double-blind treatment period for the patients enrolled in the parent studies. Upon entry into the OLE study, patients were receiving their original treatment allocation of either alirocumab 75 mg Q2W or alirocumab 150 mg Q2W, or placebo. Patients that participated in the Long-Term study had an eight-week off-treatment period before commencing the ODYSSEY OLE study.

In the ODYSSEY OLE study, patients were initiated on alirocumab 75 mg Q2W as a starting dose, regardless of the



At the start of the open-label extension study, patients were on treatment (75 or 150 mg) alirocumab Q2W or placebo
[1]Up-titration of alirocumab dose at the investigators discretion permitted at week 12 if LDL-C was ≥ 1.8 mmol/l

Fig. 1. Study flow of the ODYSSEY Open label study.

alirocumab dose during the parent studies. However, all eligible patients from High FH received a starting dose of alirocumab 150 mg Q2W because this study had selected patients with LDL-C > 4.14 mmol/l at baseline. Alirocumab was self-administered by the patient via subcutaneous injection using a pre-filled pen injector.

LDL-C levels were unblinded from week 8 to allow for dose adjustment at the investigator's discretion. Up-titration to alirocumab 150 mg Q2W could occur from week 12 onwards if LDL-C was > 1.8 mmol/l. In addition, down-titration to alirocumab 75 mg Q2W was possible at the investigator's discretion. Background treatment, including statin and other lipid-modifying treatment, were to be maintained unchanged unless tolerability warranted adjustment.

Site visits were performed at weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 and 108. During these visits lipid parameters, liver function tests, creatinine phosphokinase, haematological and chemistry investigations were performed. Anti-alirocumab antibodies were assessed by the Regeneron Clinical Bioanalysis group from serum samples, as previously described.[8]

This study was conducted in accordance with the principles laid down by the 18th World Medical Assembly and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for good clinical practice. This clinical trial was recorded in clinicaltrials.gov (NCT01954394).

Written informed consent was obtained before a patient's participation in the clinical trial and all patients were given a copy of the signed informed consent. This clinical trial protocol was approved by the relevant private and public sector ethics committee. The clinical events committee was responsible for defining, validating and classifying cardiovascular events, as well as validating the classification of the cause of all deaths.

Table 2. Baseline characteristics and medical history for ODYSSEY OLE participants in South Africa

Variables	*Placebo in parent study (n = 62)*	*Alirocumab in parent study (n = 105)*	*All (n = 167)*
Age (years), mean (SD)	55.4 (10.7)	55.6 (12.6)	55.5 (11.9)
Gender (%, male)	45.2	39.0	41.3
Race (%)			
White	85.5	87.6	86.8
Asian	1.6	0	0.6
Other	0	3.8	2.4
Black	9.7	4.8	6.6
White/Asian	3.2	3.8	3.6
Body mass index (kg/m²), mean (SD)	29.97 (6.09)	30.90 (6.40)	30.55 (6.28)
Heterozygous familial hypercholesterolaemia (%)			
Confirmation by genotyping	22.6	18.1	19.8
WHO/Simon Broome criteria	77.4	81.9	80.2
Atherosclerotic cardiovascular disease (%)	56.5	42.9	47.9
Coronary heart disease* (%)	54.8	41.9	46.7
Myocardial infarction (%)	24.2	21.0	22.2
Unstable angina (%)	16.1	9.5	12.0
Ischaemic stroke (%)	8.1	3.8	5.4
Peripheral arterial disease (%)	3.2	1.9	2.4
Coronary revascularisation procedures (%)	32.3	26.7	28.7
Hypertension (%)	58.1	47.6	51.5
Type 1 or 2 diabetes mellitus (%)	19.4	10.5	13.8
Family history of premature CHD	58.1	57.1	57.5

*According to information gathered and adverse events recorded during the parent study as well as during the pre-treatment period of the OLE study.

Statistical analysis

As this study was an open-label extension for patients from previous studies, no calculation of sample size was performed. Safety analyses were performed on the safety population, which consisted of patients receiving at least one dose or a partial dose of alirocumab in the current study. Efficacy analyses were performed on patients receiving at least one dose or a partial dose of alirocumab in the current study, with a baseline (from the parent study) LDL-C value available and with at least one LDL-C value available in the period from first alirocumab injection in the current study to last injection plus 21 days; a modified intention to treat (mITT) analysis.

Safety analysis [adverse events (including adjudicated cardiovascular events), laboratory, vital signs] was descriptive, based on the safety population. The safety analysis focused on the Treatment Emergent Adverse Events (TEAE) period defined as the time from the first dose of the current study to the last dose of alirocumab plus 70 days (10 weeks).

Efficacy variables were explored through descriptive statistics at each scheduled visit of the current study; 95% confidence intervals are provided for percent changes from baseline and success rate to reach targets.

Results

The study enrolled 167 South African patients at 14 sites. Baseline characteristics and medical history for the participants are indicated in Table 2.

All patients received treatment with lipid-modifying therapy (LMT) at study entry (Table 3). High-dose statin and ezetimibe use was 64.7 and 27.5%, respectively. Data specifying specific combinations of statins and ezetimibe used during the study were not recorded. During the OLE study, concomitant LMT was adjusted at the investigator's discretion.

Of the 42 patients for whom a change in statin therapy was reported during the OLE study, 18 reported a change in statin type, 15 reported dose adjustments in statin therapy, while nine patients discontinued statins. The reasons provided included adverse events, supply issues, treatment cost and other.

The mean (± SD) baseline LDL-C was 3.65 ± 1.9 mmol/l. Mean LDL-C level was reduced by 48.7% at week 144; mean on-treatment LDL-C was 2.30 ± 1.24 mmol/l at week 144. At week 144, 40 of 98 patients with data available (40.8%) reached target LDL-C < 1.81 mmol/l and/or ≥ 50% reduction from the parent study baseline, and 64/98 (65.3%) patients reached LDL-C < 2.59 mmol/l. During the OLE study, calculated LDL-C values < 0.65 mmol/l were reported on two consecutive occasions for four patients (Table 4, Fig. 2).

Table 3. Background lipid-modifying therapy at baseline of the ODYSSEY OLE study

Lipid-modifying therapy	*All, n (%) (n = 167)*
High-intensity statin	108 (64.7)
Atorvastatin (40 or 80 mg)	61 (36.5)
Rosuvastatin (20 or 40 mg)	45 (26.9)
Simvastatin (40 or 80 mg)	37 (22.1)
Ezetimibe	46 (27.5)
Nutraceuticals	4 (2.4)
Change in statin therapy after enrolment in OLE	42 (25.1)

Used in combination with statins or not. May include ezetimibe.

Table 4. Lipid parameters at baseline of the parent and ODYSSEY OLE studies

Lipid parameters	*Baseline at start of parent study (n = 167)*	*Baseline at the start of ODYSSEY OLE study*		
		Placebo in parent study (n = 62)	*Alirocumab in parent study (n = 105)*	*All patients included in OLE study (n = 167)*
Calculated LDL-C (mmol/l), mean (SD)	4.39 (1.56)	4.50 (1.60)	3.14 (1.96)	3.65 (1.95)
Non-HDL-C (mmol/l), mean (SD)	5.10 (1.64)	5.35 (1.68)	3.89 (2.09)	4.44 (2.07)
HDL-C (mmol/l), mean (SD)	1.24 (0.35)	1.28 (0.40)	1.32 (0.38)	1.31 (0.39)
Total cholesterol (mmol/l), mean (SD)	6.3 (1.59)	6.63 (1.60)	5.22 (2.01)	5.75 (1.98)
Fasting triglycerides (mmol/l), mean (SD)	1.53 (0.78)	1.74 (1.14)	1.56 (0.78)	1.63 (0.93)
Lipoprotein (a) (nmol/l), mean (SD)	101.75 (103.3)	106.7 (118.75)	89.5 (87)	91.5 (99.5)

A total of 76 patients (54.3%) were maintained on 75 mg Q2W for the duration of the study, while titration of alirocumab dose from 75 mg Q2W to 150 mg Q2W occurred in 64 (45.1%) patients. Down-titration to 75 mg Q2W occurred in six patients (6.6%), either due to adverse events or at the discretion of the investigator due to low LDL-C values. Compliance with alirocumab was recorded as 98.2% during the OLE study.

Nine deaths were recorded during the study: five due to cardiovascular causes (acute myocardial infarction, heart failure and other) and four due to non-cardiovascular causes (Table 5). Eight patients reported injection-site reactions with one treatment discontinuation. Treatment emergent anti-drug antibodies were identified in five patients (three persistent, two transient) but these were non-neutralising and did not affect the efficacy (Table 6).

Discussion

HeFH remains a challenging condition to manage effectively. The safety and efficacy of treatment with alirocumab in patients

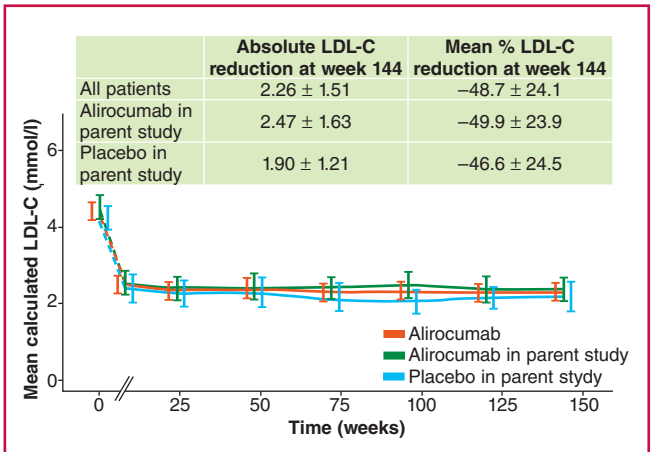


Fig. 2. Reduction in LDL-C levels observed over the 144-week study period, indicating alirocumab during the parent study, placebo during the parent study or entire ODYSSEY OLE cohort, irrespective of treatment stratification in the parent studies. Note that change in LDL-C level from the baseline of the parent study to the start of the OLE study is indicated as dotted lines based on the mITT analysis.

Table 5. Primary cause of deaths as per investigator's reports

Variables	*Placebo in parent study (n = 62)*	*Alirocumab in parent study (n = 105)*	*All (n = 167)*
Death on study, *n* (%)	4 (6.5)	5 (4.8)	9 (5.4)
Any cardiovascular event, *n* (%)	2 (3.2)	3 (2.9)	5 (3.0)
Acute myocardial infarction, *n* (%)	0	2 (1.9)	2 (1.2)
Heart failure or cardiogenic shock, *n* (%)	1 (1.6)	1 (1.0)	2 (1.2)
Other cardiovascular causes, *n* (%)	1 (1.6)	0	1 (0.6)
Non-cardiovascular event, *n* (%)	2 (3.2)	2 (1.9)	4 (2.4)

with HeFH have been reported in previous phase 3 studies.[8-10] However, while these studies were conducted over a period of 78 weeks, the long-term safety of treatment with alirocumab in this patient population had not previously been investigated. The ODYSSEY OLE study provides data on a further 144 weeks of treatment with open-label alirocumab.

The South African arm of the ODYSSEY OLE study confirmed the safety, tolerability and sustained, persistent, long-term reduction of LDL-C levels in South African patients with HeFH. The LDL-C reduction observed in the South African arm of the OLE study at week 144 was 48.7%, mimicking the reported LDL-C reduction in the parent studies as well as the LDL-C reduction observed in the global OLE study (47.9% at week 96).[13]

The global ODYSSEY OLE study enrolled a total of 985 patients diagnosed with HeFH. At baseline, 977 (99.2%) patients were on treatment with statins, while 571 (58.0%) patients

Table 6. Adverse events and safety laboratory values (safety population)

Adverse event	*Placebo in parent study n (%) (n = 62)*	*Alirocumab in parent study n (%) (n = 105)*	*All, n (%) (n = 167)*
Treatment-emergent adverse events (TEAE)	58 (93.5)	98 (93.3)	156 (93.4)
Treatment-emergent serious adverse events	29 (46.8)	30 (28.6)	59 (35.5)
TEAEs leading to death	4 (6.5)	5 (4.8)	9 (5.4)
TEAEs leading to permanent discontinuation	5 (8.1)	9 (8.6)	14 (8.4)
Death	4 (6.5)	5 (4.8)	9 (5.4)
TEAEs occurring in ≥ 5% in either group			
Gastroenteritis	5 (8.1)	12 (11.4)	17 (10.2)
Dental and oral soft tissue infections	4 (6.5)	8 (7.6)	12 (7.2)
Tooth abscess	3 (4.8)	8 (7.6)	11 (6.6)
Bronchitis	6 (9.7)	10 (9.5)	16 (9.6)
Upper respiratory tract infection	8 (12.9)	21 (20.0)	29 (17.4)
Urinary tract infection	9 (14.5)	7 (6.7)	16 (9.6)
Influenza	9 (14.5)	15 (14.3)	24 (14.4)
Viral upper respiratory tract infection	5 (8.1)	9 (8.6)	14 (8.4)
Headache	2 (3.2)	7 (6.7)	9 (5.4)
Angina pectoris	4 (6.5)	4 (3.8)	8 (4.8)
Hypertension	6 (9.7)	5 (4.8)	11 (6.6)
Hiatus hernia	4 (6.5)	1 (1.0)	5 (3.0)
Gastritis	4 (6.5)	6 (5.7)	10 (6.0)
Diarrhoea	2 (3.2)	6 (5.7)	8 (4.8)
Arthralgia	6 (9.7)	10 (9.5)	16 (9.6)
Osteoarthritis	5 (8.1)	4 (3.8)	9 (5.4)
Muscle spasms	3 (4.8)	6 (5.7)	9 (5.4)
Back pain	2 (3.2)	6 (5.7)	8 (4.8)
Pain in extremity	1 (1.6)	7 (6.7)	8 (4.8)
Injection-site reaction	2 (3.2)	6 (5.7)	8 (4.8)
Fatigue	4 (6.5)	1 (1.0)	5 (3.0)
Influenza-like illness	2 (3.2)	7 (6.7)	9 (5.4)

received ezetimibe treatment.[13] In the South African cohort, statin treatment was reported by 143 (85.6%) and ezetimibe treatment by 46 (27.5%) patients. It is not clear how many patients were on combination LMT.

Higher reductions in LDL-C would have been expected if more participants were up-titrated to the maximum dose of alirocumab. A total of 76 patients (54% of the SA cohort) remained on treatment with 75 mg of alirocumab Q2W for the duration of the study, even though up-titration of the dose was allowed at the investigator's discretion.

A greater LDL-C reduction of 61% was reported in the ODYSSEY Long-Term study at week 24.[9] However, all the participants in the active arm of the ODYSSEY Long-Term study received the maximum dose of alirocumab (150 mg every two weeks), as opposed to only 46% of participants receiving the maximum dose of alirocumab in ODYSSEY OLE.

In South Africa the diagnosis of HeFH is based mainly on clinical criteria as per the Simon Broome criteria.[11] or the Dutch Lipid Network criteria with a score > 8.[12] Genetic testing is rarely performed due to cost.

According to the 2017 European Society of Cardiology/ European Atherosclerosis Society guidelines for the use of PCKS9i, HeFH patients should be considered for treatment with PCSK9i in two scenarios: patients on treatment with maximum tolerated doses of statins and/or ezetimibe where LDL-C remains > 4.5 mmol/l, or where additional risk factors are present and LDL-C remains > 3.6 mmol/l.[14]

In the present study, treatment-emergent anti-drug antibodies were identified in five patients during the study but were reported to be non-neutralising. Indeed, sustained LDL-C reduction was observed in all patients over the 144-week study period.

Drug-neutralising anti-drug antibodies were induced by treatment with bococizumab, a humanised antibody containing approximately 3% murine sequence, resulting in attenuated LDL-C reduction.[15] Alirocumab is, however, a fully humanised PCSK9 inhibitor. A review of 10 alirocumab studies has shown that while anti-drug antibodies were observed in approximately 5.1% of patients receiving the active treatment, LDL-C reduction was not attenuated.[16]

Additional adverse effects observed in the study were comparable to those reported in previous studies with alirocumab,[8-10,13] and included injection-site reactions and athralgia. The safety results must be interpreted with caution as the sample size was relatively small, and rare adverse events may not have been detected. Nevertheless, the safety profile of alirocumab, especially related to muscle symptoms, was favourable. This is especially relevant give that statin-associated muscle symptoms and statin intolerance may limit adherence to statins.[17]

An advantage of the ODYSSEY OLE study is that the data collected partially represent real-world evidence of the safety and efficacy of alirocumab: during the study alirocumab was self-administered by patients, LMT and alirocumab doses were adjusted at the investigator's discretion, and study visits were fewer than in previous studies in the ODYSSEY programme.

Conclusion

Results from the South African cohort enrolled in the ODYSSEY OLE study confirm that alirocumab was safe, efficacious and well tolerated in the South African HeFH patients.

All authors were investigators in the study. Sanofi was the sponsor of the study. AvT and PN are employees of Sanofi. Neither AvT nor PN owns stocks in Sanofi. DB has received clinical trial fees, and honoraria for advisory board participation and for speaking from Sanofi. FR has received research grants, honoraria or consulting fees for professional input and/or delivered lectures from Sanofi, Regeneron, Amgen and The Medicines Company.

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Inflammation, the possible link between heart disease and depression

People with heart disease are more likely to suffer from depression, and the opposite is also true. Now, scientists at the University of Cambridge believe they have identified a link between these two conditions: inflammation – the body's response to negative environmental factors, such as stress.

While inflammation is a natural response necessary to fight off infection, chronic inflammation, which may result from psychological stress as well as lifestyle factors such as smoking, excessive alcohol intake, physical inactivity and obesity, is harmful.

The link between heart disease and depression is well documented. People who have a heart attack are at a significantly higher risk of experiencing depression. Yet scientists have been unable to determine whether this is due to the two conditions sharing common genetic factors or whether shared environmental factors provide the link.

'It is possible that heart disease and depression share common underlying biological mechanisms, which manifest as two different conditions in two different organs, the cardiovascular system and the brain,' says Dr Golam Khandaker, a Wellcome Trust intermediate clinical fellow at the University of Cambridge. 'Our work suggests that inflammation could be a shared mechanism for these conditions.'

Khandaker and colleague Dr Stephen Burgess led a team of researchers from Cambridge who examined this link by studying data relating to almost 370 000 middle-aged participants of UK Biobank. First, the team looked at whether family history of coronary heart disease was associated with risk of major depression. They found that people who reported at least one parent having died of heart disease were 20% more likely to develop depression at some point in their life.

Next, the researchers calculated a genetic risk score for coronary heart disease, a measure of the contribution made by the various genes known to increase the risk of heart disease. Heart disease is a so-called 'polygenic' disease – in other words, it is caused not by a single genetic variant, but rather by a large number of genes, each increasing an individual's chances of developing heart disease by a small amount. Unlike for family history, however, the researchers found no strong association between the genetic predisposition for heart disease and the likelihood of experiencing depression.

Together, these results suggest that the link between heart disease and depression cannot be explained by a common genetic predisposition to the two diseases. Instead, it implies that something about an individual's environment, such as the risk factors he/she is exposed to, not only increases the risk of heart disease, but at the same time increases the risk of depression.

This finding was given further support by the next stage of the team's research. They used a technique known as Mendelian randomisation to investigate 15 biomarkers – biological 'red flags' – associated with increased risk of coronary heart disease. Mendelian randomisation is a statistical technique that allows researchers to rule out the influence of factors that otherwise confuse, or confound, a study, such as social status. Of these common biomarkers, they found that triglycerides and the inflammation-related proteins interleukin-6 (IL-6) and C-reactive protein (CRP) were also risk factors for depression.

Both IL-6 and CRP are inflammatory markers that are produced in response to damaging stimuli, such as infection, stress or smoking. Studies by Khandaker and others have previously shown that people with elevated levels of IL-6 and CRP in the blood are more prone to develop depression, and that levels of these biomarkers are high in some patients during acute depressive episodes. Elevated markers of inflammation are also seen in people with treatment-resistant depression. This has raised the prospect that anti-inflammatory drugs might be used to treat some patients with depression.

Khandaker is currently involved in a clinical trial to test tocilizumab, an anti-inflammatory drug used for the treatment of rheumatoid arthritis that inhibits IL-6, to see if reducing inflammation leads to improvement in mood and cognitive function in patients with depression.

While the link between triglycerides and coronary heart disease is well documented, it is not clear why they, too, should contribute to depression. The link is unlikely to be related to obesity, for example, as this study has found no evidence for a causal link between body mass index and depression.

'Although we don't know what the shared mechanisms between these diseases are, we now have clues to work with that point towards the involvement of the immune system,' says Burgess. 'Identifying genetic variants that regulate modifiable risk factors helps to find what is actually driving disease risk.'

Dr Sophie Dix, director of research at MQ, says: 'This study adds important new insight into the emergence and risk of depression, a significantly under-researched area. Taking a holistic view of a person's health, such as looking at heart disease and depression together, enables us to understand how factors like traumatic experiences and the environment impact on both our physical and mental health.

'This research shows clearly the shared biological changes that are involved. This not only opens opportunities for earlier diagnosis, but also creates a solid foundation for exploring new treatments or using existing treatments differently. We need to stop thinking about mental and physical health in isolation and continue this example of bringing sciences together to create real change.'

Source: Medical Brief 2019

Clinical outcome of intracoronary versus intravenous high-dose bolus administration of tirofiban in diabetic patients undergoing primary percutaneous coronary intervention

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Abstract

Background: Previous trials remain inconsistent regarding the advantages and hazards related to intracoronary (IC) compared with intravenous (IV) administration of thrombolytics. We aimed to evaluate the safety and effectiveness of IC versus IV tirofiban administration in diabetic patients (DM) with acute ST-segment elevation myocardial infarction (STEMI) during primary percutaneous coronary intervention (PCI).

Methods: This trial included 95 patients who were randomised to high-dose bolus plus a maintenance dose of tirofiban administered either IV or IC. The groups were compared for the incidence of composite major adverse cardiac events (MACE) at 30 days. Levels of cardiac markers were recorded pre- and post-intervention for myocardial perfusion.

Results: The MACE were not different between the groups, but post-procedure myocardial blush grade (MBG) 3 and thrombolysis in myocardial infarction (TIMI) 3 flow were significant in the IC group (p = 0.45, 0.21, respectively), favouring the IC strategy. Peak values of both creatine kinase-muscle/brain (CK-MB) and high-sensitivity troponin T (hs-TnT) were significantly lower in the IC group (155.68 ± 121, 4291 ± 334 ng/dl) versus the IV group (192.4 ± 86, 5342 ± 286 ng/dl) (p = 0.021, p = 0.035, respectively). The peak value was significantly lower in the IC group than the IV group in terms of ST-segment resolution and 30-day left ventricular ejection fraction (LVEF) (p = 0.016 and 0.023, respectively).

Conclusion: Thirty days post PCI, IC tirofiban was more efficient in ameliorating blood flow in the coronary arteries and myocardial tissue perfusion in DM patients after STEMI despite bleeding events, and MACE rates showed no significant difference between the groups. The IC group showed better improvement in LVEF.

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Impaired glucose metabolism accelerates the risk of arteriosclerosis and 80% of patients with diabetes mellitus (DM) die from cardiovascular diseases.[1] Previous trials have demonstrated a positive correlation between hyperglycaemia and the occurrence of heart failure, arrhythmia and other complications. Moreover, hyperglycaemia significantly increased the mortality rate of patients with diabetes complicated by myocardial infarction (MI).[2]

Acute occlusion of the major epicardial coronary artery usually leads to acute ST-segment elevation myocardial infarction (STEMI). Successful recanalisation and patency of the occluded vessels with percutaneous coronary intervention (PCI) or fibrinolytics diminishes the infarction size, saves the function of the ventricle and decreases morbidity and mortality rates.[3,4]

Several consequences, such as no reflow and slow flow, associated with more major adverse cardiac events (MACE), complications and high mortality rates have been observed in patients with DM complicated by acute MI (AMI) and undergoing primary PCI.[5,6] Platelet aggregation into the distal microvasculature or thrombus embolisation immediately after successful intervention impairs microvascular flow. Administration of glycoprotein IIb/IIIa inhibitors (GPI) and many catheter-based strategies have been attempted to overcome this phenomenon.[7,8]

American guidelines recommend tirofiban during PCI in patients with STEMI for high burden of thrombus or patients who received inadequate loading of P2Y12 inhibitors, and in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) and high risk.[9,10] European guidelines recommend tirofiban use in PCI for bailout situations if there is angiographic evidence of massive thrombus, slow or no reflow, or thrombotic complications.[11,12]

This trial attempted to assess whether intracoronary (IC) administration of high-dose bolus plus a maintenance-dose infusion of tirofiban would lead to better efficacy and safety and enhance clinical outcomes better than the standard intravenous (IV) bolus-plus-infusion regimen during PCI for diabetic patients with acute STEMI.

Methods

The study evaluated 95 consecutive diabetic patients undergoing primary PCI for STEMI. Patients were recruited to receive 25 µg/kg tirofiban bolus plus a maintenance dose of 0.15 µg/kg/min infusion either IV (group A: $n = 50$) or IC (group B: $n = 45$) for 24 hours.

We included adult patients between 18 and 75 years with a clinical presentation of STEMI and specific ECG criteria in the form of ST-segment elevation ≥ 1 mm in two or more contiguous leads, except V2 and V3 had to be ≥ 1.5 mm in females, ST-segment elevation ≥ 2.5 mm in males less than 40 years or ≥ 2 mm in males more than 40 years, or the presence of new-onset or presumed new left bundle branch block.[13]

The institutional ethics committee approved the study and all patients signed informed consent.

Patients with marked uncontrolled hypertension (≥ 180/110 mmHg), rescue PCI and emergency coronary artery bypass grafting were excluded. Other exclusion criteria included patients presenting with cardiogenic shock, severe liver or kidney failure, bleeding diathesis, hypersensitivity or thrombocytopaenia with tirofiban, platelets < 150 000 cells/mm^3, active internal bleeding, history of ischaemic or haemorrhagic stroke within the last 30 days, atrioventricular malformation or aneurysm, neoplastic aortic dissection, acute pericarditis, haemorrhagic retinopathy and chronic haemodialysis.

Before the intervention all patients were treated with acetylsalicylic acid (300 mg) and clopidogrel (600 mg). After securing vascular access through the right femoral or radial arteries, a total of 70–100 IU/kg unfractionated heparin IV bolus was given, then an additional weight-adjusted unfractionated heparin was given to achieve approximately 250 seconds of activated clotting time (ACT).

In both groups, a bolus of 25 µg/kg of tirofiban was given immediately after the guidewire crossed the lesion successfully and antegrade flow was restored, aiming to secure maximum concentration of the drug at the culprit lesion site and distal microvascular bed. A bolus dose of tirofiban was given through the guiding catheter in the infarct-related artery (IRA) at 30 seconds in the IC group. Maintenance IV tirofiban of 0.15 µg/kg/min for 18 hours was started in both groups after the bolus dose. An aspiration thrombectomy catheter was used if necessary and, finally, a suitable drug-eluting stent (FDA approved) was employed in the IRA in all patients.

Acetylsalicylic acid, a P2Y12 inhibitor (clopidogrel 75 mg), a high-intensity statin, beta-blocker and an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker were prescribed as per the guidelines. When the activated clotting time (ACT) was < 160 seconds and/or four hours after anticoagulation, the vascular sheath was removed by manual compression.

The time to reperfusion was recorded from the onset of chest pain until the visualisation of at least thrombolysis in myocardial infarction (TIMI) 2 flow in the IRA during PCI. Before and after coronary intervention, TIMI flow grades[14] and myocardial blush grade (MBG)[15] were evaluated blindly by two interventional cardiologists. For evaluation of left ventricular ejection fraction (LVEF), the biplane modified Simpson's method was used 48 hours after PCI and then again after 30 days.

The groups were compared for TIMI flow grades before and after the intervention, and MBG, maximum C-reactive protein (CRP) level, peak levels of both high-sensitivity troponin T (hs-TnT) and CK-MB, time to peak for hs-TnT and CK-MB, time to 50% ST resolution, and composite MACE rates at 30 days were recorded. Safety endpoints such as significant and minor bleeding and thrombocytopenia were noted.

According to the dye density, the MBG score was classified as grade 3 = normal myocardial contrast density compared to contrast density of a contra- or ipsilateral non-IRA, 2 = moderate myocardial blush where contrast density is less than that obtained from a contra- or ipsilateral non-IRA, 1 = minimal myocardial blush or contrast density, and grade 0 = no myocardial blush.[16]

MACE[17] included cardiovascular death, recurrent myocardial infarction, stent thrombosis or target vessel revascularisation in hospitalisation at one month. Thrombocytopenia was defined as platelet count < 100 000 cells/mm^3.[16] Intracranial haemorrhage and decrease in haemoglobin concentration ≥ 5 g/dl were considered as major bleeding. Minor bleeding was defined as 10 to 15% decrease in haematocrit, blood loss with 3 to 5 g/dl decrease in haemoglobin concentration, or ≥ 4 g/dl decrease in haemoglobin concentration with no observed blood loss.[18]

Statistical analysis

Patients' data were collected, revised and analysed using the statistical package for social sciences (SPSS) version 25.0 for windows (IBM Corp, Armonk, NY, USA). Data are presented as mean ± standard deviation (SD), frequency and percentage. Categorical variables were compared using the chi-squared (χ^2) test. Continuous variables were compared with the Student's *t*-test (two-tailed) and one-way ANOVA test for parametric data with Bonferroni *post hoc* test to detect differences between subgroups. The level of significance was accepted if the *p*-value was < 0.05.

Results

The two groups showed no statistically significant differences in cardiovascular risk factors, baseline characteristics or medication (Table 1). The mean age was 58.5 ± 10.18 years in the IV group and 55.90 ± 11.66 years in the IC group. The groups showed no significant differences in baseline level of glycated haemoglobin (HbA_{1c}) ($p = 0.08$), onset-to-balloon and door-to-balloon times ($p = 0.08$, 0.3, respectively). Killip class frequency > 1 was 18% in group A (IV) and 24% in group B (IC) ($p = 0.33$) (Table 1).

Peak CK-MB value was significantly lower in the IC group than in the IV group (155.68 ± 121, 192.4 ± 86 U/l respectively) ($p = 0.021$). Peak hs-TnT value was significantly lower in the IC group than in the IV group (4291 ± 334, 5342 ± 286 ng/dl; $p = 0.035$). The percentage of patients with 50% resolution of ST-segment was significantly higher in the IC group than in the IV group ($p = 0.016$) (Fig. 1). The maximum CRP level, peak and time to peak of both CK-MB and hs-TnT showed statistically significant differences, as shown in Table 2. There was no significant difference in LVEF between the groups 48 hours after PCI ($p = 0.632$), but 30 days after PCI, the average LVEF in the IC group was higher than in the IV group ($p = 0.023$).

Angiographic characteristics of the two groups are presented in Table 3. Post-procedure TIMI 3 flow (Fig. 2) and MBG 3 were significant in the IC group ($p = 0.045$, 0.021, respectively).

Table 1. Baseline characteristics of both groups

Parameters	*Group A (IV)* (n = 50)	*Group B (IC)* (n = 45)	t/χ^2	p-*value*
Age (mean ± SD)	58.56 ± 10.18	55.90 ± 11.66	0.72	0.41
Gender, *n* (%)				
Male	27 (54)	23 (51.1)	0.69	0.49
Female	23 (46)	22 (48.9)		
Body mass index (kg/m²) (mean + SD)	26.1 ± 6.5	25.4 ± 8.2	0.1	0.78
Smoking, *n* (%)	34 (68)	31 (68.8)	0.69	0.48
Hypertension, *n* (%)	20 (40)	19 (42)	0.08	0.78
Family history of coronary artery disease, *n* (%)	9 (18)	7 (15.5)	0.61	0.54
Killip class > 1, *n* (%)	9 (18)	11 (24)	1.025	0.33
Aspirin, *n* (%)	49 (98)	43 (95.5)	0.05	0.87
Clopidogrel, *n* (%)	50 (100)	44 (97.7)	0.84	0.64
Beta-blockers, *n* (%)	41 (82)	39 (86.6)	0.06	0.85
ACEI or ARBs, *n* (%)	39 (78)	36 (80)	0.12	0.79
Statin, *n* (%)	44 (88)	39 (86.6)	0.15	0.73
Warfarin, *n* (%)	3 (6)	1 (2.2)	0.8	0.068
Onset-to-balloon time (min) (mean ± SD)	167 ± 12.4	151 ± 18.3	5.8	0.089
Door-to-balloon time (min) (mean ± SD)	46.8 ± 8.9	44 ± 7.6	1.72	0.38
Fasting glucose (mg/dl) (mean ± SD)	168 ± 29.8	192 ± 46.6	3.64	0.074
Glycated haemoglobin (HbA_{1c}) (mean ± SD)	7.8 ± 2.2	9 ± 1.3	3.1	0.087
Creatinine (mg/dl) (mean ± SD)	1.17 ± 0.41	1.08 ± 0.56	2.56	0.251
Low-density lipoprotein cholesterol (mg/dl) (mean ± SD)	132.6 ± 46	147.09 ± 51	2.79	0.091

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

Comparison between the groups in terms of the culprit vessel affected and multivessel frequency showed no significant differences.

The incidence of MACE and major and minor bleeding during the hospital stay and at follow up are shown in Table 3. Only one patient developed major bleeding due to upper gastrointestinal bleeding. Five patients developed minor bleeding in group A (three patients developed access-site bleeding and two developed haematuria). In group B, one patient developed major bleeding in the lower gastrointestinal system and four developed haematuria.

Table 2. Comparison between the groups regarding cardiac biomarkers and left ventricular ejection fraction

Parameters	*Group A (IV)* (n = 50)	*Group B (IC)* (n = 45)	t	p-*value*
Peak CK-MB (U/l)	192.4 ± 86	155.68 ± 121	6.43	0.021*
Time to peak CK-MB (s)	12.9 ± 5.8	8.96 ± 3.2	11.4	0.001*
Peak hs-TnT (ng/dl)#	5342 ± 286	4291 ± 334	5.9	0.035*
Time to peak hs-TnT (s)	13.5 ± 3.1	9.24 ± 2.8	10.7	0.001*
50% ST-segment resolution (%)	56	77	7.6	0.016*
LVEF at 48 hours (%)	38.6 ± 5.3	41.5 ± 3.2	0.84	0.632
LVEF at 30 days (%)	42.6 ± 4.2	48.2 ± 6.1	6.23	0.023*
Maximum C-reactive protein level (ng/dl)	9.2 ± 2.3	5.7 ± 1.4	6.1	0.026*

#Normal high-sensitivity troponin level up to 14 ng/dl.
CK-MB: creatine kinase-muscle/brain; hs-TnT: high-sensitivity troponin T; LVEF: left ventricular ejection fraction.

Discussion

Diabetic patients usually have microangiopathy and microvascular dysfunction. After restoration of normal blood flow in the coronary arteries, there is still insufficient myocardial tissue reperfusion (i.e. no reflow and slow flow) in up to 30% of patients.[19,20] Higher incidence of re-infarction, heart failure, stroke and death was previously documented in diabetic than in non-diabetic patients.[21]

The main cause of slow flow and no reflow is thrombosis and microvascular embolisation. These microvascular complications are higher in AMI and primary PCI. Visible thrombus in coronary angiography can be removed by a suction catheter, but it was found that 61% of the thrombus was invisible in AMI.[22] Imperfect inhibition of platelet aggregation during PCI may increase the MACE. The use of adjuvant medical drugs such as GPIs considerably decrease the incidence of distal embolisation and thrombotic outcomes in STEMI patients.[23,24]

This study demonstrated that IC tirofiban administered for thrombotic complications or bail-out situations, in addition to loading oral antiplatelets in diabetic patients, was associated with greater reduction of peak hs-TnT, CK-MB levels and ST-segment resolution compared with IV tirofiban. Both regimens showed similar results for MACE and major and minor bleeding events during hospitalisation and after one month of follow up. The risk of bleeding did not appear to increase with

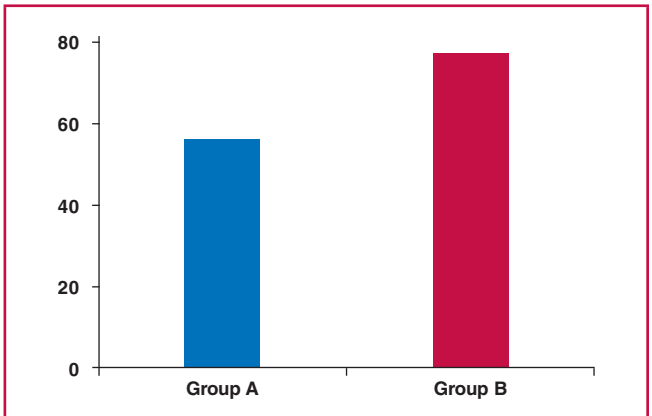

Fig. 1. Frequency of 50% ST-segment resolution in the groups.

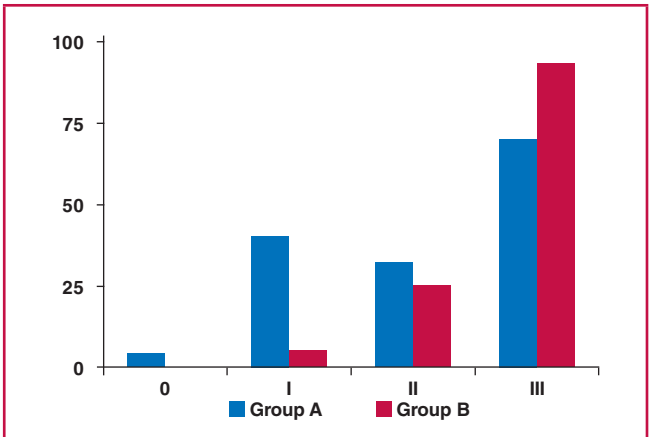

Fig. 2. Comparison of TIMI flow post intervention in the groups.

Table 3. Summary of angiographic characteristics, MACE and bleeding events in both groups

Parameters	*Group A (IV)* (n = *50*)	*Group B (IC)* (n = *45*)	χ^2/t	p-*value*
TIMI 3 flow after procedure, *n* (%)	39 (78)	42 (93)	4.02	0.045*
MBG 3 after procedure	34 (68)	41 (82)	5.34	0.021*
Infarct-related vessel, *n* (%)				
Left anterior descending artery, *n* (%)	30 (60)	25 (55)	0.38	0.72
Circumflex artery, *n* (%)	7 (14)	5 (11.1)	0.072	0.91
Right coronary artery, *n* (%)	10 (20)	13 (28.8)	0.065	0.92
Triple vessels, *n* (%)	3 (6)	2 (4.4)	0.00	1.00
Balloon, *n* (%)	10 (20)	13 (28.8)		0.98
In-hospital MACE, *n* (%)				
In-hospital death, *n* (%)	2 (4)	1 (2.2)	0.00	1.00
In-hospital stroke, *n* (%)	0	0	0.00	1.00
In-hospital re-infarction, *n* (%)	1 (2)	0	0.05	0.993
In-hospital stent thrombosis, *n* (%)	1 (2)	0	0.05	0.993
In-hospital TVR, *n* (%)	0	0	0.00	1.00
1-month MACE, *n* (%)				
1-month death, *n* (%)	1 (2)	0		1.00
1-month stroke, *n* (%)	0	0	0.00	1.00
1-month re-infarction, *n* (%)	1 (2)	1 (2.2)	0.00	1.00
1-month stent thrombosis, *n* (%)	1 (2)	1 (2.2)	0.00	1.00
1-month TVR, *n* (%)	1 (2)	1 (2.2)	0.00	1.00
TIMI major bleeding, *n* (%)	1 (2)	1 (2.2)	0.00	1.00
TIMI minor bleeding, *n* (%)	5 (10)	4 (8.8)	0.02	0.95
Thrombocytopenia, *n* (%)	2 (4)	2 (4.4)	0.00	1.00

TIMI: thrombolysis in myocardial infarction; MBG: myocardial blush grade; MACE: major adverse cardiac events; TVR: target vessel restenosis.

IC administration of tirofiban.

Topol *et al.* showed that tirofiban in comparison with abciximab provided more platelet inhibition in diabetic patients during follow up and helped to prohibit PCI-related ischaemic and thrombotic complications.[25] The theory is to achieve a high drug concentration in the culprit epicardial vessel and small vasculature by administering IC tirofiban during PCI. Compared with IV delivery of tirofiban, IC delivery was associated with greater procedural success (e.g. TIMI grade 3 flow).[26]

Our findings revealed that no reflow and slow flow were effectively reduced and TIMI flow and MBG had better outcomes with IC injection of tirofiban. These results were in concordance with recent studies that proved that IC[27] and intralesional delivery of tirofiban through an aspiration catheter had better myocardial perfusion and fewer complications, even in complex PCI.[28]

Loss of endothelium-dependent vasodilation, inflammatory reaction and platelet-dependent micro-thrombosis are enhanced by hyperglycaemia, thereby aggravating the perfusion disturbance of coronary microcirculation.[29] The mortality rate was much higher in patients when MBG decreased to 0 to 1.[6,30]

To the best of our knowledge, this is the first study to demonstrate short-term outcomes and safety of IC injection of high-dose bolus tirofiban plus a maintenance IV, compared with IV tirofiban in diabetic patients with STEMI. We showed that IC tirofiban resulted in decreased inflammation in MI, which was evidenced by a significant reduction in peak CRP level. Previous studies have reported on the predictive value of CRP in determining the risk of future cardiovascular events.[31,32] Other studies have documented a post-procedure CRP rise in relation to myonecrosis.[33] The efficient inhibition of platelet aggregation by tirofiban led to inhibition of inflammatory mediators.[34]

In spite of no significant differences in bleeding events and MACE rates during the 30-day follow up after PCI, the IC tirofiban group showed an improvement in left ventricular function. However, we need large, long-term, multicentre, randomised trials to assess whether IC injection of tirofiban at the time of primary PCI improves clinical outcome in diabetic patients.

The results of this study have certain limitations. We used non-random selection of patients for IC tirofiban, the patient number was relatively small, and we evaluated IC tirofiban on STEMI but did not compare the effects in NSTE-ACS. Despite including elderly patients in the study, we did not compare major and minor bleeding incidence and platelet level reduction in different-aged populations. A possible improvement in clinical outcome could be observed with longer follow-up periods as left ventricular systolic function was improved.

Conclusion

IC tirofiban improved coronary blood flow and myocardial tissue perfusion effectively in diabetic STEMI patients during primary PCI. Improved LVEF was also observed 30 days post primary PCI. However, bleeding events and MACE rates showed no significant difference between the groups.

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Review Article

Renal denervation: dark past, bright future?

Marshall Heradien, Felix Mahfoud, Doug Hettrick, Paul Brink

Abstract

The purpose of this review is to update the reader on the relevance of autonomic nervous system imbalance in clinical cardiology. Increased sympathetic tone associates with the metabolic syndrome, hypertension and cardiac arrhythmias. With the kidneys playing a pivotal role in increased peripheral resistance, sodium and water retention and other mechanisms, renal denervation (RD) may theoretically restore autonomic imbalance and improve cardiovascular outcomes. Landmark RD trials and novel uses for RD in cardiac arrhythmia management are discussed.

Keywords: autonomic imbalance, hypertension, hypertensive heart disease, atrial fibrillation, renal denervation

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What is autonomic imbalance?

The autonomic nervous system consists of a sympathetic and parasympathetic system. Autonomic imbalance (AI) defines a state of relatively increased sympathetic tone (IST) and/or decreased parasympathetic tone. AI is associated with many disease components including heart failure, atrial fibrillation, obesity and chronic kidney disease.[1-4] Our modern lifestyle of high stress levels, reduced exercise and poor diets rich in salt and carbohydrates undoubtedly fuels both the metabolic syndrome and AI.

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AI and sudden cardiac death

Interestingly, AI is also associated with sudden cardiac death (SCD) during severe emotional stress.[5] Congenital long-QT syndrome also illustrates this association particularly well.[6] Symptomatic mutation carriers typically experience syncope and sometimes SCD during situations associated with IST, such as excitement, swimming or exercise. Conversely, higher resting vagal tone seems to be protective, and anti-sympathetic therapy such as beta-blockers or left cardiac sympathetic denervation (LCSD) are established therapies for this inherited cardiac ion channelopathy.

Another example where AI was associated with and even predicted SCD, came from a prospective cohort of apparently healthy young male French civil servants.[7] Here, Jouven and co-workers used exercise-related heart rate profiles as surrogate markers of cardio-autonomic tone. They found that faster resting heart rate (> 75 bpm), indicative of IST, and slower post-exercise recovery of heart rate (< 25 bpm), indicating reduced parasympathetic tone, were associated with a significantly higher SCD risk later in life.

The kidneys play a central role in autonomic dysfunction

With the kidneys playing a pivotal role in increased peripheral resistance, sodium and water retention and other mechanisms, renal denervation (RD) may theoretically restore autonomic imbalance and improve cardiovascular outcomes.[8] Innovative endovascular techniques provide minimally invasive access to reduce sympathetic brain–kidney cross-talk, which may restore AI and prevent its associated complications.

Renal nerve supply: anatomy and physiology

Anatomical and physiological knowledge of the renal nerve supply supports the hypothesis that RD should lower blood pressure and consequently produce beneficial cardiac effects.[9] The afferent renal nerves, mostly located in the renal pelvis, transmit signals via the dorsal spinal cord to the brain when activated by stretch forces (Fig. 1). Activated centres in the brain include the nucleus tractus solitarius, medulla oblongata and paraventricular hypothalamic nuclei. These signals increase vasopressin and oxytocin release, accompanied by increased activation of efferent sympathetic neurons. These neurons run along paravertebral ganglia and large blood vessels, where they exit to vital organs located in the thoraco-lumbar region. In the thorax, sympathetic nerves terminate in the sino-atrial node, atrio-ventricular node and ventricles. Here, sympathetic stimulation increases chronotropy, dromotropy and inotropy,

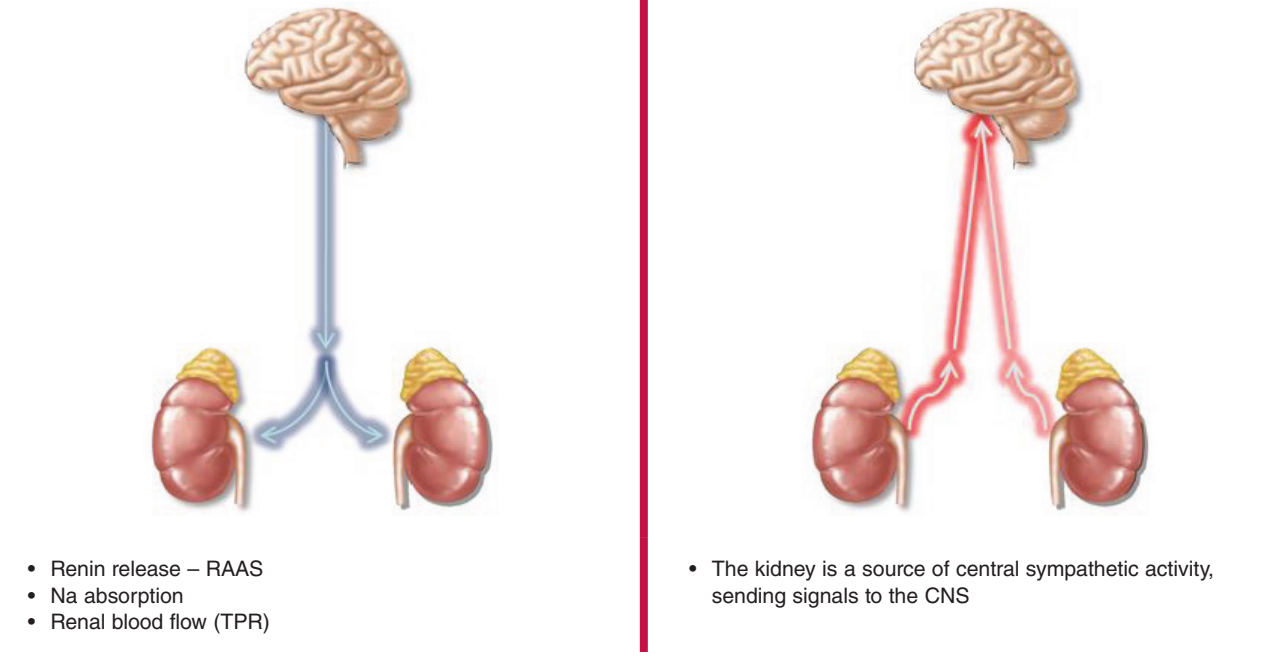

Fig. 1. Renal sympathetic nerves facilitate brain–kidney cross-talk and play a central role in BP control and regulation of autonomic tone (supplied by Medtronic, Inc).

respectively. Cumulatively, these effects increase cardiac output and systolic blood pressure.

In the lumbar region, the efferent sympathetic nerves enter the kidneys via the renal arteries. They arborise alongside the renal artery, running in the vasa vasorum and terminate in the efferent glomerular arteriole (EGA), juxta-glomerular apparatus (JGA) and renal tubules. JGA activation results in renin release, which activates the renin–angiotensin–aldosterone system (RAAS). End-products of RAAS activation, angiotensin II (AT-II) and aldosterone induce vasoconstriction and tubular sodium and water retention, respectively. AT-II constricts the EGA, which raises intra-glomerular pressure and filtration rate. AT-II also increases peripheral resistance, which increases diastolic blood pressure, cardiac afterload and coronary perfusion.

It is almost incomprehensible that mere stretching of the renal pelvis by increased urine production would produce such a cascade of events that result in increased cardiac output, augmented glomerular filtration and subsequent adrenal activation. The primary renal aim would be to restore water and sodium balance acutely. Chronic and inappropriate activation of this system results in hypertension and its sequelae. Although IST is not the only cause of essential hypertension, there is strong evidence that the autonomic nervous system plays a critical role in hypertension pathogenesis and endothelial health.[10,11]

Hypertensive heart disease and cardiac arrhythmia

Uncontrolled hypertension often results in hypertensive heart disease (HTHD), which provides an ideal arrhythmic substrate.[12] Interstitial cardiac fibrosis, promoted by aldosterone secretion, fractionates the depolarising electrical wave front. Left ventricular hypertrophy (LVH) associates with increased myocardial oxygen consumption, and in the presence of concomitant coronary atherosclerosis, the endocardium remains at an increased risk of hypo-perfusion and myocardial death. Often, coronary plaques rupture because of a sudden surge in blood pressure or increased intra-plaque inflammation. IST has been shown to associate with both precipitants.[13] Additionally, in patients with obstructive sleep apnoea, sympathetic surges followed by intense vagal reflexes have been shown to precipitate paroxysmal atrial fibrillation (AF) and associate with nocturnal SCD.[14]

Renal denervation to modulate autonomic activity: human proof-of-principle studies

The hypothesis that denervation of the renal sympathetic nerves should result in blood pressure reduction was successfully tested in clinical trials. In humans, non-selective surgical splanchnicectomy, which includes RD, was frequently performed as primary hypertension (HT) treatment,[15] but common side effects, such as impotence, orthostatic hypotension and incontinence, led to its disappearance from current-day practice. This led to the concept that the efferent nerves in the renal artery adventitia might yield an easily accessible target. The advent of endovascular therapy made access to the renal arteries possible through femoral artery puncture (Fig. 2). Heradien *et al*. recently reported that RD could also be performed via brachial or radial artery puncture.[16] This unique form of RD vascular access eliminates the risk of groin-related hypertensive arterial bleeding and allows same-day hospital discharge.

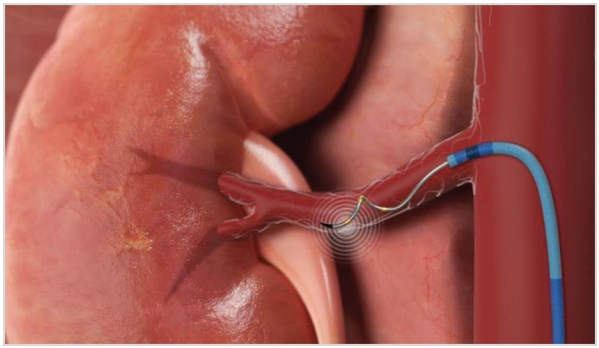

Fig. 2. Renal denervation is accomplished with a quadripolar radiofrequency catheter via arterial puncture. The catheter is advanced over a guidewire into the distal renal artery, the wire is removed and the catheter conforms in a spiral form to make close contact with the vessel wall. Radiofrequency heat energy is then delivered in an attempt to destroy the efferent renal nerves in the vasa vasorum (copyright for figure obtained from Medtronic, Inc).

Landmark RD trials

The landmark endovascular RD trials are often colloquially referred to as the Symplicity HTN Trilogy. The first trial that kindled interest was published a decade ago. SYMPLICITY HTN-1 was a multicentre, non-randomised, safety and proof-of-principle cohort study.[17] Patients with so-called resistant HT, defined as an office blood pressure (BP) ≥ 160/90 mmHg on three drugs, including a diuretic, underwent bilateral RD.[17] Compared to baseline, follow-up office BP was dramatically reduced and the scientific world was sensitised that RD might offer a potential cure for the proverbial 'silent killer'.[18]

SYMPLICITY HTN-2 was the first randomised, controlled trial (RCT) that tested the hypothesis that RD was superior to medical therapy in the management of resistant HT.[19] Again, similarly to SYMPLICITY HTN-1, office systolic BP was reduced with RD by 32 mmHg at the six-month follow up. This trial resulted in an all-time high interest and a flickering hope that RD might add an important new weapon in the fight against HT. Whereas the procedure was registered for use in European countries, the Food and Drug Administration insisted on a further trial before registration in the USA; hence, the SYMPLICITY HTN-3 trial was designed.[20]

SYMPLICITY HTN-3 randomised 535 treatment-resistant hypertensive patients to RD or sham RD. The results were interesting but unexpectedly disappointing. Although both groups had significant office BP reductions at the six-month follow up, RD did not meet the primary efficacy endpoint of the mean difference between groups of 5-mmHg reduction in office systolic blood pressure (SBP). These surprising results brought the 'speeding RD train to a grinding halt'.[21] However, several confounders have been identified that may have contributed to the failure of SYMPLICITY HTN-3.[22]

Despite rigorous trial design and execution, several unaccounted for factors may have contributed to the failure of SYMPLICITY HTN-3 to demonstrate RD efficacy relative to the sham control.[23] These include patient demographics, medication adherence, the Hawthorne effect, the placebo effect, trial conduct, regression to the mean, operator experience and catheter design.

Patient demographics: Unlike previous SYMPLICITY trials, SYMPLICITY HTN-3 also recruited African-American (AA) patients (26% of the prospective cohort). Compared to the non-AA sub-group, AA patients in the sham group had a 9.2-mmHg greater decline in office SBP at six months. This change in sham office SBP was nearly twice as large in AA as non-AA patients. In a *post hoc* analysis, the authors concluded that this unexpected BP reduction in a sham group was likely due to increased post-randomisation medication adherence and that the change after renal denervation was probably not confounded by race.[24]

Although this exploratory report does not provide definitive evidence that the SBP response to RD differed by race, it is generally accepted that hypertensive patients of African ancestry are poor responders to angiotensin converting enzyme (ACE) inhibitor and beta-blocker therapy.[25] This dogma was recently challenged in the Creole study where investigators found that black Africans responded better to perindopril–amlodipine than to perindopril–thiazide combination therapy.[26] Despite these encouraging results that black Africans may respond to ACE inhibitor therapy, it remains to be proven that blacks are poor RD responders.

In the current South African environment, however, racial confounding in science led to the retraction of a controversial article that was recently published.[27] Unfortunate events like these may hamper expedient ethical approval of BP studies investigating different racial responses to antihypertensive treatment.

Many have hypothesised that the beneficial effects of RD may be attenuated in patients with later-stage peripheral artery disease or increased vascular stiffness, which might limit the capacity for reverse vascular remodelling following the procedure. Indeed, several reports indicate that various indices of increased arterial stiffness predict improved BP response following RD.[28-31] Likewise, Mahfoud and colleagues showed in two separate retrospective analyses that patients with isolated systolic hypertension, a course but easily determined identifier of increased arterial stiffness (defined as office SBP > 140 mmHg and DBP < 90 mmHg), had more significant BP drops than patients with combined systolic and diastolic hypertension.[32] For this reason, patients with isolated systolic hypertension were explicitly excluded from the sham controlled RCTs that followed SYMPLICITY HTN-3.

Medication adherence: Although patients were encouraged to continue taking their prescribed medication diligently throughout follow up, urine or blood levels of antihypertensive drugs were not measured. Surprisingly, about 40% of the patients changed their antihypertensive medication regime after randomisation. Furthermore, recent evidence from multiple hypertension trials, including RDN trials, clearly indicates that non-adherence to prescribed medications is common, perhaps greater than 50%, and may vary within patients even during the clinical trial follow-up period.[33]

Such rampant non-adherence may be due to multiple factors, including lack of understanding of the risks and benefits

of hypertension therapy, socio-economic factors limiting drug access, social support, depression and anxiety, regimen complexity and side effects. Taken in context with the significant drop in BP in the sham group, it is reasonable to suspect that unpredictable variable adherence to antihypertensive medication may have impacted on the results of SYMPLICITY HTN-3. This concern led to the design of 'off-medication' trial designs following SYMPLICITY HTN-3. These are discussed below.

Hawthorne effect: This effect describes the adjusted behaviour of trial participants to seemingly please/impress study investigators.[34] Examples of such behaviour include patients taking their medication more diligently, reducing their salt intake and exercising more regularly. It is difficult, if not impossible, to reduce this type of behaviour.

Regression to the mean (RTM): RTM is defined as the tendency for an extreme measurement on one occasion to become less extreme when measured again. This may explain why, unlike previous SYMPLICITY trials, SYMPLICITY HTN-3 showed only a –4.1-mmHg between-group SBP treatment difference. To reduce this niggly statistical phenomenon, statisticians recommended that, rather than a Student's *t*-test, analysis of covariance (ANCOVA) might be a more appropriate test to use in future RDN trials.[35]

Finally, it is essential to note that the potential biases introduced by both the Hawthorne effect and regression to the mean can be addressed by randomisation.

Operator experience and catheter design: In SYMPLICITY HTN-3, 112 operators performed an average of 3.3 procedures per operator.[20] Less than five procedures were performed per site, and more than 50% of the operators performed two or fewer procedures in the trial. Several technical challenges may face the inexperienced operator: difficult intubation with poor guide catheter back-up, accessory polar renal arteries (smaller than the main vessel) that could not be treated, the 'hostile' groin, e.g. morbid obesity and inability to visualise anatomically whether a successful four-quadrant ablation was performed, using a two-dimensional fluoroscopic image. Operators were also instructed to avoid distal renal arteries, but Sakakura *et al.* subsequently discovered that in human cadavers, the renal nerves run closer to the arterial lumen distal to the renal bifurcation than proximally (2.6 mm vs 3.4 mm).[36] These sites, although being typical 'sweet spot targets' for denervation, were therefore missed in most cases. Animal studies have shown that RDN success is very much dependent on distal denervation.[37,38]

The Flex catheter (Medtronic Inc) is a single-point denervation system that uses a proprietary algorithm of retraction, flexion and rotation to focus radiofrequency energy points in recommended anatomical sites of the renal artery. It was challenging to perform enough four-quadrant ablations with the old system but the newer Symplicity Spyral catheter, which is an over-the-wire system, is a safer, more intuitive system that not only associates with more four-quadrant ablations but also enables the operator to safely perform distal ablations without the danger of perforation or dissection. The newer system typically requires less fluoroscopy time with less ionising radiation and lower doses of iodine contrast agent, resulting in better renal function outcomes post-procedurally.

A new generation of sham, controlled RCTs

Recently reported positive results from three new randomised sham, controlled trials might have rekindled interest in RD. All three trials were designed to compensate for the confounding factors identified in SYMPLICITY HTN-3. Although smaller in scope than SYMPLICITY HTN-3, the sham controlled SPYRAL HTN OFF-MED trial tested the hypothesis that RD would reduce BP in the absence of antihypertensive drugs.[39] Patients with milder HT were asked to discontinue their BP medication for at least one month before and during the trial duration. Similar to SYMPLICITY HTN-3, patients were randomised to RD or sham RD. Compliance was checked with urine drug levels throughout the trial. RD was performed by experienced proceduralists, who also denervated the distal renal arteries with a second-generation quadripolar catheter (Symplicity Spyral).

Results were reported at three months and albeit much less than previous trials, showed that RD reduced office and ambulatory BP in hypertensive drug-naïve patients, confirming the proof of concept. Likewise, the sham, controlled SPYRAL HTN ON-MED trial showed similar, if not greater improvements in both office and 24-hour blood pressure six months post-RD in a similar population treated with one to three antihypertensive agents.[40]

Finally, the sham, controlled RADIANCE HTN SOLO trial employed a design quite similar to SPYRAL HTN OFF-MED but using an ultrasound-based catheter denervation system (Otsuka/ReCor Paradise).[41] Interestingly this catheter was not advanced into the distal renal arteries but only into the main vessel. The results after two months showed significant reductions in office and ambulatory BP comparable to the SPYRAL HTN trials.

Together, these trials blew new life into endovascular RD and provided the much-needed hope that RD does indeed lower BP in selected patients when the right technique is used by experienced renal denervationists. Now the world waits with bated breath for the final RD trial that will use the knowledge learned from hard lessons, and hopefully either bury or enthrone RD in its rightful place in HT management.

Types of patients likely to benefit from RD

Three types of patients will likely benefit from RD. The first and most prevalent group are those who are non-adherent to their antihypertensive therapies (AHT). Almost one-third of all hypertensive patients never start with their prescription of antihypertensive drugs when first diagnosed.[42] The variable plasma half-life of AHT also explains why some AHT lack true 24-hour cover and why uncontrolled hypertensive patients experience most of their events during the early morning hours when drug levels reach their nadir. The 'always-on effect' of RD may help to reduce these pharmacological shortcomings.

The second group that may also benefit are those patients with clinical signs of IST, for example a resting heart rate of ≥ 75 bpm in beta-blocker-naïve subjects, patients with non-dipping or during 24-hour ABPM.[7,43] The dipping of blood pressure at night is mediated by reduction of daytime sympathetic tone and increase in nocturnal vagal tone. Finally, the group that will probably benefit most are patients with the metabolic syndrome.[44]

Shortcomings of RD treatment for HT

These can be divided into two subgroups: technical challenges, and patients who will show an inadequate response to RD. The first shortcoming of current RD treatment is that the completeness of RD cannot be accurately assessed. The operator, therefore, has no indication if he has successfully denervated the kidney. Second, since patients with polar renal arteries and challenging renal artery anatomy (aneurysms, renal artery stenosis and calcification) were excluded from trials, there are no data on whether these subgroups will respond to RD. Patients with isolated systolic hypertension will also show less response to RD.[45] RD has not been tested in patients with secondary HT, but it could theoretically reduce BP in patients with inoperable paragangliomas, since RD reduces circulating catecholamine levels.[46] Finally, although RD probably reduces BP, if correctly performed, patients should continue to take their BP medication.

Can future studies address current uncertainties in RD?

Future studies should include an objective method to assess the completeness of RD during the procedure. Non-adherence to AHT and RTM phenomena confound RCTs. These challenges can be reduced by combination AHT (reduced pill burden) and advanced statistical tests.

AF: current management and iatrogenic side effects

Paroxysmal AF, which is a common complication of uncontrolled HT and HTHD, originates from the muscular sleeves inside the pulmonary veins where they enter the left atrium.[47] Current rhythm-control treatment of paroxysmal AF can be accomplished through drugs or pulmonary venous isolation (PVI) techniques. Drug treatment with amiodarone is often life-long, which associates with dangerous side effects, including thyroid dysfunction, corneal deposits, hepatic enzyme abnormalities and irreversible lung fibrosis.

PVI, on the other hand, is performed under general anaesthesia with either hot or cold ablation in an attempt to electrically isolate the pulmonary veins from the left atrium. Hot ablation uses radiofrequency (heat) energy to induce scar tissue around the pulmonary venous ostia. Cold ablation uses liquid nitrogen to freeze the pulmonary venous–atrial junctions. A high cure rate can be achieved with these techniques that require atrial trans-septal puncture. The Fire and Ice trial confirmed that cold ablation is non-inferior to hot ablation.[48] Despite these technological advances, PVI is associated with rare but dangerous side effects, including cardiac perforation, tamponade, phrenic nerve palsy and fatal atrio-oesophageal fistula.

Can RD treat paroxysmal AF?

RD, which has an excellent safety profile, may improve outcomes of catheter ablation in hypertensive patients with AF.[49] Canine studies suggest that RD induced morpho-electrophysiological changes that reduced the AF substrate.[50,51] These include changes in the atrial effective refractory period, P-wave duration, AF cycle length and reduced atrial fibrosis regarding substrate modification. Meta-analyses of human studies have shown that RD was associated with regression of both LVH and left atrial hypertrophy.[52]

Pokushalov and colleagues have also shown in an RCT that RD, when coupled with pulmonary venous isolation as paroxysmal AF treatment, significantly reduced incidental AF during follow up.[53] The trial was criticised for its small sample size and the lack of AF monitoring with an implantable loop recorder. Another small non-randomised trial has shown evidence that RD alone may reduce AF triggers and AF burden in patients with both HT and paroxysmal or persistent AF.[54] Results of a larger prospective trial where RD was used as stand-alone, upstream therapy to prevent AF in patients with HTHD are currently awaited (NCT01990911).[55]

Conclusion

AI plays a vital role in many prevalent cardiac diseases. Restoration of AI provides the promise of upstream modification and prevention of these disease complications. With the kidneys at the proverbial eye of the hypertensive cyclonic storm, RD may provide an alternative treatment for HT and many of its notorious complications, including paroxysmal AF. Results of prospective, randomised, sham, controlled trials are eagerly awaited.

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Cholesterol-cutting injections may cut risk of heart attacks

A new, currently unlicensed drug treatment that works by 'silencing' genes can help to halve levels of low-density lipoprotein (LDL) cholesterol with just two injections per year, according to a study. The findings come from the largest clinical trial to date of the cholesterol-lowering drug inlcisiran, which helps patients to reduce their LDL cholesterol, or so-called 'bad cholesterol'.

In a phase III study of more than 1 600 patients with increased risk of cardiovascular disease and taking statins, researchers found that giving regular but infrequent doses of the drug helped to reduce LDL cholesterol by half on average. Researchers believe the drug could help more patients who are unable to take statins or who fail to take their current cholesterol-lowering medication properly.

Professor Kausik Ray, from Imperial College London School of Public Health and principle investigator of the Orion-11 trial, presented the findings this week during a late-breaking session at the European Society of Cardiology Congress 2019 in Paris. 'The cumulative effects of long-term uncontrolled LDL cholesterol continue to place millions of people at increased cardiovascular risk,' explained Ray. He added that the treatment provided assurance that cholesterol can be lowered 'in a sustained fashion over the long term with an infrequent dosing regimen'.

In the trial, 1 617 patients received infrequent injections of inclisiran (300 mg) over the course of a year – at the start, then three months later, and then every six months.

The new data show that patients taking the treatment had sustained reductions in their cholesterol levels (by an average of 50%) over the course of 18 months, compared to patients on statins and taking a placebo injection. In addition, the treatment was shown to be safe over the period, with few adverse events. The findings will now be submitted to a peer-reviewed journal, where the full study findings, including limitations, will be published.

Currently, millions of patients in the UK are eligible to take cholesterol-lowering medications, such as statins, every day to reduce their LDL cholesterol levels, and reduce their long-term risk of cardiovascular disease. But many patients may not take their medication as advised – taking it infrequently or failing to take it at all – meaning the treatment is not as effective due to poor adherence.

To tackle the problem of poor patient adherence, scientists are exploring new classes of longer-lasting treatments that could be delivered less frequently, but maintain the therapeutic effect of daily medication. One of these drugs is the PCSK9 inhibitors, part of a class of drugs called RNA interference therapies (siRNA). These treatments target key proteins, effectively silencing the genes that produce it.

The PCSK9 protein breaks down receptors on the surface of liver cells that help to remove LDL cholesterol from the blood. But short fragments of RNA – the molecule that carries information from the genes to the cell's protein-making machinery – can be used to target and 'silence' the gene that encodes the protein, stopping PCSK9 from being made and so stopping the receptors on the cells from being broken down. The result is a sustained reduction in cholesterol levels.

Inclisiran is not currently available in the UK and needs to be approved by the UK regulator before it could be made available on the NHS. However, the latest findings add to growing evidence that shows that the treatment is safe and effective in patients. Ray added: 'This is a ground-breaking new approach for preventing atherosclerotic cardiovascular disease, with exciting implications at a population health level.'

Source: Medical Brief 2019

Workshop at P5 Africa conference

Familial hypercholesterolaemia workshop for leveraging point-of-care testing and personalised medicine in association with the Lipid and Atherosclerosis Society of Southern Africa

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Abstract

Familial hypercholesterolaemia (FH) is a common autosomal dominantly inherited disorder in which impaired clearance of plasma low-density lipoprotein cholesterol causes premature atherosclerotic vascular disease and tendon xanthomata. This workshop aimed to consolidate information on the diagnosis and management of FH in South Africa. The genetic causes include mutations in the LDL receptor, apolipoprotein B100 and proprotein convertase subtilisin/kexin type 9 (PCSK9). Additionally, the concatenation of multiple gene variants can result in polygenic FH.

Therapeutic measures include a healthy lifestyle, statins and cholesterol-absorption inhibitors that will achieve control of the dyslipidaemia in the majority of cases. The recently introduced monoclonal antibodies to PCSK9 can improve achievement of target concentration in severe cases.

FH is present in all sectors of the South African population but there is sparse documentation in the indigenous African populations. FH should be actively sought, diagnosed and treated with judicious pharmacotherapy and screening of relatives.

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This article summarises the presentations and discussion at a workshop on familial hypercholesterolaemia (FH) at the P5 Africa conference for leveraging point-of-care testing and personalised medicine to advance healthcare, held in Newlands, Cape Town, on 24 March 2016. The purpose of this workshop was to summarise the experience in South Africa and to provide an update on recent developments in FH in general, and in particular, the additional availability of monoclonal antibodies that neutralise proprotein convertase subtilisin/kexin type 9 (PCSK9). The importance of recognising and treating FH and what needs to be done in the future was discussed. Only the most pertinent references are supplied.

FH was recognised as a clinical entity with autosomal dominant inheritance in 1938 by Müller.[1] The underlying cause for the severe elevation of plasma low-density lipoprotein cholesterol (LDL-C) was unravelled through studying homozygotes for FH by Brown and Goldstein whose Nobel Prize celebration[2] indicated that the error is at the LDL receptor. The underlying mechanism is therefore defective clearance of LDL-C.

The high prevalence of FH was recognised through the host of homozygous hypercholesterolaemia patients of Afrikaner (mostly European) ancestry in Johannesburg,[3] and research in South Africa exposed the underlying genetic mutations.[4] The lifelong severe LDL hypercholesterolaemia of heterozygous FH confers premature heart disease: typically in the middle of the fifth decade of life for men,[5] and much earlier in homozygous FH. [2]

Effective treatment became available with the advent of hydroxy-methylglutaryl coenzyme A reductase inhibitors, now referred to as statins, and the improvement in the prognosis is evident, with an overall risk reduction of 76% on statins before the advent of high doses.[6] While bile acid sequestrants have been available since the middle of the previous century, ezetimibe[7] has replaced these as second choice in FH because the newer agent is better tolerated.

The workshop had a series of presentations in a progression from laboratory findings to clinical experience, a discussion on how single-nucleotide variants (SNV) could culminate in a similar state, and treatment. The relevance of FH to a previously poorly studied subgroup of the South African population was indicated before a discussion and formulation of recommendations.

Laboratory diagnosis of FH (Prof MJ Kotze)

The central issue of a raised plasma LDL-C concentration was indicated, along with the genes that are responsible for this metabolic derangement. An autosomal dominant pattern of inheritance relates to mutations in the LDL receptor, apolipoprotein B100 (the ligand for the LDL receptor) and PCSK9. This latter protein, in gain-of-function mutations, results in greater degradation of LDL receptors. An autosomal recessive form of LDL hypercholesterolaemia occurs with mutations in the LDL receptor adaptor protein 1 (*LDLRAP1*) gene. Whereas the preceding disorders are monogenic, it is also possible that several mutations with relatively low impact on LDL-C concentration can together result in LDL hypercholesterolaemia in the range seen with the monogenic disorders.

In South Africa, three mutations were identified in the LDL receptor in the Afrikaner population: in decreasing prevalence, designated Afrikaner 1 (D206E), Afrikaner 2 (V408M) and Afrikaner 3 (D154N). This meant that only a few mutations needed to be sought specifically to confirm the disorder at a genetic level after a clinical diagnosis. This was applied to the diagnosis in children and even to prenatal diagnosis when the diagnosis of homozygous FH could be considered for termination of pregnancy. The polymerase chain reaction (PCR) has made it possible for primers to amplify a selected series of nucleotides of interest in a given gene, where after changes could be identified.

The techniques used ranged from Sanger sequencing that demonstrates a different nucleotide in the chain of nucleotides, through restriction-length polymorphism where a change of nucleotides either creates or abrogates the cutting site for a sequence-specific nucleotide, or by amplification-resistance mutations where an alteration in nucleotide sequence does not hybridise with a primer that initiates amplification in the PCR. Such investigations revealed a three-nucleotide deletion in a Pedi patient, a six-nucleotide deletion in other patients of indigenous African ancestry, a mutation in patients of Indian ancestry, and several mutations in patients of mixed ancestry. A reverse hybridisation strip assay was designed for founder mutations.

There are several reasons for making a precise genetic diagnosis. Not only is the clinical diagnosis confirmed but cascade screening is more accurate. New genes could be discovered when known genes in LDL hypercholesterolaemia are excluded – this led to the discovery of a locus on chromosome 1, which was later identified as the gene for PCSK9. Genetic studies can also determine genes that modulate FH, including interactions with environmental factors,[8] as well as finding polygenic causes for FH. A polygenic cause for FH was investigated in an Afrikaner family suspected of having FH. After exclusion of the common three LDL receptor (*LDLR*) mutations and a complete sequence of the *LDLR*, whole-exome sequencing (WES) was performed. None of the four above-mentioned genes was implicated as the cause of FH by WES.

The Global Lipid Genetic Consortium (GLGC) six-SNV panel for polygenic hypercholesterolaemia includes the following genes: *APOE* (E2 and E4), *ABCG8*, *APOB*, *CELSR2* and *LDLR*. This investigation did not meet the criteria for making the diagnosis of FH and indicates that not all causes of hypercholesterolaemia can be ascertained by currently known genes. As indicated in Fig. 1, the extension of screening to the 12-nucleotide gene score in a pedigree suspected of FH showed an incremental gene score that may be responsible for hypercholesterolaemia.

Genetics of heterozygous FH in Cape Town (Prof AD Marais)

The genetic investigation of FH over more than 20 years at a referral hospital lipid clinic was reported. The heterozygous FH phenotype was defined as definite if a tendon xanthoma was present, and probable if there was LDL hypercholesterolaemia > 5 mmol/l and a dominant pattern of inheritance of premature heart disease and/or hypercholesterolaemia in the family of the index case. The heterozygous phenotype of LDL hypercholesterolaemia, tendon xanthomata and ischaemic heart disease after the age of 25 years was contrasted with the homozygous FH phenotype in which LDL hypercholesterolaemia exceeds 12 mmol/l, tendon and cutaneous xanthomata sets in during childhood and ischaemic heart disease mostly occurs before the age of 25 years when no intervention is done. The heterozygous FH phenotype includes the genes already mentioned but in the experience of the clinic, also homozygotes for sitosterolaemia (a rare autosomal recessive disorder).

Polygenic FH was not specifically investigated in Cape Town but is a consideration in the light of recent experience. The homozygous FH phenotype was attributable to two LDL receptor defects while it was stressed that experience with homozygous apolipoprotein B100 or PCSK9 was limited. Although also manifesting dose-dependent effects, the latter two causes of the homozygous FH phenotype may be somewhat milder; this also appears to be the case for autosomal recessive hypercholesterolaemia due to *LDLRAP1* mutations. Sitosterolaemia mostly presents as the homozygous FH phenotype but may be milder if the diet is low in cholesterol and plant sterols.

The Medical Research Council (MRC) of South Africa contributed towards research in FH after full evaluation of patients referred with severe hypercholesterolaemia. Not only were the history, family tree and physical findings carefully assessed, but secondary causes were specifically excluded and electrophoresis confirmed that the hypercholesterolaemia was due to elevations of LDL-C. Consent for research was obtained. The known LDL receptor mutations were first sought before this gene was explored exon by exon. Assessment for large-fragment insertions and deletions was not available although some regions were examined. Hereafter exons 26 and 29 of apolipoprotein B were explored for mutations that disrupt ligand function. *PCSK9* was then explored exon by exon.

The systematic approach was done for the first 993 unrelated patients with FH but hereafter the commonest mutations were performed in new patients. The original methods were PCR with restriction digests or single-strand conformational polymorphism but in the past decade the introduction of high-

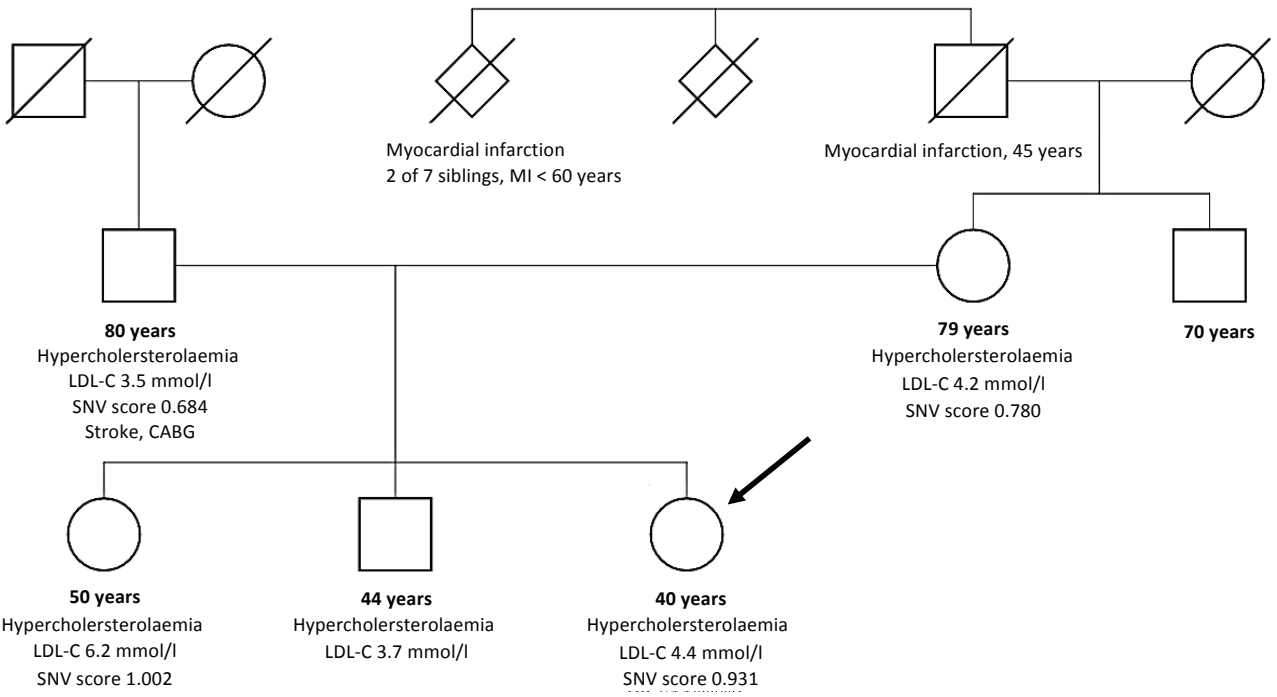

Fig. 1. Pedigree of an Afrikaner family, with a clinical diagnosis of FH, subjected to whole-exome sequencing (WES), after exclusion of the common three LDL receptor mutations (D154N, D206E, V408M) in the index case. The LDLR studies were combined with APOE genotyping.[8] WES confirmed the presence of the low-penetrance APOE e-4 allele (rs429358) in the father and sister, who shares APOB rs1367117 with the index case, as inherited from their mother. The sister tested positive for all four GLGC risk alleles detectable by WES while the index case had only three and a somewhat milder LDL-C level. Subsequent to the congress, the 12 SNP polygenic LDL-C genotype score was found to be higher in the index case (0.931) and sister (1.002) compared to the mother (0.78) and father (0.684), as a result of the contribution of both parents.

resolution melting has significantly improved the investigation for mutations.

The patient population meeting the phenotypic criteria for FH comprised indigenous Africans (< 1%), subjects of Indian ancestry (1%) and mixed ancestry (45%), and whites (53%). In all, 2 200 patients with FH have been genotyped to detect mutations in exons 4, 7, 8 and 9 of the LDL receptor. The proportion of FH patients in whom pathogenic mutations were identified is 57%, of which 96% was in the LDL receptor, 3% in apolipoprotein B and 1% in PCSK9. In all there were 87 mutations in the LDL receptor gene, four in apolipoprotein B and four in PCSK9 but some novel mutations have not been resolved. The 10 commonest mutations in the LDL receptor were in exons 4, 7, 8 and 9: D206E, V408M, D154N, D200G, del197, G361V, C356Y, R329X and F382S, and a splice-site mutation at c.941-4G>A.

Several observations were made about possible founder or regional predelictions for mutations. In the Afrikaner, additional mutations were identified beyond the original three mutations. Certain mutations predominated in persons of Jewish and Indian (Gujerat) origin. The six commonest mutations in the LDL receptor accounted for > 90% of the first 10 mutations (Table 1), and below this the numbers are low for each of the remaining mutations (< 1% of cohort of identified genotypes).

The importance of recognition of the FH phenotype was stressed as this has a high and remediable risk of coronary artery disease with a special need for testing the family owing to the dominant inheritance of the monogenic causes. A genetic diagnosis is vital in certain settings, such as in counselling heritability in pregnancy planning and borderline cases of hypercholesterolaemia. Genotype–phenotype correlations are of interest as well as genes aggravating or ameliorating the outcome. Special clinics for clinical and laboratory evaluation are important until lipidological skills are improved at undergraduate and

Table 1. The commonest LDL receptor mutations in the FH phenotype at a Cape Town lipid clinic. The Afrikaner LDL receptor defects predominated and explain almost 80% of those with an identifiable defect in this gene. Testing for mutations in three exons identified the majority of the subjects with mutations.

Mutations	*Number*	*Percent*
D206E*	519	50.1
V408M#	239	23.1
D154N*	63	6.1
D200G*	53	5.1
Del197*	45	4.3
G361V$	32	3.1
C356Y$	25	2.4
R329X†	22	2.1
F382S#	19	1.8
c.941-4G>A†	19	1.8
E207K*	13	1.3

(…87 mutations)
Patients with successful genotype: 1 196.
Total with heterozygous FH phenotype: 2 200.
*Exon 4 (5), †exon 7 (2), $exon 8 (2), #exon 9 (2).

specialist level as severe disorders such as phytosterolaemia may be overlooked. A register for FH may enhance support for treatment and allow efficient introduction of new treatment strategies.

Genotype to phenotype in FH (Prof SE Humphries)

According to many recent guidelines on the identification and management of FH,[9] all patients with a clinical diagnosis of FH ought to be investigated for the presence of a pathogenic mutation in the genes known to cause FH. The purpose of the genetic testing is not only for confirmation of the diagnosis but also to support cascade testing of the family. Ideally there should be a genetic diagnosis together with a phenotypic description by LDL-C concentration. There is strong evidence that LDL-C concentration on its own does not accurately discriminate between affected and unaffected family members of patients with FH;[10] and accuracy worsens with age, with an unacceptably high rate of false-positive and false-negative diagnoses based on measuring LDL-C concentration. Since half of the offspring and siblings of an index case are expected to inherit the condition, genetic diagnosis is preferred because it can unambiguously identify carriers of the monogenic causes of FH who can then be offered early and effective lipid-lowering treatment along with lifestyle advice.

In patients referred to the lipid clinic with a clinical diagnosis of FH, an FH-causing mutation can only be found in about 50% of the cases in the UK. Talmud *et al.*[11] therefore examined the hypothesis that, despite small effects individually on LDL-C concentration, inheritance of a larger-than-average number of common LDL-C-raising variants in the genes for the LDL receptor, apolipoprotein B, PCSK9, apolipoprotein E and several others, could in combination produce a similar degree of hypercholesterolaemia to FH.[11] At first, 12 variants were used in the identification as indicated in Fig. 2 but this was simplified to include only the six variants having the largest effect.[12] The polygenic cause appears to explain at least 80% of the FH patients in whom no monogenic cause could be found. The same common variants also significantly modify the phenotype of monogenic FH patients.

Patients with LDL hypercholesterolaemia ascribed to a polygenic cause were slightly older and had higher plasma triglyceride levels and the LDL-C concentration was a little lower.[12] Furthermore, such patients had a lower degree of atherosclerosis in their carotid arteries as determined by ultrasound that measured an increased carotid intima–media thickness. This is presumed to be due to later onset of the influence of the polymorphic genes in contrast to the higher level of LDL-C since birth in patients with monogenic FH.

The recognition of polygenic FH is important as it can cut short extensive and expensive genetic screening in the context of diagnosing patients, and allows the scarce resources of nurses and lipid clinic doctors to focus on monogenic families and to offer cascade testing and maximum lipid-lowering treatment. In subjects with a polygenic cause, cascade testing will be less cost effective and the patients themselves can be more easily treated in general practice. The approach to genetic testing is outlined in Fig. 3.

Treatment of FH (Prof FJ Raal)

Worldwide, it is estimated that one baby is born with FH every minute and should be treated to reduce the high risk of cardiovascular disease. This risk is estimated to be more than 80-fold for persons in the fourth decade of life when

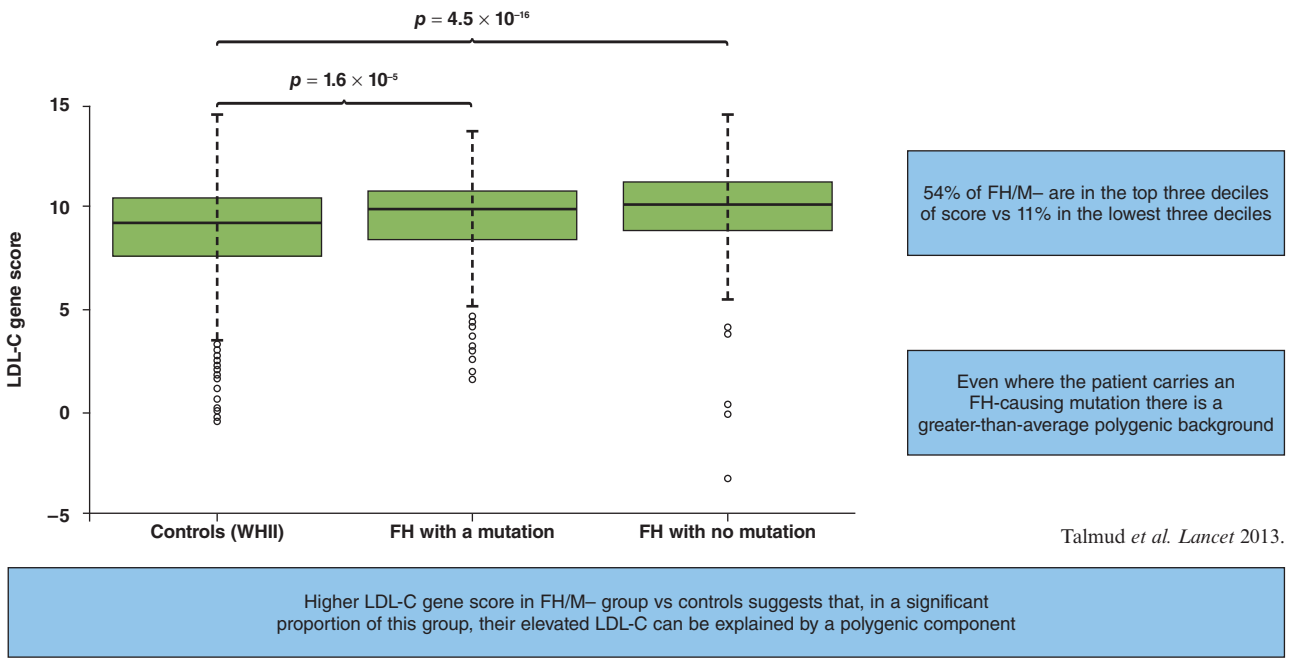

Fig. 2. A comparison of the gene score for polygenic FH between control, monogene-negative and polygene FH.

matched for other risk factors with their peers.[13] The impact of plasma LDL-C on arterial disease is related to the amount of exposure, a function of concentration and time.[14] Statins significantly improve the outcome in heterozygous FH,[6] and even in homozygous FH, where their impact on LDL-C reduction is less.[15] The addition of ezetimibe to statins results in a significant further reduction in LDL-C concentration.

Other strategies to lower LDL-C have been researched. Some drugs such as squalene synthetase inhibitors and thyromimetics that influence the production of cholesterol and LDL receptor expression, respectively, have been discontinued owing to adverse effects. Limiting the production of apolipoprotein B by antisense oligonucleotides had a significant LDL-C-lowering effect in homozygous FH[16] and therefore could be of benefit in heterozygous FH not controlled by more conventional therapy. Lomitapide, an inhibitor of microsomal triacylglycerol transfer protein, also limits lipoprotein production but has not yet been marketed in South Africa. It affects both the liver and the intestine and can cause significant hepatic steatosis. The management algorithm is indicated in Fig. 4 and include the use of older drugs such as niacin and fibrates with lesser impact.

The powerful effect of PCSK9 on LDL receptor activity is underscored by the significantly lower plasma LDL-C concentrations in loss-of-function variants, and the appearance of the FH phenotype in gain-of-function variants. Paradoxically, lowering hepatocyte cholesterol content results in an upregulation of not only HMGCoA reductase and the LDL receptor, but also increases the expression of PCSK9. Antibodies that prevent the binding of PCSK9 to the LDL receptor and subsequent lysosomal degradation of this receptor enhance the recycling of receptors and consequently enhance clearance of LD-C from the plasma.

Alirocumab and evolocumab have been approved for the market internationally but not in South Africa. These humanised monoclonal antibodies are injected subcutaneously with tremendous additional effect on LDL-C reduction in heterozygous FH.[17] As is the case for statins, the efficacy is generally related to the function of the normal LDL receptor allele. It is therefore expected that every heterozygous FH patient, if tolerant of the combination of statin, ezetimibe and anti-PCSK9 medication, can achieve the target LDL-C concentration of 3 mmol/l or less.

Despite the effectiveness of statins, FH remains a seriously under-recognised and therefore under-treated condition. The estimated proportion of FH subjects identified has been disappointing, except for the Netherlands (71%).[18] In South Africa this figure is placed at 1%.

The way forward (Prof PJ Talmud)

The importance of diagnosing FH was emphasised as there is currently effective control with statins, and additional agents have been developed when additional treatment is advisable. Although FH has a long history as a clinical entity and obtained a mechanistic explanation in the 1970s, genetic explanations were proved in the LDL receptor gene and apolipoprotein B100. The story of PCSK9 is remarkable. Within a decade of the

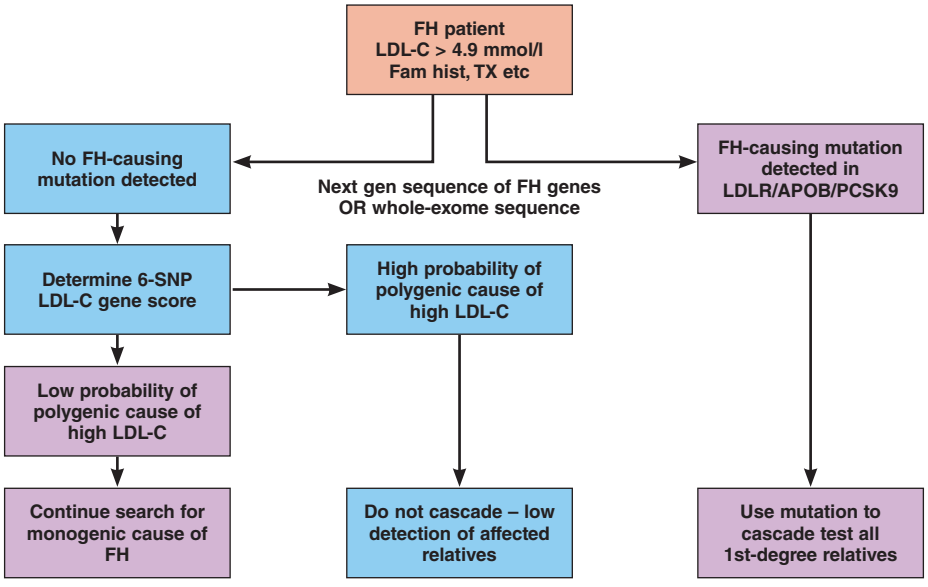

Fig. 3. The diagnostic approach to FH.[21] After the six-SNP LDL-C gene score has been determined there are two different care pathways. If the score is in the lowest quintile (i.e. < 20th percentile), a polygenic cause for the patient's high LDL-C level is statistically very unlikely. Since mutation in *LDLR*/*APOB*/*PCSK9* has already been ruled out, this suggests that the phenotype may be caused by a (monogenic) mutation in a yet-to-be-identified gene, and the patient can usefully be consented and recruited into a research project to find this gene using whole-exome or whole-genome sequencing. By contrast, if the score is in the top four quintiles (i.e. > 20th percentile), the high LDL-C level can safely be assumed to be due to a 'polygenic' cause (i.e. the inheritance of a greater-than-average number of common LDL-C-raising variants of small effect that in combination cause the phenotype).

discovery of PCSK9 as a protein that influences LDL receptor turnover, a therapeutic strategy was developed based on this action. Although the polygenic nature of FH has been identified and contributes to the understanding of this clinical phenotype with high cardiovascular risk, it is possible that more monogenic causes may be found.

Ideally, a genetic basis should be sought in all patients with a clinical suspicion of FH, either for a monogenic disorder or a polygenic form of the disease using a condensed six-SNV genetic risk score (*CELSR2*/*SORT1*, *APOB*, *ABCG5*/*8*, *LDLR*, and two SNPs in *APOE*). An outline for a diagnostic approach through genetic testing is presented in Fig. 3. In South Africa, founder effects may lead to identification of a large number of patients with a few selected mutations by more traditional methods, but next-generation sequencing technologies such as WES offer more extensive screening. In cases where monogenic FH is excluded, confirmation of polygenic FH would indicate that cascade genetic testing for identification of affected family members would not be cost effective. In the remainder of FH patients without an identifiable mutation, or high polygenic risk score, additional research for a causal mutation in novel and unknown gene(s) may be justified.

Much work needs to be done in South Africa for the detection of monogenic and polygenic FH as a phenotype. The application of the single-nucleotide variants to the polygenic FH risk score needs to be confirmed or adapted, to be reliable in populations with ancestry other than European.

Discussion

The recognition of hypercholesterolaemia and coronary artery disease in South Africa dates back many years. Prof K Steyn indicated that Dr Jan Pretorius already drew attention to dyslipidaemia when it was being recognised by Prof Harry Seftel with the diagnosis of so many homozygous FH patients in the region of Johannesburg. Prof Steyn also described work done at the MRC. In a rural study of Afrikaners and testing hypercholesterolaemia above the 80th percentile, the prevalence of FH assessed by the three known mutations in the *LDLR* gene was one in 72.

The genetic investigation as well as counselling for FH was discussed. Ms M Schoeman, an experienced HPCSA-registered genetic counsellor working in Cape Town, indicated that she had few referrals for counselling and these predominantly related to inheritance in Afrikaners.

Prof Talmud indicated that founder effects made the detection of LDL receptor mutations somewhat easier and that next-generation sequencing could simultaneously provide information on all FH-associated genes as well as on the genes operating in polygenic FH. However, in the latter case, the utility of the polymorphisms used in Europe needs to be established before applying this set to local dyslipidaemias.

Prof Kotze mentioned that medical schemes controlling expense for healthcare could consider supporting the analysis of SNVs, which could identify polygenic FH. This could be incorporated as part of a pre-screen algorithm for selection of patients eligible for WES.

The need to develop a local gene score for polygenic FH was emphasised by Prof Humphries. Prof Raal indicated that a genetic investigation of six common mutations in the LDL receptor would be of great help in the diagnosis of FH since there are strong founder effects in South Africa. Such a diagnostic service is not available at teaching hospitals. Mutations specific to regions and ancestral lineage could be selected to make the genetic diagnosis more cost effective.

The cost of treatment was discussed briefly. The practical point is that the medical practitioner treats the phenotype with medication to certain targets, as indicated by the South African guidelines.[19] The generic statins have made the treatment much more affordable. Prof Marais indicated atorvastatin and rosuvastatin should be preferred in the treatment of FH. The cost of the 80-mg daily dose of atorvastatin is in the range of

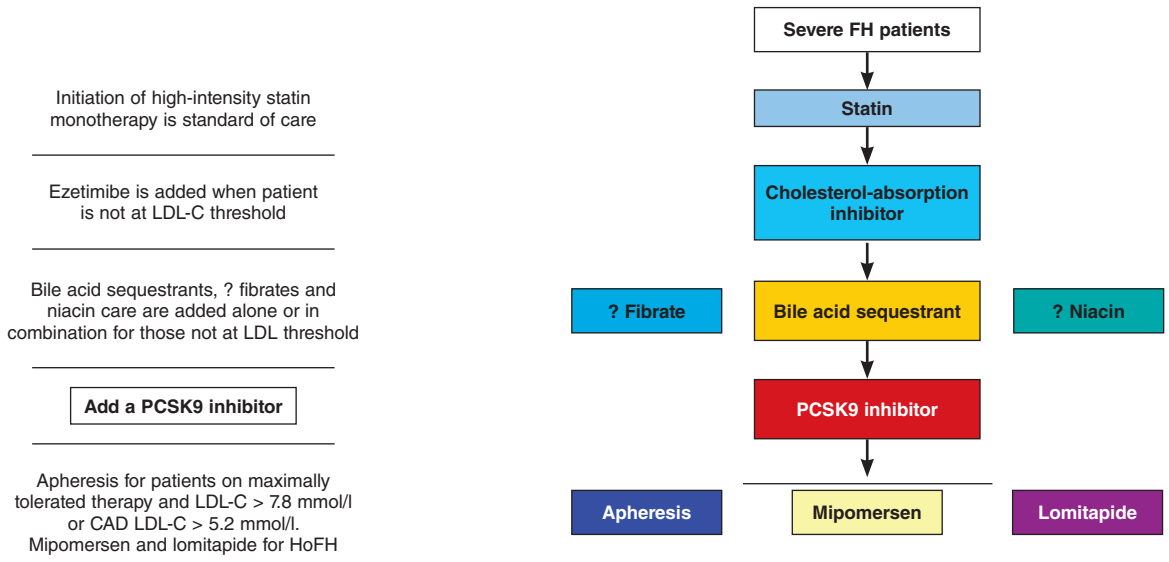

Fig. 4. Treatment strategies for FH.

R150 per month. The approximate lowering by 50% of LDL-C concentration is adequate for a large proportion of patients with FH. There is poor support for additional medication such as ezetimibe, which may be necessary to improve prevention of atherosclerotic complications.

A formal diagnosis, including a register of FH, could be used to support treatment better. It is also important to consider establishing special clinics at medical schools or larger centres and that at least one laboratory should be available nationally to ensure that severe dyslipidaemia is diagnosed correctly. While newer treatment strategies are often researched in South Africa, these take time to come to the market. Furthermore, the newer agents are expensive and may not be supported by state healthcare and private medical schemes. Nevertheless, cases where currently available treatment leaves the patient at very high risk, treatments such as monoclonal antibodies to PCSK9 could be considered.

Hypercholesterolaemia in the indigenous African population was discussed in more depth. Dr AA Khine reviewed requests and results for lipid profiles in South African black patients from in- and out-patient departments at a tertiary hospital in Gauteng.[20] There were 24 656 requests for 6 348 patients. It appears that there certainly is a strong awareness of the additional risk for atherosclerosis from dyslipidaemia in the setting of hypertension and diabetes, as well as for dyslipidaemia in association with secondary causes such as nephrotic syndrome. During one year there were 120 requests from the cardiac intensive care unit; dyslipidaemia was present in 40% of these patients. One should bear in mind that there may be a false low level with an acute-phase response that may mask severe hypercholesterolaemia. Statins were prescribed in some patients.

The number of patients without diabetes and hypertension who had ischaemic heart disease was 19. Severe hypercholesterolaemia (> 7 mmol/l) was seen in 299 (4.7%) patients and extreme hypercholesterolaemia (> 12 mmol/l) in 30 (0.5%) patients. High LDL-C levels (> 5 mmol/l) occurred in 80 (1.3%) patients and > 10 mmol/l in 19 (0.3%) patients. The diagnosis of FH was not specifically sought or entertained. The ages ranged from 50 to 84 years and there were five males among the patients with hypercholestrerolaemia > 10 mmol/l. It is likely that FH is the diagnosis in these more extreme cases of hypercholesterolaemia, but there was also one male with no other explanation for hypercholesterolaemia of 6.2 mmol/l and ischaemic heart disease at the age of 37 years.

Dr D van Velden indicated that as an undergraduate in the early 1970s, he was taught that atherosclerosis was not observed in the African population. It was mentioned that Isaacsohn published the finding of atherosclerosis in Johannesburg at autopsies in the 1970s. Only three African subjects have been identified with the homozygous FH phenotype. All three were worked up to an accurate diagnosis: one was a true homozygote for a six-nucleotide deletion in the LDL receptor gene, one had autosomal recessive hypercholesterolaemia and one had sitosterolaemia.

Ongoing research in FH in South Africa is justified, given the prevalence and severity of this disorder. The Heart and Stroke Foundation of South Africa and the MRC could not be represented at the meeting but would be important participants in future research. Medical schemes serving private as well as government healthcare should translate the diagnosis and treatment of FH to improve outcomes. Newer agents that are under development to lower LDL-C levels may be very expensive and will have to be carefully evaluated for special cases, in consultation with expert assessment.

Recommendations

Although not tasked with the provision of guidelines, the consensus was that:

- FH should be recognised at the clinical practice level because, owing to its high prevalence in general and particularly in certain communities, it will be encountered in primary healthcare. It is treated well with relatively inexpensive medication.
- Through increased awareness and cascade screening of affected index cases, it is hoped that primary prevention will be possible.
- Treatment with statins, and best with atorvastatin and rosuvastatin owing to their greater power, may achieve target levels set in general, but a proportion of FH patients will need additional treatment with ezetimibe. An even smaller proportion may require newer treatment strategies.
- Genetic testing should be supported, and especially for the six common LDLR mutations or targeted according to inheritance from populations with known mutations. This will enable precise cascade testing. If no mutation is identified in the *LDLR*, *APOB* or *PCSK9* genes, then a polygenic profile may establish this diagnosis and indicate that the cholesterol test will be the most suitable for detection of FH. Genetic or trained nurse counsellors are skilled in facilitating cascade testing and are important in this process.
- Special clinics and possibly a central laboratory should evaluate patients with severe dyslipidaemias as these patients are at very high risk and expertise is required for best management. A national register should be established based on this experience.
- More research is necessary on the local causes of FH and other severe dyslipidaemias.
- Advances in treatment need to be translated to this high-risk population, including novel treatment strategies and even gene editing.

The FH workshop was based on research supported by the National Research Foundation (grant number 98069) but the responsibility for opinion, findings, conclusions or recommendations remains with the investigators. The previous support of the Medical Research Council is acknowledged for the genetic work-up as well as the NHLS Research Trust (grant number 004_ 94675). Profs Dirk Blom and C Vorster are thanked for their contribution to the discussion, and Drs A Peeters and S Hector for assistance with the investigation of the polygenic FH family. Dr Nicole van der Merwe is thanked for assistance with the pedigree.

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Sudan Country Report

PASCAR and WHF Cardiovascular Diseases Scorecard project

Awad A Mohamed, Jean M Fourie, Wihan Scholtz, Oana Scarlatescu, George Nel, Saad Subahi

Abstract

On behalf of the World Heart Federation, the Pan-African Society of Cardiology (PASCAR) co-ordinated data collection and reporting for the country-level Cardiovascular Diseases (CVD) Scorecard to be used in Africa. The objective of the scorecard is to create a clear picture of the current state of CVD prevention, control and management per country for 12 African countries. The Sudan Heart Society assisted PASCAR in collating and verifying the data through Drs Awad Mohamed (president, Sudan Heart Society) and Saad Subahi (PASCAR president, based in Sudan). 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 Organisation and government publications.

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Part A: Demographics

According to the World Bank (2018), Sudan is a lower-middle-income country with 66% of its people living in rural areas. In 2009, 14.9% of the population were living below the US$1.9-a-day ratio. Life expectancy at birth in 2016 was 63 years for men and 66 years for women. The general government health expenditure was 1.97% of the gross domestic product (GDP) in 2015, while the country GDP per capita was US$2 898.5 in 2017.[1]

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Part B: National cardiovascular disease epidemic

National response to cardiovascular disease (CVD) and non-communicable diseases (NCD)

In comparison to neighbouring countries Ethiopia and Egypt (6 and 16%, respectively), Sudan's premature deaths attributable to CVD (age 30–70 years) centred at 10% in 2010. In 2017, the age-standardised total CVD death rates were high at 33.03%, which was lower than that of Egypt at almost 47% but slightly higher than the 31.8% for the Global Burden of Disease (GBD) data.[2] The percentage of disability-adjusted life years (DALYs) resulting from CVD for men was 12.69% and for women 11.74%, which is lower than the GBD at 14.66% for both genders. Atrial fibrillation (AF) and arterial flutter was 0.14%, while the prevalence of rheumatic heart disease (RHD) was 0.64% compared to that of the GBD data (0.53%). The total RHD mortality rate was 0.38% of all deaths, which is lower than the GBD data (0.51%) (Table 1).[2]

Tobacco and alcohol

The prevalence of tobacco use in adult men and women (15+ years old) was 27.9 and 0.8%, respectively.[3] Comparative Global Health Observatory (GHO) data are 36.1% for men and 6.8% for women.[4] In the young population (13–15 years old) the prevalence was 9.5% in boys and 4.3% in girls, which is the lowest among those African countries in our sample for which we have data.[4] This prevalence is also lower than the GHO data.[4] For 2018, the estimated annual direct cost of tobacco use was US$5.91.[3] The premature CVD mortality attributable to tobacco is 1% of the total mortality rate and much lower than that of the global 10%. The three-year (2015–2017) average recorded alcohol consumption per capita (15+ years) was 0.0 litres (Table 1).[4]

Raised blood pressure and cholesterol

STEPS data released in 2018 indicated 31% of men and 32.1% of women had raised blood pressure levels [systolic blood pressure (SBP) ≥ 140 or diastolic blood pressure (DBP) ≥ 90 mmHg],[3] which is higher than the respective GHO levels of 24.1 and 20.1%.[4] Conversely, the percentage of individuals with raised total cholesterol levels (≥ 5.0 mmol/l or currently on medication for raised cholesterol) was 13.6% compared to GHO data (38.9%).[3,4] The percentage of DALYs lost because of hypertension was 7.49%, the mortality rate caused by hypertensive heart disease (2.15%) was higher compared to the 1.65% for global data in 2017 (Table 1).[2]

Physical activity

In 2010, the percentage of 11–17-year-old adolescents who were insufficiently active (less than 60 minutes of moderate- to vigorous-intensity physical activity daily) was 91.9% (global data = 80.7%).[4] The age-standardised estimate for adults who were insufficiently active (less than 150 minutes of moderate-intensity physical activity per week, or less than 75 minutes of vigorous-intensity physical activity per week) was 14.1% (global data = 27.5%) (Table 1).[3]

Overweight and obesity

In 2018, the prevalence of overweight [body mass index (BMI) ≥ 25– < 30 kg/m^2] and obesity (BMI ≥ 30 kg/m^2) in adults 25 years and older was 28.2 and 10.3%, respectively.[3] Compared to global data, both these indicators are somewhat lower than that of 38.9% for overweight and 13.1% for obesity (Table 1).

Diabetes

The percentage of the population defined with fasting glucose levels ≥ 7.0 mmol/l or on medication for raised blood glucose (age standardised) in 2018 was 5.1% for men and 7% for women.[3] In 2017, the prevalence of age-adjusted (18–99 years) diabetes was 15.7%, which is much higher than that of Africa or the world (Table 1).[5]

Part C: Clinical practice and guidelines

Health system capacity

The country had an average of 3.14 physicians and 11.57 nurses per 10 000 of the population in 2008 and 2014, respectively. For every 10 000 people, there were eight hospital beds in 2013.[4]

Locally relevant clinical tools to assess CVD risk have been adopted since 2015.[6] Sudan was one of the lower-middle-income countries to participate in the REMEDY study that reported a hospital-based registry for RHD.[7]

Locally relevant (national or sub-national) clinical guidelines for the management of acute rheumatic fever (ARF) and RHD are also available.[8] No national guidelines for the treatment of tobacco dependence or for the detection and management of AF and pharyngitis have been set up. In 2011, the Federal Ministry of Health (FMOH) NCD directorate, in collaboration with the World Health Organisation (WHO), developed the Sudan diabetes mellitus guidelines.[9]

Essential medicines and interventions

ACE inhibitors, aspirin, β-blockers, statins, insulin, warfarin and clopidogrel are included in the list of essential medicines in primary-care facilities in the public health sector. However, metformin is not included.[4]

Table 1. Cardiovascular disease indicators for Sudan

Indicators	*Male*	*Female*	*Total*	*Year*
Status of national CVD epidemic				
Premature CVD mortality (age 30–70 years) (% of deaths)	–	–	10	2012
Total CVD mortality (% of deaths)	32.9	33.1	33 (31.8)*	2017
Total RHD mortality (% of deaths)	0.3	0.5	0.4 (0.5)*	2017
Percentage of DALYs attributable to CVD (%)	12.7	11.7	12.3 (14.7)*	2017
Percentage of AF and arterial flutter (%)	0.2	0.1	0.1 (0.5)*	2017
Prevalence of RHD (%)	0.6	0.7	0.6 (0.5)*	2017
Tobacco and alcohol				
Prevalence of adult tobacco use (15+ years old) (%)	27.9 (36.1)*	0.8 (6.8)*	–	2018
Prevalence of youth (13–15-year-olds) tobacco use (%)	9.5	4.3		2009
Estimated direct (e.g. healthcare related) cost of tobacco use in your population (in current US$)			5.91	2018
Proportion of premature CVD mortality attributable to tobacco (%)	–	–	1 (10)*	2012
Recorded alcohol consumption per capita (15+ years) (in litres of pure alcohol) (three-year average)			0	2015–17
Raised blood pressure and cholesterol				
Percentage of population with raised blood pressure (SBP ≥ 140 or DBP ≥ 90 mmHg) (%)	31 (24.1)*	32.1 (20.1)*	–	2018
Percentage of population with raised total cholesterol (≥ 5.0 mmol/l) (%)	8.8	19.5	13.6 (38.9)*	2018
Percentage of DALYs attributable to hypertension (%)	7.6	7.4	7.5 (8.7)*	2017
Mortality caused by hypertensive heart disease (% of deaths)	1.7	2.8	2.2 (1.7)*	2017
Physical activity				
Percentage of adolescents (ages 11–17) who are insufficiently active (< 60 min of moderate- to vigorous-intensity physical activity daily) (%)	91.2	92.3	91.9 (80.7)*	2010
Percentage of adults (age-standardised estimate) who are insufficiently active (< 150 minutes of moderate-intensity physical activity per week, or < 75 minutes of vigorous-intensity physical activity per week) (%)	11.4	17.3	14.1 (27.5)*	2018
Overweight and obesity				
Percentage of adults who are overweight (BMI ≥ 25– < 30 kg/m^2) (%)	22.6	35.6	28.2 (38.9)*	2018
Prevalence of obesity (BMI ≥ 30 kg/m^2) (%)	6.7	14.9	10.3 (13.1)*	2018
Diabetes				
Percentage of defined population with fasting glucose ≥ 126 mg/dl (7.0 mmol/l) or on medication for raised blood glucose (age standardised) (%)	5.1 (9)*	7 (8)*	–	2018
Prevalence of diabetes (ages 20–79) (%)	–	–	15.7 (8.6)**	2017

*WHO Global data.[4]
**IDF Diabetes Atlas.[5]

WORLD HEART FEDERATION

Cardiovascular Disease Scorecards – Africa

SUDAN – DECEMBER 2018

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

Country Demographics

World Bank Classification

Lower-middle income

66%
of population living in rural areas
60% (Sub-Sahara Africa)

0.38%
of total mortality caused by **RHD**
Global data: **0.51%**

0.64%
Prevalence of rheumatic heart disease **(RHD)**
Global data: **0.53%**

1%
of premature CVD mortality attributable to **tobacco**
Global data: **10%**

MALE **27.9%** **0.8** **FEMALE**
Prevalence of **tobacco** use **age ≥15**
Global data: **36.1%** (male) **6.8%** (female)

2.15%
of deaths caused by **hypertensive heart disease**
Global data: **1.65%**

30.6% **29.6%**
MALE **FEMALE**
of population with raised **blood pressure** (SBP ≥140 or DBP ≥90)
Global data: **24.1%** (male) **20.1%** (female)

SUDAN

10.3%
Prevalence of obese adults (BMI of ≥30 kg/m2)
Global data: **13.1%**

33.03%
of **deaths** caused by CVD
Global data: **31.8%**

13.6%
of population with raised total **cholesterol** (≥5.0 mmol/L)
Global data: **38.9%**

15.7%
Prevalence of diabetes **(ages 20-79)**
3.3% (Africa)

WORLD HEART FEDERATION

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Health System Capacity

3.14
Number of physicians (per 10,000 population)

11.57
Number of nurses (per 10,000 population)

8
Number of hospital beds (per 10,000 population)

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

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Clinical Practice and Guidelines

Locally-relevant (national or subnational level):

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

Clinical Guidelines for:

- The detection and management of atrial fibrillation
- The detection and management of acute rheumatic fever
- The detection and management of rheumatic heart disease
- The detection and management of diabetes
- CVD prevention (within the last 5 years)
- A system to measure the quality of care provided to people who have suffered acute cardiac events

Cardiovascular Disease Governance

A national strategy or plan that addresses:

- CVDs and their specific risk factors
- NCDs and their risk factors
- Rheumatic heart disease prevention and control as a priority
- A national surveillance system that includes CVDs and their risk factors

Stakeholder action

- Non-governmental organizations' advocacy for CVD policies and programmes
- Civil society involved in developing and implementing of national CVD prevention and control plan

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

No data were available for CVD risk stratification in primary healthcare facilities, total cholesterol measurement at the primary healthcare level, and secondary prevention of ARF and RHD in public-sector health facilities.[4]

Secondary prevention and management

The percentage of hypertensive persons receiving medical treatment is 31.5%.[3] However, no data are available on high-risk patients with AF who are being treated with oral anticoagulants. The percentage of people with a history of CVD taking aspirin, statins and at least one antihypertensive agent is also unknown.

Part D: Cardiovascular disease governance

A national strategy or plan that addresses CVD, and specifically their risk factors, was developed by the national NCD directorate and is functional.[6] However, no dedicated budget or unit is in place to ensure its implementation. The FMOH also developed a plan that addresses NCD and their risk factors and RHD prevention and control as a priority, which is in use.[8] Sudan has formulated a national tobacco control plan and multisectoral co-ordination mechanism for tobacco control.[10] A national surveillance system including CVD and their risk factors is in the process of being implemented.[3,10]

There are no collaborative projects between the Ministry of Health and non-health ministries for CVD interventions, and the percentage of total annual government expenditure on cardiovascular healthcare is not known. The benefits of CVD prevention and control for health and the economy of this population have not been modelled.

Assessment of policy response

Legislation that mandates health financing for CVD/NCD has been developed and implemented, along with that of essential CVD medicines at affordable prices.[11] However, no judicial orders protecting patients' rights and mandating improved CVD interventions, facilities, health-system procedures or resources have been implemented.

Regarding tobacco control, legislation on the following has been implemented:

- banning of smoking in indoor workplaces, public transport, indoor public places and other public places
- clear and visible warnings on at least half of the principal display areas of tobacco packs
- banning all forms of tobacco advertising, promotion and sponsorship
- measures to protect tobacco control policies from tobacco industry interference.[10]

The percentage of the excise tax of the final consumer price of tobacco products in Sudan is 230% and that of the final consumer price of alcohol products is unknown.[12]

The country does not have policies that ensure equitable nationwide access to healthcare professionals and facilities or screening of high-risk CVD individuals. No sustainable funding is available for CVD from taxation of tobacco and or other 'sin' products.

As far as food legislation and that of physical activity is concerned, no policy exists for the following:

- taxes on unhealthy foods or sugar-sweetened beverages
- banning the marketing of unhealthy foods to minors
- mandating clear and visible warnings on foods that are high in calories/sugar/saturated fats
- interventions that promote a diet that reduces CVD risk
- interventions that facilitate physical activity.

Alcohol is banned in Sudan therefore no other legislation or policies need to be in effect.

Stakeholder action

Non-governmental organisation (NGO) advocacy has been demonstrated for CVD policies and programmes, while the Epidemiological Laboratory (EpiLab), a private, not-for-profit NGO in Khartoum, was involved in the development and implementation of a national tobacco-control plan.[13] Unfortunately, there is no known active involvement of patients' organisations in the advocacy for CVD/NCD prevention and management.

Advocacy champions and/or patient engagement for RHD groups are also not available. Involvement of civil society in the development and implementation of a national CVD prevention and control plan and the national multisectoral co-ordination mechanism for NCD/CVD is also lacking. Specific activities by cardiology professional associations aimed at a 25% reduction in premature CVD mortality by 2025 and hypertension screening by businesses at workplaces have not yet been addressed.

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

Strengths

The NCD National Strategic Plan (NSP) 2010–2015 for Sudan was developed by the national NCD directorate at the FMOH in response to the NSP for the health sector (2003–2027), which is an indication of a sound governmental commitment towards NCD.[6]

Guidelines for the management of ARF and RHD are available. A national surveillance system including CVD and their risk factors is in the process of being implemented.

Sudan, through EpiLab, became a pioneer in developing countries through its ground-breaking research demonstrating the feasibility and sustainability of the development and implementation of a national tobacco-control plan.[13] Legislation regarding tobacco control is in place, as is an excise tax. Legislation that mandates essential CVD medicines at affordable prices has been implemented.[11]

Threats

The percentage of deaths caused by CVD is very high (33%), with Tunisia (51.5%) and Egypt (46.6%) having higher levels compared to the other selected countries and global data (31.8%). DALYs attributable to CVD ranked slightly lower than that of the global data (Table 1). Deaths caused by hypertensive heart disease are also higher compared to the global data, as is raised blood pressure for men and women.

Overweight and obesity tend to be a problem in most African countries, although Sudan has a lower prevalence (28 and 10%, respectively) compared to global data (38.9 and 13.1%,

respectively). In Sudan, the prevalence of diabetes (15.7%) is the highest after Egypt (17.3%) for those countries under investigation and the rest of the world (8.6%) (Table 1).

Weaknesses

National guidelines to treat tobacco dependence are lacking, as are locally relevant (national or sub-national) clinical guidelines to detect and manage AF. A system to measure the quality of care provided to people who have suffered acute cardiac events is also not available. Although guidelines for diabetes have been developed, its prevalence remains high.

Sustainable funding for CVD along with taxes on unhealthy foods or sugar-sweetened beverages are lacking. Policies and legislation banning the marketing of unhealthy foods to minors and mandating clear and visible warnings on foods are non-existent. There are no policies promoting diets and physical activity to reduce CVD risk.

Priorities

Comprehensive interventions or programmes are needed to address nutrition, physical inactivity and obesity among adults and children, as has been done for tobacco control. Given the high rates of obesity, overweight and diabetes, front-of-package labelling and higher taxes are needed for unhealthy foods, including sugar-sweetened beverages.

A percentage of the total annual government expenditure should be set apart for cardiovascular healthcare, and the benefits of CVD prevention and control for population health and the economy need to be modelled.

This publication was reviewed by the PASCAR governing council and approved by the president of the Sudan Heart Society.

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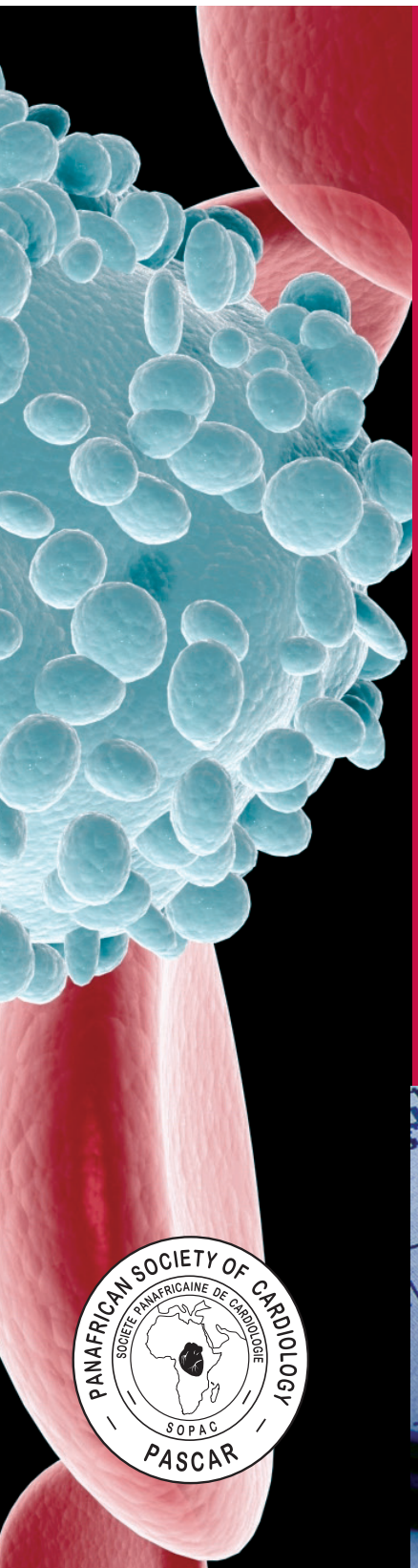

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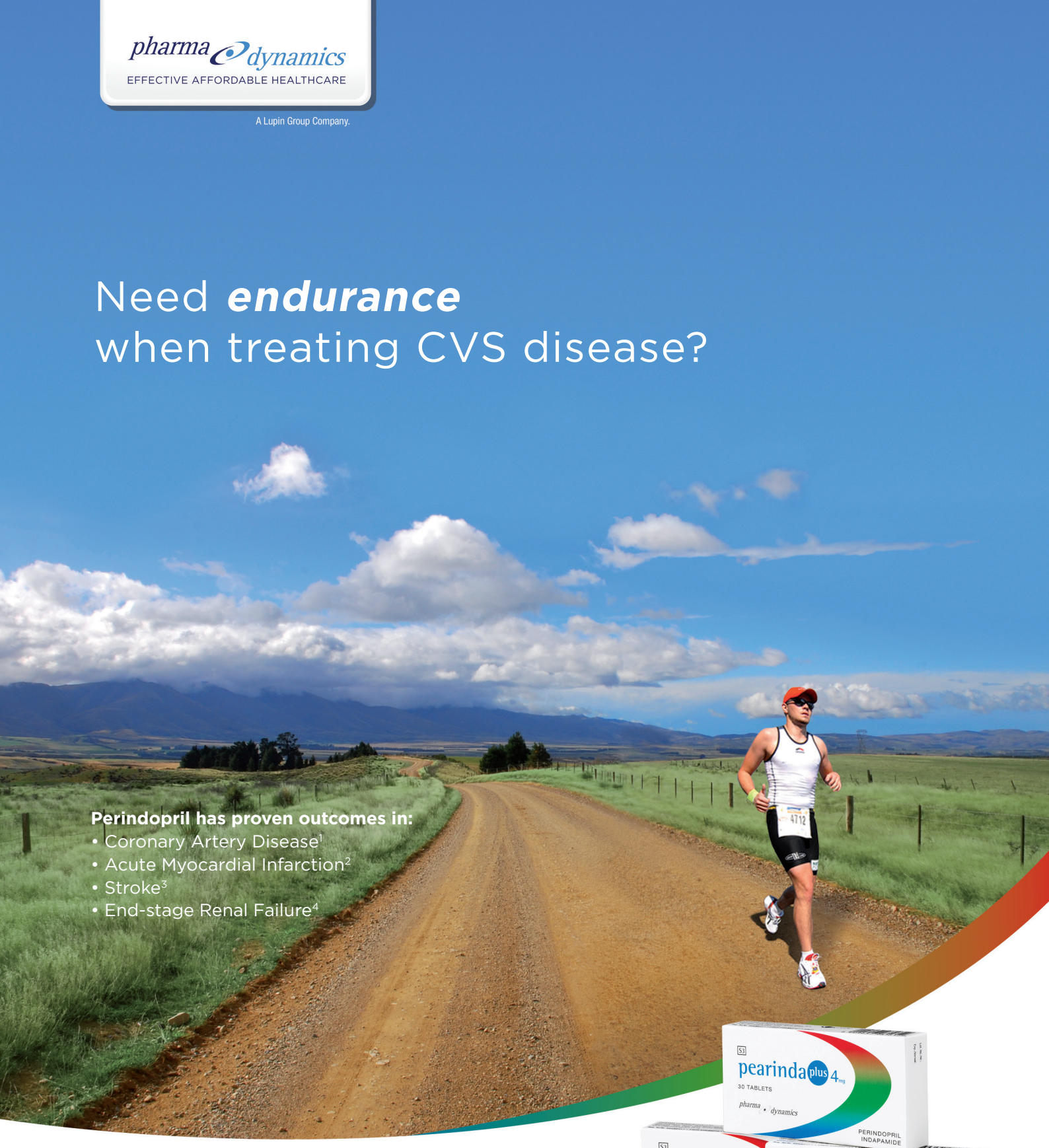

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