SAJDVD

The South African Journal of DIABETES & VASCULAR DISEASE

The electronic version of the journal is available at www.diabetesjournal.co.za

November 2018 Volume 15 Number 2

Featured in this issue:

pharma dynamics
EFFECTIVE AFFORDABLE HEALTHCARE
A Lupin Group Company.

RESTORE
cardiac function

CARVEDILOL:

- is indicated **twice daily** for mild to moderate stable symptomatic congestive heart failure
- is indicated **once daily** for essential mild to moderate hypertension
- **has a positive effect** on metabolic parameters.[1]

carvetrend
CARVEDILOL

6,25 mg | 12,5 mg | 25 mg

For further product information contact **PHARMA DYNAMICS** P O Box 30958 Tokai Cape Town 7966 **Fax** +27 21 701 5898
Email info@pharmadynamics.co.za **CUSTOMER CARE LINE** 0860 PHARMA (742 762) / +27 21 707 7000 **www.pharmadynamics.co.za**

CARVETREND 6,25, 12,5, 25 mg. Each tablet contains 6,25, 12,5, 25 mg carvedilol respectively. S3 A37/7.1.3/0276, 0277, 0278. NAM NS2 08/7.1.3/0105, 0104, 0103. BOT S2 BOT1101790, 1791, 1792. For full prescribing information, refer to the professional information approved by SAHPRA, December 2014. **1)** Panagiotis C Stafylas, Pantelis A Sarafidis. Carvedilol in hypertension treatment. *Vascular Health and Risk Management* 2008;4(1):23-30.
CDE479/07/2018.

ISSN 1811-6515

THE SOUTH AFRICAN JOURNAL OF
Diabetes & Vascular Disease

VOLUME 15 NUMBER 2 • NOVEMBER 2018
www.diabetesjournal.co.za

CONTENTS

CONTENTS

Production Editor
SHAUNA GERMISHUIZEN
TEL: 021 785 7178
FAX: 086 628 1197
e-mail: shauna@clinicscardive.com

Financial & Production Co-ordinator
ELSABÉ BURMEISTER
TEL: 021 976 8129
CELL: 082 775 6808
FAX: 086 664 4202
e-mail: elsabe@clinicscardive.com

Content Manager
MICHAEL MEADON
(Design Connection)
TEL: 021 976 8129
FAX: 086 655 7149
e-mail: michael@clinicscardive.com

The *South African Journal of Diabetes and Vascular Disease* is published twice a year for Clinics Cardive Publishing (Pty) Ltd and printed by Durbanville Commercial Printers/Tandym Print. Online Services: Design Connection.

All correspondence to be directed to:
THE EDITOR
PO BOX 1013
DURBANVILLE
7551
or elsabe@clinicscardive.com

TEL: 021 976 8129
FAX: 086 664 4202
INT: +27 (0)21 976-8129

To subscribe to the journal or change address, email elsabe@clinicscardive.com

Full text articles available on: www.diabetesjournal.co.za via www.sabinet.co.za

From the Editor's Desk

In this issue, the main areas of interest are cardiovascular risk factors, including hypertension in Africa, and renal disease in type 2 diabetes.

Amadi and co-workers (page 44) assessed the cluster of high cardiovascular risk factors in male long-distance truck drivers in Nigeria, with a view to improving health awareness in this group.

The prevalence of hypertension in patients with diabetes is approximately two-fold higher than in similar individuals without this disease. Muddu *et al.* (page 57) found very high rates of hypertension in newly diagnosed type 2 diabetes patients in Uganda, and few were aware of their hypertension status. Routine assessment and treatment was found to be necessary to prevent complications and death.

This is a common theme in this issue of the journal. Hypertension is a clear public health target in Africa.

Dzudie and colleagues, for the PASCAR task force on hypertension (page 74), outline such a programme in excellent detail. The aim of the programme was to develop guidance on implementation strategies for effective detection, treatment and control of hypertension in sub-Saharan Africa. They highlight a 10-point action plan that they wish to be implemented by African governments to reduce the incidence of hypertension by 25% by 2025. They should be complimented and supported for initiating this essential health plan.

Shogade *et al.* (page 64) describe a clear association between microalbuminuria and left ventricular diastolic dysfunction. The association between microalbuminuria and renal impairment in diabetes has been described,[1] as has the association between macroalbuminuria and cardiovascular death.[1] This study shows that the cardiac changes occur at an earlier stage than expected and that microalbuminuria can be used as a marker for renal and cardiac involvement. This can be used clinically to intervene more aggressively in the management of the patient at an earlier stage.

Rayner elegantly reviews the renal protective effect of sodium glucose transporter 2 (SGLT-2) inhibitors used in the treatment of patients with type 2 diabetes, outlining the mechanisms at play. One of the SGLT-2 inhibitors is dapagliflozin, which the DECLARE study affirms to be safe for use in terms of cardiovascular risk.[2]

Demir and co-workers looked at whether the choice of statin matters; they compared endothelial function after one-year use of atorvastatin or rosuvastatin. There was no difference between the two statins and both showed a beneficial change in measurements of endothelial function.

Correspondence to: FA Mahomed
Head of Clinical Unit; Endocrinology, Department of Internal Medicine, University of the Free State, Bloemfontein
e-mail: MahomedFA@ufs.ac.za

S Afr J Diabetes Vasc Dis 2018; 1**5**: 43

References

1. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003; **63**(1): 225–325.
2. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *New Engl J Med* 2018; Nov 10. doi: 10.1056/NEJMoa1812389. [Epub ahead of print].

Prevalence of cardiometabolic risk factors among professional male long-distance bus drivers in Lagos, south-west Nigeria: a cross-sectional study

CASMIR E AMADI, TIM P GROVE, AMAM C MBAKWEM, OBIANUJU B OZOH, OYEWOLE A KUSHIMO, DAVID A WOOD, MICHAEL AKINKUNMI

Abstract

Background: **Professional drivers are known to be at high risk of cardiovascular disease (CVD). This study was carried out to highlight these risk factors and their predictors among male long-distance professional bus drivers in Lagos, southwest Nigeria, with a view to improving health awareness in this group.**

Methods: **Socio-demographic data, anthropometric indices, blood pressure, fasting plasma blood glucose levels and lipid and physical activity profiles of 293 drivers were measured.**

Results: **Mean age of the study population was 48 ± 9.7 years; 71.0 and 19.5% of the drivers used alcohol and were smokers, respectively; and 50.9% were physically inactive. The prevalence of overweight and obesity was 41.7 and 21.1%, respectively, while 39.7 and 13.9% were hypertensive and diabetic, respectively. Ninety (31.3%) subjects had impaired fasting glucose levels while 56.3% had dyslipidaemia. Predictors of hypertension were age and body mass index (BMI). BMI only was a predictor of abnormal glucose profile.**

Conclusion: **Professional male long-distance bus drivers in this study showed a high prevalence of a cluster of risk factors for CVD.**

Keywords: cardiovascular disease, risk factors, long-distance drivers

Atherosclerotic cardiovascular disease (CVD), typified by coronary heart disease (CHD) and stroke, is a pre-eminent cause of preventable and premature mortality globally, accounting for about 30% of global deaths.[1] This is expected to increase by almost 50% by 2030.[2] It is also a major cause of mass disability and a somatic cause of loss of productivity globally, with over 150 million disability adjusted life years (DALYS).3 About 80% of this burden from CVD is borne by low- and middle-income countries (LMIC).[1]

Globally, CVD prevalence is on the increase, remarkably so in the LMIC. This is largely due to increased urbanisation and its corollary of better socio-economic opportunities and Westernisation of lifestyles, such as sedentary living, unhealthy dietary choices, tobacco use, psycho-social stress and harmful use of alcohol.[4] These behavioural risk factors predispose to intermediary or metabolic risk factors, such as hypertension, abnormalities in blood glucose levels, dyslipidaemia, overweight and obesity.[5,6]

One of the socio-economic consequences of urbanisation is mass transit of people, goods and services across regions and long distances via land, air and waterways. The consequence of this is the creation of effective road transport systems in urban areas, with an increase in the number of people engaged in professional driving.

Professional drivers as an occupational group are at increased risk of CVD. Morris *et al*., in their seminal research in 1953, documented that London bus drivers were at increased risk for CHD compared to the more active bus conductors.[7] Several other occupational epidemiological studies have provided evidence that professional drivers (short- and long-distance drivers) suffer more and die from CVD.[8-11] This excess of CVD morbidity and mortality risk among this group is attributable to a high prevalence of CVD risk factors, such as obesity, hypertension, sedentary living, diabetes, smoking and unhealthy diets found in them.[12-14]

Beyond these conventional risk factors for CVD, various driving-related activities, such as traffic congestion, ergonomic factors, long-distance driving, shift work, and anxiety and tension from the job of driving have also been implicated. These are known to cause various neuroendocrine and neurocardiological responses, such as increased secretion of cortisol and catecholamines, and decreased heart rate variability, which may also be possible mediators of CVD.[15,16] They can also be considered a vulnerable group with social gradients of inequalities; they usually belong to the lower socio-economic class, are not well educated/informed and are not usually covered by public health policies. They also work under immense anxiety and stress. These further heighten their risk for CVD. Lagos is the second most populous city in Nigeria, the second fastest growing city in Africa and the seventh in the world.[17] It is the economic hub of the country with well-developed intra-city, inter-city and trans-African highway routes for easy mass transit of people, goods and services across geographical barriers,[18] making road transportation and the transportation business important features of its economy. Therefore many companies engage in long-distance transportation, with professional drivers employed to provide this service.

In Nigeria there are few studies on the CVD risk profile of this

Correspondence to: Casmir E Amadi
Department of Medicine, College of Medicine, University of Lagos, Nigeria
e-mail: acetalx@yahoo.com

Amam C Mbakwem, Obianuju B Ozoh
Department of Medicine, College of Medicine, University of Lagos, Nigeria

Tim P Grove, David A Wood
National Heart and Lung Institute, Imperial College, London

Oyewole A Kushimo, Michael Akinkunmi
Department of Medicine, Lagos University Teaching Hospital, Nigeria

Previously published in *Cardiovasc J Afr* 2018; **29**(2): 106–114

S Afr J Diabetes Vasc Dis 2018; **15**: 44–51

important but vulnerable group. These studies show that long-distance drivers have a significant burden of hypertension and overweight/obesity, comparable to or even higher than in the general population.[19-21] Hypertension is a common and important CVD risk factor. Its prevalence among long-distance bus drivers in Nigeria is 22.5%,[19] which was also the pooled prevalence of hypertension in the general population in 2012.[22] However, none of these studies screened the drivers for diabetes/abnormal glucose profiles or dyslipidaemia.

Considering the potential risk associated with professional driving, the importance of bus drivers to the country's socio-economic development and the paucity of data on the cardiovascular risk profile of long-distance bus drivers, it became necessary to investigate the prevalence of cardiometabolic and lifestyle-related risk factors for CVD and their predictors in this segment of the Nigerian working population in Lagos, south-west Nigeria. The findings from this study will also help create awareness of their risk burden and possibly help shape policies to address this risk.

Methods

This was a cross-sectional study involving male long-distance bus drivers in major motor parks in Lagos. The parks were selected based on their size and the routes they serve. Long-distance driving was defined as a distance of 160-km radius from the terminal of departure.[23]

The calculated sample size was 268 based on the prevalence of hypertension in the general population.[22] To allow for 15% attrition rate, the sample size was increased to 308. However, 15 of the drivers did not have complete data and were not included in the data analysis, giving a response rate of 95%. Therefore 293 was the final sample size used in the data analysis. Ethical approval for the study was obtained from the Health Research Ethics Committee of the Lagos University Teaching Hospital.

We used a stratified cluster-sampling method to recruit longdistance drivers registered with the Transport Workers' Union from selected motor parks in Lagos between March and July 2015. The motor parks were then stratified based on whether or not they organised mandatory annual health and safety training for their drivers (AHS motor parks). Only two motor parks employing 400 drivers met this criterion. The drivers in the AHS motor parks only operate from their company terminals. We selected one of these for inclusion in the study because its annual health and safety programme coincided with the study period. All 168 drivers agreed to participate but three (1.8%) later declined.

The second category of (non-AHS) motor parks comprised independent drivers and drivers working for small transport companies that operate from general and less regulated motor parks in Lagos and who do not routinely receive formal health and safety checks. We divided these motor parks into two; those serving the northern and southern parts of the country, respectively. We then randomly selected two motor parks from each of these strata for inclusion in the study, thereby selecting four in total. Finally, we used a convenience sample of 50 drivers from each of these four parks and recruited 143 of them (71.5% response rate). Those who declined did so due to time constraints and undisclosed personal reasons. Fig. 1 shows the consort diagram on how the participants were recruited.

On a mutually agreed day, the consenting drivers were approached in groups and were given a talk on the importance of healthy living and they were also briefed on the usefulness of the study. They were told to observe an overnight fast on the day of the medical screening. We used a structured questionnaire administered by trained interviewers to obtain their sociodemographic data and relevant medical history. Those who couldn't read or write were assisted to complete the questionnaire by interviewers who could speak their native languages.

Thereafter their body weights were measured in kilograms with an Omron HN289 (Osaka, Japan) digital weighing scale, placed on a firm, flat ground, with participants wearing light clothing and with no footwear or cap. Measurements were taken to the nearest 0.5 kg, after ensuring that the scale was always at the zero mark.

Their heights were measured in centimetres with a Seca model 216 (GmbH, Hamburg, Germany) stadiometer with the participant standing erect, back against the height metre rule and occiput and heels making contact with the height metre rule. BMI was calculated as weight in kilograms divided by height squared in metres.[24] BMI was categorised as underweight < 18.0 kg/m^2; normal weight 18.0–24.9 kg/m^2; overweight 25.0–29.9 kg/m^2; class I obesity 30.0–34.9 kg/m^2; class II obesity 35.0–39.9 kg/m^2 and class III obesity > 40.0 kg/m^2.

Participants' waist circumferences were measured with an inextensible, inelastic 1-cm-wide tape snug around the body at the level of the midpoint between the lower margin of the last palpable rib and the top of the anterior iliac crest. Measurements were taken at the end of normal respiration and ≥ 102 cm was regarded as abdominal obesity.[25] Their neck circumferences were also measured with an inextensible, inelastic 1-cm-wide tape at the level of the cricoid cartilage. A neck circumference ≥ 40 cm defined obesity.[26]

The blood pressure (BP) of the participants was measured by the research assistants after five minutes of rest, with the participant seated comfortably, feet on the floor, arm at the level of the heart and free of any constricting clothing. Appropriate-sized cuffs and bladder connected to an Omron HEM7233 (Osaka, Japan) digital sphygmomanometer were used in measuring the BP, which was taken initially on both arms, and the arm with the higher value was used in subsequent measurements. Three BP readings were taken at two- to three-minute intervals. The average of three readings was taken for analysis. Hypertension was defined as BP ≥ 140/90 mmHg, self-volunteered history of hypertension and/or use of anti-hypertensives.

Venepuncture was done on each participant while observing aseptic techniques. Five millilitres of venous blood was put in fluoride oxalate and lithium heparin vacutainer specimen bottles for fasting plasma glucose and fasting lipid profiles, respectively, and sent to the laboratory for processing and analysis with a Beckman (Pasadena, CA, USA) automated clinical chemistry autoanalyser using standard reagents/kits from Randox Laboratories.[27] Participants with a fasting plasma glucose value of ≥ 126 mg/dl (6.99 mmol/l), self-volunteered history of diabetes and or use of insulin/oral hypoglycaemic agents were regarded as diabetic, while a fasting plasma glucose level between 100 and 125 mg/dl (5.55–6.94 mmol/l) was regarded as impaired fasting glucose.[28] For the purpose of this study, abnormal glucose profile was defined as a combination of impaired fasting glucose and frank diabetes.

Abnormal lipid profile was determined from the ATP III guidelines of 2001; total cholesterol (TC) ≥ 240 mg/dl (6.22 mmol/l), high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dl (1.04 mmol/l), and low-density lipoprotein cholesterol (LDLC) > 160 mg/dl (4.14 mmol/l) and triglycerides > 150 mg/dl (1.70 mmol/l).[29] Atherogenic

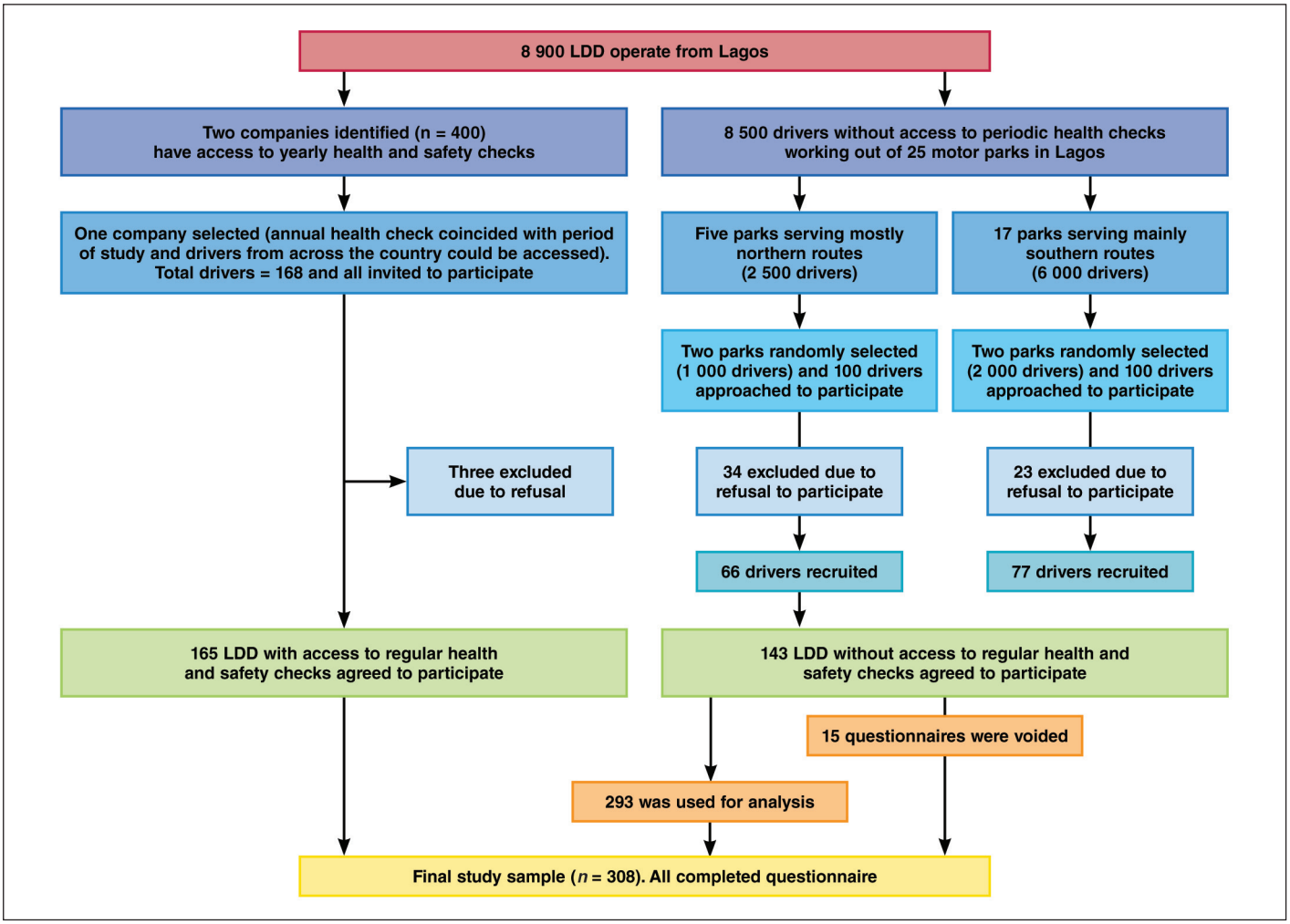


Fig. 1. Consort diagram describing how participants were recruited into the study. LDD: long-distance commercial drivers.

dyslipidaemia was defined by the Castelli index as TC/HDL-C > 3.4.[30]

The physical activity level of participants was assessed with the World Health Organisation (WHO) Global Physical Activity Questionnaire-2 (GPAQ-2), which assesses physical activity in four domains of work, travel, recreational and resting.[31] The product of the exercise intensity in metabolic equivalents (METs), duration of activity in hours and the number of times per week, expressed as METs/hour was regarded as exercise volume. A MET/hour value less than 600 per week was taken as physical inactivity.[31]

Statistical analysis

Data entry and analysis were done with the Statistical Package for the Social Sciences 17.0 version (SPSS, Inc, Chicago, IL, USA). Continous data are presented as mean and standard deviation. Categorical variables are expressed as proportions. Pearson's correlation was used to determine how some independent numerical variables (age, BMI, number of years of professional driving and number of driving hours/week) correlated with the major outcome variables (systolic and diastolic BP, and abnormal glucose profile). Furthermore, the independent variables were dichotomised to look for an association between them and the outcome variables, hypertension and abnormal glucose profile using the chi-squared test. Level of statistical significance was set at $p < 0.05$ and confidence interval at 95%.

Multivariate analysis was done using a forward stepwise binary logistic regression in order to assess for independent predictors of hypertension and abnormal glucose. We included predictor variables with associations at a significance level of $p \leq 0.2$ on univariate analysis in order to accommodate for important risk factors.

Results

A total of 308 drivers were recruited for the study. Fifteen were excluded due to incomplete data. Therefore 293 were used for data analysis, giving a response rate of 95.1%.

The age range of the study population was between 25 and 76 years with a mean of 44.8 ± 9.7 years. Two hundred and eighty six (97.6%) of the subjects were aged between 25 and 65 years. The rest of their socio-demographic characteristics is shown in Table 1.

Fifty-seven of the drivers (19.5%; 95% CI: 14.9–24.0%) were active smokers while 217 (74.1%) and 19 (6.5%) were non-smokers and ex-smokers, respectively. The prevalence of alcohol intake was 71.1% (95% CI: 65.7–76.2%). The majority consumed various types of alcoholic beverages: beer, spirits and alcohol-based

Table 1. Socio-demographic characteristics of the subjects

Parameters	Mean ± SD	*n* (%)
Age (years)	44.8 ± 9.7	
25–44		147 (50.2)
45–64		139 (47.4)
> 65		7 (2.4)
Educational level		
Primary 77 (26.3)		
Secondary 177 (60.4)		
Tertiary 37 (12.6)		
Marital status		
Married 265 (90.4)		
Single 22 (7.5)		
Widowed 3 (1.0)		
Divorced 3 (1.0)		
Number of years as a professional driver	20.0 ± 10.4	
Number of hours driven per week	41.9 ± 28.7	
Smoking pattern		
Active smokers		57 (19.5)
Non-smokers		217 (74.1)
Ex-smokers		19 (6.5)
Alcohol use		
User		208 (71.1)
Teetotaler		85 (29.0)

herbal medications. The intake of alcohol was about four bottles of beer per week (Table 1).

The mean BMI of the subjects was 27.2 ± 9.6 kg/m^2, with 121 (41.7%) and 61 (21.1%) being in the overweight and obese categories, respectively. The prevalence of overweight and obesity were 41.7% (95% CI: 36.0–47.4%) and 21.1% (95% CI: 16.3–25.6%), respectively, giving a combined prevalence of 62.8% (95% CI: 57.2–68.3%) (Table 2). Fig. 2 shows the frequency of the various classes of obesity.

The mean waist circumference (WC) of the study population was 94.9 ± 11.9 cm, while the prevalence of abdominal obesity, WC ≥ 102 cm, was 24.1% (95% CI: 19.2–29.0%). The mean neck circumference of the study population was 39.2 ± 2.8 cm, with 28.8% having a neck circumference ≥ 40 cm (Table 2).

Table 2. Measures of obesity, BP and glucose profile of the subjects

Parameters	Mean ± SD	*n* (%)
BMI (kg/m^2)	27.2 ± 9.6	
Waist circumference (cm)	96.4 ± 0.9	
Proportion < 102 cm		168 (66.4)
Proportion ≥ 102 cm		125 (43.3)
Neck circumference (cm)	39.2 ± 2.8	
Proportion < 40 cm		171 (59.6)
Proportion ≥ 40 cm	131 (41.6)	
Blood pressure		
SBP (mmHg)	136.3 ± 20.9	
DBP (mmHg)	83.2 ± 13.6	
Total number of hypertensives		116 (39.7)
Newly diagnosed		88 (75.9)
Previously known hypertensives		29 (9.6)
Blood glucose		
Fasting blood glucose (mg/dl)	108.2 ± 39.7	
Normoglycaemia		158 (54.9)
Impaired fasting glucose		90 (31.3)
Total number of diabetics		40 (13.9)
Newly diagnosed diabetics		33 (82.5)
Previously known diabetics		7 (17.5)

SBP: systolic blood pressure; DBP: diastolic blood pressure.

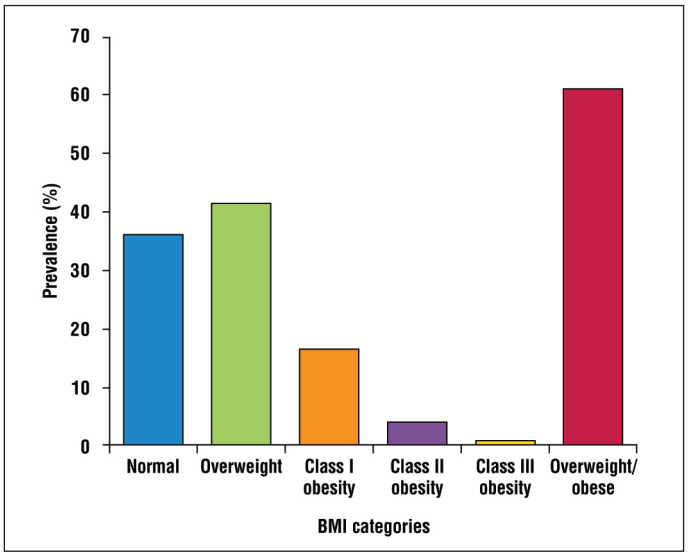


Fig. 2. Prevalence of the various categories of BMI.

The mean systolic blood pressure (SPB) and diastolic blood pressure (DBP) of the subjects were 136.3 ± 20.9 and 83.2 ± 13.6 mmHg, respectively. One hundred and sixteen cases of hypertension were identified, giving a prevalence rate of 39.7% (95% CI: 34.0–45.25%). Eighty-eight (75.9%) were detected for the first time during the study. Twenty-eight (24.1%) were previously known hypertensives, with six (21.4%) having good BP control (Table 2).

The mean fasting blood glucose level (FBG) of the study population was 108.2 ± 39.7 mg/dl (6.01 ± 2.2 mmol/l). Forty of the subjects (13.9%; 95% CI: 9.7–17.6%) had diabetes and seven (2.4%) were previously known diabetics. Ninety (31.3%) had impaired fasting glucose levels. Prevalence of abnormal glucose profiles (diabetes + impaired FBG) was 45.2% (95% CI: 39.3–50.7%) (Table 2).

The mean TC of the study population was 218.4 ± 33.2 mg/dl (5.66 ± 0.86 mmol/l). The overall lipid profile is presented in Table 3. One hundred and twenty-eight (43.7%) of the subjects had normal lipid profiles while 165 (56.3%) had one form of dyslipidaemia or another. The prevalence of dyslipidaemia in the study was 56.3% (95% CI: 50.6–62.0%), while the prevalence of atherogenic dyslipidaemia, i.e. elevated TC/HDL-C was 33.1% (95% CI: 27.7–38.5%) (Table 3).

Table 3. Pattern of lipid profiles of the subjects

	Mean ± SD		
Parameter	mg/dl	mmol/l	*n* (%)
TC	218.4 ± 33.2	5.66 ± 0.86	
LDL-C	136.4 ± 33.6	3.53 ± 0.87	
HDL-C	57.7 ± 15.3	1.49 ± 0.40	
TG	122.7 ± 64.1	1.39 ± 0.72	
Non-HDL-C	161.0 ± 31.5		
TC/HDL-C	3.8 ± 1.9		
TG/HDL	3.7 ± 2.6		
Abnormal profiles			
Elevated TC			81 (27.8)
Elevated LDL-C			72 (24.6)
Low HDL-C			19 (6.5)
Elevated TC/HDL-C			96 (33.1)
Elevated TG/HDL-C			38 (13.0)

TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides.

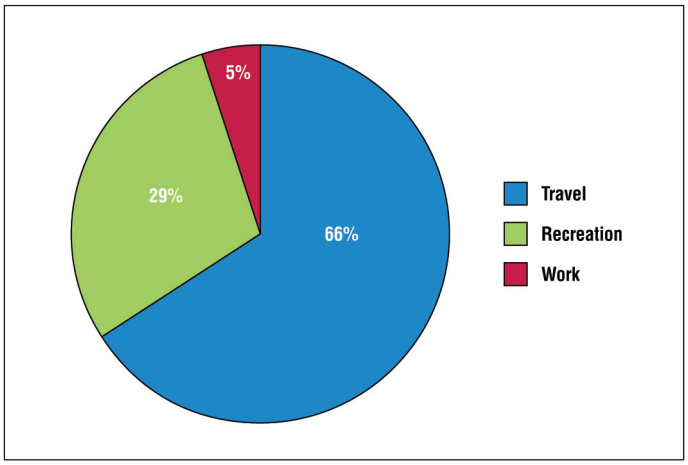


Fig. 3. Contributions of the GPAQ2 domains to total physical activity of the subjects.

The mean METs/hour of the subjects was 638.8 ± 565.5, with 66% of them spending most of their time in the travel domain (Fig. 3). The prevalence of physical inactivity in the study population, defined as total METs/hour in all four domains < 600 per week was 50.9% (95% CI: 53.1–64.3%). Two hundred and thirty-four (80.4%) of the subjects were inactive, 56 (19.2%) were low active, while one (0.3%) was medium active. None was highly active.

One hundred and thirty-two (45.1%) subjects had co-occurrence of two or more risk factors. The most prevalent combination was the duo of hypertension and abnormal glucose profile. Fig. 4 shows the common single risk factors, while common risk factor combinations are shown in Fig. 5. Alcohol use and physical inactivity were the commonest behavioural risk factors, while overweight/obesity, hypertension and dyslipidaemia were the three most common metabolic risk factors in the subjects (Fig. 6).

Pearson's correlation was used to determine how some independent numerical variables (age, BMI, number of years of professional driving and number of driving hours/week) correlated with the major outcome variables (SBP, DBP and fasting blood glucose level). Age correlated significantly with SBP (r = 0.362, p < 0.001) and DBP (r = 0.335, p < 0.001). BMI also correlated

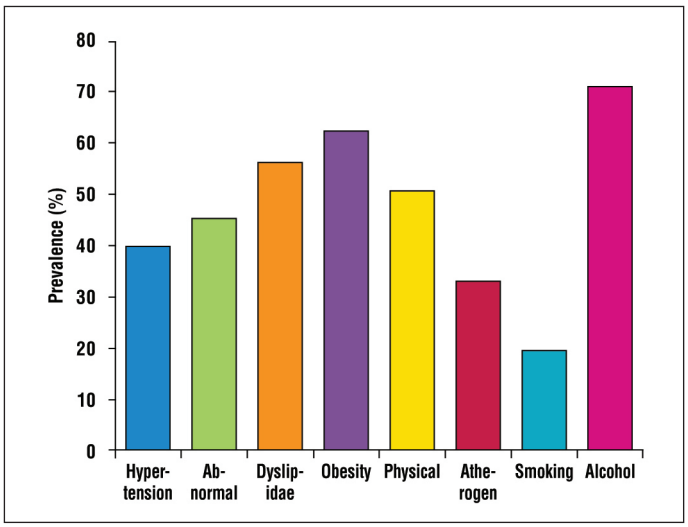


Fig. 4. Prevalence of single risk factors among the subjects.

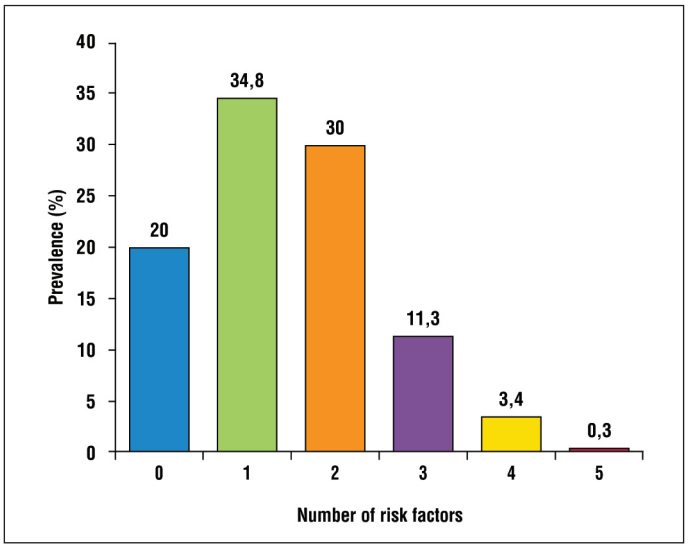


Fig. 5. Prevalence of multiple risk factors among the subjects.

significantly with SBP (r = 0.288, p < 0.001) and DBP (r = 0.208, p < 0.001). BMI alone correlated significantly with fasting glucose (r = 0.136, p = 0.021).

Furthermore, the independent variables were dichotomised to look for an association between them and outcome variables of hypertension and abnormal glucose profile. In this model only age, BMI, number of years of professional driving and waist circumference had significant associations with hypertension, while none of these except BMI had a significant association with abnormal glucose levels (Table 4).

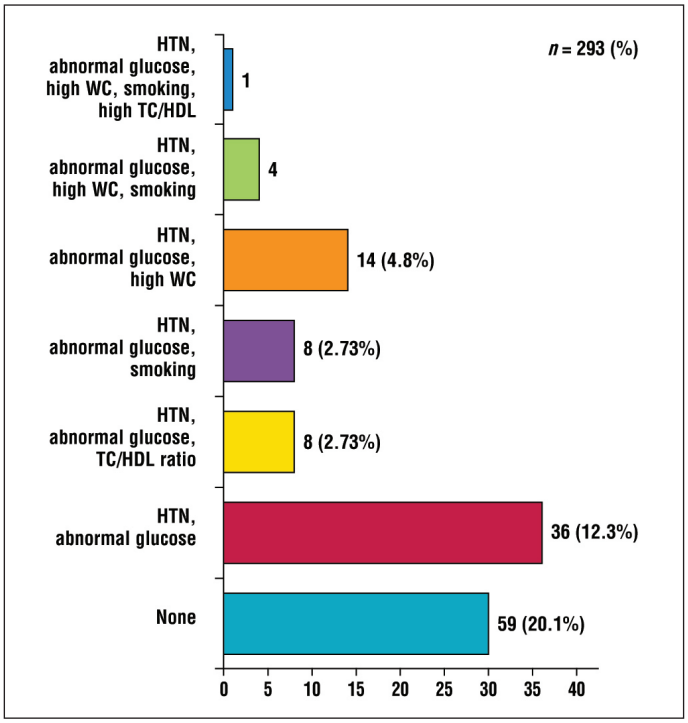


Fig. 6. Prevalence of different combinations of risk factors in the subjects. HTN: hypertension; WC: waist circumference; TC: total cholesterol; HDL: high-density lipoprotein cholesterol.

Table 4. Association between independent variables and hypertension and abnormal glucose levels

	Hypertension		Abnormal glucose levels	
Parameter	**% (95% CI)**	***p*-value**	**% (95% CI)**	***p*-value**
Driving hours/week		0.250		0.076
≥ 36	42.9 (35.0–50.9)		35.6 (27.9–43.2)	
< 36	36.3 (28.5–44.2)		25.9 (18.6–33.2)	
Years of professional driving		< 0.001		0.320
≥ 20	56.2 (43.1–64.4)		33.1 (25.4–40.8)	
< 20	23.1 (16.2–30.0)		27.7 (20.3–35.0)	
Physical activity		0.279		0.205
< 600 METs/week	42.6 (34.6–50.5)		27.6 (20.3-34.9)	
≥ 600 METs/week	36.3 (28.5–44.2)		34.5 (26.7-42.3)	
BMI		< 0.001		0.002
Overweight/obese	48.4 (41.1–55.6)		37.8 (30.7–44.9)	
Normal	25.9 (17.7–34.2)		19.8 (12.2–27.4	
Alcohol use		0.840		0.807
Yes	40.1 (33.4–46.8)		31.2 (24.9–37.6)	
No	38.8 (28.5–49.2)		29.8 (20.0–39.5)	
Smoking		0.477		0.808
Yes	43.9 (31.0–56.7)		32.1 (19.9-44.4)	
No	38.7 (28.5-49.2)		30.5 (24.6-36.4)	
WC (cm)		< 0.001		0.076
> 102	61.4 (50.0–72.8)		39.7 (28.1–51.3)	
≤ 102	33.0 (26.8–39.2)		28.3 (22.3–34.3)	
Age		< 0.001		0.499
≥ 45	54.5 (46.4–62.6)		32.6 (25.0–40.3)	
< 45	25.2 (18.2–32.2)		29.0 (21.6–36.3)	

BMI: body mass index; WC: waist circumference; METs: metabolic equivalents.

Multivariate analysis was done using a forward stepwise binary logistic regression in order to assess for independent predictors of hypertension and abnormal blood glucose levels. We included predictor variables with associations at a significance level of $p \leq 0.2$ on univariate analysis in order to accommodate for important risk factors. The final logistic regression model (Table 5) showed that as age and BMI increased, the chances of becoming hypertensive increased 1.09 and 2.99 times (OR 1.09; 95% CI: 1.06–1.1, $p < 0.0001$; OR 2.99; 95% CI: 1.69–5.31, $p < 0.0001$), respectively.

For abnormal glucose level with increasing BMI, the chances of having abnormal glucose level increased 2.5 times (OR 2.39; 5% CI: 1.33–4.30; $p = 0.004$). Other variables such as physical activity, number of driving hours, waist circumference and professional driving years were not independently associated with our outcome parameters and were excluded from the final regression model.

Table 5. Logistic regression on predictors of hypertension and abnormal glucose levels

	Hypertension[a]		Abnormal glucose levels[b]	
Variables	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Age	1.090 (1.058–1.23)	< 0.0001	ns	ns
Overweight/obesity	2.99 (1.69–5.32)	< 0.0001	2.39 (1.33–4.3)	0.04

[a]Variables excluded from the final model were: physical activity, number of driving hours, waist circumference and professional driving years.
[b]Variables excluded from the final model were: age, physical activity, number of driving hours, waist circumference and professional driving years.

Discussion

The major finding of this study was that male long-distance bus drivers had a higher prevalence of clustering of cardiometabolic risk factors than the general population, and in addition, most them were unaware of their risk status.[12,14] This clustering places them at a higher risk for CVD and contributes significantly to the already burgeoning CVD burden in the general population. Importantly, a CVD event in a driver while driving portends grave danger to him, the passengers and other road users.

The prevalence of hypertension in this study was 39.7%, with 75.9% being newly diagnosed. This is higher than the recent pooled national prevalence rate of 28.9% but lower than the 44.9% prevalence from a national study on blindness and hypertension.[32,33] Previous local studies reported prevalence rates ranging from 21.4 to 33.5%.[19-21] Studies from Brazil and Iran reported prevalence rates of 45.6 and 44.6%, respectively, much higher than their national prevalence rates.[12,13]

Professional drivers, by nature of their occupation, are largely sedentary and indulge in dietary indiscretions, which could lead to obesity. From this study, obesity was a predictor of hypertension. Furthermore, BMI and longer duration of years of professional driving significantly correlated with the risk of hypertension, similar to findings by Sangaletti *et al*.[12] This association is plausible, as drivers who drive for long hours over many years tend to gain weight inappropriately due to physical inactivity and dietary indiscretion.

In addition to high prevalence of hypertension, optimal blood pressure control was equally low among the subjects. Among the 9.6% previously known hypertensives, only 21.4% had optimal BP control. BP control is generally very low in Nigeria, ranging between five and 29.4%.[34,35] Ignorance, long travel times, poor access to standard medical care, the asymptomatic nature of hypertension and the relative lack of self-care among males have been suggested as possible causes of poor BP control among long-distance drivers.[12]

The prevalence of abnormal glucose profiles in this study was 45.2%, comprising 31.3 and 13.9% for impaired fasting gliucose levels and diabetes mellitus (DM), respectively. Most of the diabetics were diagnosed for the first time during this study. There are no local studies for comparison but the reported prevalence of DM from this study is much higher than the 4.5% reported by the International Diabetes Federation (IDF) and the eight to 10% from a study on the general population.[36,37] In Iran, the prevalence of DM among drivers was 17.5%, comparable to the value obtained from this study, but higher than the 8.5% prevalence reported by the IDF in 2014.[13] Obesity is a risk factor for type 2 DM. From our study, BMI was a predictor of abnormal glucose profiles, similar to the findings by Sangaletti *et al*.[12]

The prevalence of dyslipidaemia in this study was 56.3%, comparable to the national average of 60.1%.38 The predominant dyslipidaemia was elevated TC levels in 27.8% of the subjects, followed by elevated LDL-C levels in 24.6%, elevated triglycerides in 24.6% and low HDL-C levels in 6.5%. There are no local studies of lipid abnormalities in professional drivers. The pattern obtained is at variance however with patterns reported in local studies in apparently healthy Nigerians, in which the predominant dyslipidaemia was low HDL-C levels.[38] In Iran, professional drivers have been shown to have predominantly hypertriglyceridaemia and central obesity, attributable to stressful working conditions.[13]

The combined prevalence of overweight and obesity, measured by BMI in this study, was 62.8%, comparable to the 63.4 and 64.4% reported by similar local studies,[19-21] but higher than the reported prevalence of 31 to 48% in the general Nigerian population.[39,40] Similar international studies documented a prevalence of combined overweight and obesity to be between 62.1 and 78.2%.[13,41,42] Using waist circumference, the prevalence of obesity from this study was 24.1%. This was lower than the 58.2 and 63.3% from studies in Brazil and Iran, respectively.[12,41] This difference might be methodological. In these countries the cut-off for abdominal obesity is 88 cm, less than the 102 cm used in our study.[43,44] Prolonged work stress and long hours at work contribute to the development of obesity and abdominal obesity in professional drivers.[13]

The prevalence of physical inactivity in this study was 50.9%, comparable to the 53.4% from a local study,20 but lower than the 72.8% reported by similar international studies.[12,45] Both studies were among truck drivers who probably do not have to stop on the way for passengers to alight for refreshments. Physical inactivity and dietary habits of professional drivers are known to predispose to obesity. Obesity increases the risk of hypertension and abnormal glucose profiles, as shown in this study. It is also known to increase the risk of road traffic accidents among professional drivers due to its association with obstructive sleep apnoea and excessive daytime sleepiness, consequent fatigue and reduction in alertness while driving.[46]

The prevalence of smoking in this study was 19.5%. Reported prevalence in similar local studies is between 17.8 and 31.3%, all higher than the 15% in the general population.[20,21,47,48] The lower prevalence from this study might be due to dilution effect from the 'no smoking within the bus terminal' policy of one of the transport companies used in this study. Secondly, the subjects may not have been truthful in their responses to the question on smoking status. Comparable rates of 20 and 15.6% were reported in similar international studies.[12,45]

Alcohol consumption was very common in this study group, with a prevalence rate of 71.1%. Reported local prevalence in this group ranged from 34 to 84.4%.[20,48,49] These figures are much higher than the 7.6 and 9.1% reported in the general male population.[50,51] A recent local study from Muslim-dominated north-west Nigeria documented a prevalence of 5.5% among inter-city bus drivers.[21] This very low figure might be related to a religious obligation that forbids Muslims from consuming alcohol.

It is pertinent to note that in this study, CVD risk factors co-occurred, as has been documented in the past.[52] This clustering of risk factors increases the overall CVD risk of the individual and also makes control difficult due to problems of pill burden.[53,54] In this study 45.1% of the subjects had more than two risk factors clustered together. Clustering of CVD risk factors has been documented in the general population, with prevalence rates between 12.9 and 27.5%, depending on the study population. The commonest risk-factor combinations are hypertension, obesity, abnormal glucose profile and atherogenic dyslipidaemia.[55-57] Our findings are similar to the above pattern, although the combination of hypertension and abnormal glucose level was most prevalent. These findings are similar to the pattern reported in similar studies.[12,13] There were some limitations in this study. The use of glycosylated haemoglobin would have been helpful in assessing the quality of glycaemic control among the diabetic subjects. Bus drivers with poor control of both BP and glucose levels were not assessed for medication adherence.

Conclusion

Long-distance professional drivers in Nigeria are at a higher risk for CVD than the general male population on account of the higher prevalence of a plethora of risk factors they harbour: hypertension, abnormal glucose profiles, overweight/obesity, alcohol use, smoking and atherogenic dyslipidaemia. These risk factors not only co-occur in a large number of drivers, but most are unaware of their risk. Overweight/obesity is the common driver of hypertension and abnormal glucose profiles among them, while age ≥ 45 years increases the risk of developing hypertension. Contributing to their risk is the social gradient of inequality, which affects their access to healthcare and adherence to medical intervention.

There is therefore a need to increase CVD risk awareness in this vulnerable yet important segment of our population through public awareness campaigns, banning of smoking and selling of alcoholic beverages in motor parks, compulsory annual health screening, defined maximum driving hours per week, provision of facilities to promote physical activity in the motor parks and medical facilities to diagnose, treat and monitor risk-factor control. Universal health insurance coverage as a national health policy would also help in providing healthcare/health promotional services to this group, who at the moment are not covered by the health insurance scheme.

Acknowledgements

The authors thank Drs Igebu, Anyakpele, Oyatokun, Eluogu and Oshuntokun for helping out with data collection, and Chimamaka Chibuike and Joy Alozie for their help in preparing the manuscript.

References

1. World Health Organization. Prevention of cardiovascular disease: Guidelines for assessment and management of cardiovascular risk, 2007. Geneva, Switzerland. Accessed July 22, 2015.
2. SIGN (Scottish Intercollegiate Guidelines Network). Risk estimation and the prevention of Cardiovascular Disease. A National Clinical Guideline. Report No. 97, 2007.
3. World Health Organization. Cardiovascular disease. Controlling high blood pressure, 2015. http://www.who.int/cardiovascular_diseases/en/Accessed January 6, 2015.
4. World Health Organization. Global status report on non-communicable diseases, 2010. Genera, Switzerland. Accessed February 22, 2015.
5. World Health Organization. Cardiovascular disease. Strategic priorities, 2015. http://www.who.int/cardiovascular_diseases/priorities. Accessed February 22, 2015.
6. World Health Organization. Cardiovascular diseases. Factsheet No 317, 2015. www.who.int/mediacentre/factsheets/fs317/en/index. Accessed February 22, 2015.
7. Morris JN, Heady JA, Raffle PAB, Roberts CG, Parks JM. Coronary heart disease and physical activity at work. *Lancet* 1953; **265**: 1111–1120.
8. Hannerz H, Tuchsen F. Hospital admissions among male drives in Denmark. *Occup Environ Med* 2001; **58**: 253–260.
9. Gustavson P, Alfedsson L, Brunnberg H, *et al*. Myocardial infarction among male bus taxi and lorry bus drivers in middle Sweden. *Occup Environ Med* 1996; **53**: 235–240.
10. Bigert C, Gustavsson P, Hallquist J, *et al*. Myocardial infarction among professional drivers. *Epidemiology* 2003; **14**: 333–339.
11. Tuchen F. Stroke morbidity in professional drivers in Denmark 1981–1990. *Int J Epidemiol* 1997; **26**: 989–994.
12. Sangaleti CT, Trincaus MR, Baratieri T, *et al*. Prevalence of cardiovascular risk factors among truck driver in the South of Brazil. *BMC Public Health* 2014; **14**(1063a): 1–9.
13. Mohebbi I, Saadat S, Aghassi M, *et al*. Prevalence of metabolic syndrome in Iranian professional drivers. Results from a population based study of 12,138 men. *PLoS ONE* 2012; **7**(2): e31790.
14. Hirata RP, Malosa Sampio LM, Leitao Filho FS, *et al*. General characteristics and risk factors of cardiovascular disease among interstate bus drivers. Sci W J 2012; Article ID 216702: 1–8.

15. Daleva M, Piperova-Dalbokova D, Hadjiolova I, *et al*. Changes in the excretion of corticosteroids and catecholamines in tractor-drivers. *Int Arch Occup Environ Health* 1982; **49**: 345–352.
16. Sato S, Taoda K, Kawamura M, *et al*. Heart rate variability during long truck driving work. *J Hum Ergol* (Tokyo) 2001; **30**: 235–240.
17. www.citymayor.com (2012).World's fastest growing cities and urban areas from 2006–2020. Accessed Feb 13, 2015.
18. Lagos metropolitan area transport. Lagos: Bureau of Statistics. Digest of Statistics, 2010.
19. Amoran OE, Salako EE, Jeminusi O. Screening for common occupational health disease among long distance professional drivers in Sagamu, Ogun state, Nigeria. *Int J Prev Med* 2014; **5**(4): 516–521.
20. Tobin EA, Ofili AN, Asogun DA, *et al*. Prevalence of hypertension and associated factors among inter-city drivers in an urban city in South- South Nigeria. *Int J Res Med* 2013; **2**(3): 5–12.
21. Erhiano EE, Igbokwe VU, El-Khashab MM, Okolo RU, Awosan KJ. Prevalence of hypertension among commercial bus drivers in Sokoto, Sokoto state, Nigeria. *Int J Med Med Sci* 2015; **2**(3): 34–39.
22. Ogah OS, Okpechi I, Chukwunoye II. Blood Pressure, prevalence of hypertension and hypertension related complications in Nigerian Africans: A review. *World J Cardiovascular Dis* 2012; **4**(12): 327–340.
23. www.labour.gov.bc.ca/esb/faceshts
24. Rolland-Cachera MF, Sempe M, Guilloud-Bataille M, Patois E, *et al*. Adiposity Indices in children. *Am J Clin Nutr* 1982; **36**: 178–184.
25. The WHO STEPwise approach to non-communicable disease risk factor surveillance (STEPS). www.who.int/chp/steps. Accessed April 12, 2015.
26. Ozoh OB, Okubadejo NU, Dania MG. High risk of obstructive sleep apnea and excessive daytime sleepiness among commercial intra-city drivers in Lagos metropolis. *Niger Med J* 2013; **54**(4): 224–229.
27. www.randox.com/randox_biosciences.
28. American Diabetic Association diagnostic criteria. www.diabetes.org/diabetes-basic/diagnosis; 2014. Accessed June 19, 2015.
29. National Cholesterol Education Program: ATP III Guidelines 2001. www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf. Accessed on May 20, 2015.
30. Castelli WP, Anderson K, Wilson PW, Levy D. Lipis and the risk of coronary heart disease. The Framingham Study. *Ann Epidemiol* 1992; **2**(1–2): 23–28.
31. www.who.int/steps/resources/GPAQ_Analysis_Guide.pdf. Accessed May 20, 2015.
32. Adeloye D, Basquill C, Aderemi AV, *et al*. An estimate of the prevalence of hypertension in Nigeria: a systematic review and meta-analysis. *J Hypertens* 2015; **33**(2): 230–242.
33. Murthy GVS, Fox S, Sivasubramanian S, Gilbert CE, Mahdi AM. Prevalence and risk factors of hypertension and association with ethnicity in Nigeria: results from a national survey. *Cardiovas J Afr* 2013; **24**(9): 344–350.
34. Ekwunife OI, Udeogaranya P, Nwatu I. Prevalence, awareness, treatment and control of hypertension in a Nigerian population. *Health* 2010; **2**: 731–735.
35. Iseuzo S, Sabir AA, Ohwovoriole AE, Fasanmade OA. Prevalence, associated factors and relationship between prehypertension and hypertension: a study of two ethnic African populations in northern Nigeria. *J Hum Hypertens* 2010; **25**(4): 224–230.
36. Aguiree F, Brown A, Cho NH, Dahlquist G, Dodd S, Dunning T, *et al*. In: Guariguata L, Nolan T, Beagley J, Linnenkamp U, Jacqmain O (eds). International Diabetes Federation Atlas. Basel, Switzerland: International Diabetes Federation, 2013.
37. Ogbera OA, Ekpebegh C. Diabetes Mellitus in Nigeria: The past, present and future. *World J Diabetes* 2014; **5**(6): 905–911.
38. Odenigbo CV, Oguejiofor OC, Odenigbo UM, *et al*. Prevalence of dyslipidaemia in apparently healthy professionals in Asaba, South- South Nigeria. *Nig J Clin Pract* 2008; **11**: 330–335.
39. Ono T, Guthold R, Strong K. WHO Global Comparable Estimates. Global Infobase data for saving lives 2005–2012. https://apps.who.int/ infobase/index.aspx. Accessed February 23, 2015.
40. Okafor CI, Gezawa ID, Sabir AA, Raimi TH, Enang O. Obesity, overweight and underweight among urban Nigerians. *Nig J Clin Pract* 2014; **17**: 743–749.
41. Saberi HR, Moravveji AR, Frakhanan E, Kashani, *et al*. Prevalence of metabolic syndrome in bus and truck drivers in Kashan, Iran. *Diabetol Metabolic Syndrome* 2011; **3**(1): 8.
42. Hirata RP, Malosa Sampio LM, Leitao Filho FS, *et al*. General characteristics and risk Factors of Cardiovascular Disease among Interstate Bus Drivers. *Sci W J* 2012; Article ID 216702: 1–8.
43. Barbosa PJB, Leaas I, Filho NA, Magalhaes LB, Araujo J. Criteria for central obesity in a Brazilian population: impact on metabolic syndrome. *Arq Bras Cardiol* 2006; **87**(4): 1–8.
44. Shabnam AA, Homa K, Reza MM, Bagher L, *et al*. Cut-off points for waist circumference and body mass index for detecting diabetes mellitus, hypercholestrolaemia and hypertension according to the national non-communicable risk factor surveillance in Iran. *Arch Med Sci* 2012; **8**(4): 614–621.
45. Lakshman A, Manikath N, Rahim A, Anilakumari VP. Prevalence and risk factors for hypertension among male occupational bus drivers in North Kerla, South India: A cross-sectional study. *ISRN Prev Med* 2914; Article 19 318532; 1–9.
46. Zhu S, Kim J, Ma X, Shih A, *et al*. Body mass index and risk of serious upper body injuries following motor vehicle crashes: concordance of real-world and computer-simulated observations. *PLos Med* 2010; **7**(3): e 1000250.
47. World Health Organization. Cardiovascular diseases. Factsheet No 317, 2015. www.who.int/mediacentre/factsheets/fs317/en/index. Accessed February 22, 2015.
48. Adejugbagbe AM, Fatiregun AA, Rukewe A, Alonge T. Epidemiology of road traffic crashes among long distance drivers in Ibadan. *Afr Health Sci* 2015; **15**(2): 483–488.
49. Bello S, Ndifon OO, Mpama OO, Odowole OO. Pattern of alcohol use among drivers of commercial vehicles in Calabar, Nigeria. *E Afr Med J* 2011; **88**(33): 3–6.
50. Chukwuonye II, Chuku A, Onyeonoro UU, Madukwe OO, *et al*. A rural and urban cross-sectional study on alcohol consumption among adult Nigerians in Abia state. *Int J Med Biomed Res* 2013; **2**(3): 179–185.
51. World Health Organization. Management of substance abuse. Country profiles, 2014. www.who.int/substance_abuse/publications/global_alcohol_report/profile/nga.pdf?ua=1. Accessed August 28, 2015.
52. Mancia G, Parati G, Borghi C, Ghironzi G, *et al*. Smooth investigators. Hypertension prevalence, awareness, control and association with metabolic abnormalities in San Maniano population the SMOOTH study. *J Hypertens* 2006; **24**: 837–843.
53. Mancia G,Bombelli M, Corrao G, Facchetti R, Madotto F, *et al*. Metabolic syndrome in the PAMELA study: daily life blood pressure, cardiac damage, and prognosis. *Hypertension* 2007; **49**: 40–47.
54. Mancia G, Grassi G. Systolic and diastolic blood pressure control in anti-hypertensive drug trials. *J Hypertens* 2007; **20**: 1461–1464.
55. Showande SJ, George OA, Adekunle OO. Gender-related differences in the prevalence and correlates of modifiable cardiovascular disease risk factors among seemingly healthy adult Nigerians – a cross-sectional study. *Br J Med Med Res* 2014: **4**(25): 4325–4340.
56. Mahmoud US, Kolawole WW, Bashir OY, Maruf G, Omolara VJ, Akeem G. Modifiable cardiovascular risk factors among apparently healthy adult Nigerian population – a cross-sectional study. *BMC Res Notes* 2010; **3**(11): 1–7.
57. Oladapo OO, Falase AO, Salako L, Sodiq O, Shoyinka K, Adedapo K. A prevalence of cardiometabolic risk factors among a rural Yoruba southwestern Nigerian population: a population-based survey. *Cardiovasc J Afr* 2010; **21**(1): 26–31.

The effects of treatment with atorvastatin versus rosuvastatin on endothelial dysfunction in patients with hyperlipidaemia

VAHIT DEMIR, MEHMET TOLGA DOĞRU, HÜSEYIN EDE, SAMET YILMAZ, CAĞLAR ALP, YUNUS CELIK, NESLIGÜL YILDIRIM

Abstract

Introduction: **Statins can reduce cardiovascular events and improve endothelial function. However, differences in the effect of statins on endothelial dysfunction have not been researched sufficiently. Here, we aimed to compare the effects of atorvastatin versus rosuvastatin on endothelial function via flow-mediated and endothelial-independent dilation.**

Methods: **Hyperlipidaemic subjects on treatment with statins for one year (either 20 mg/day atorvastatin or 10 mg/day rosuvastatin) were enrolled in the study. In accordance with the literature, flow-mediated dilation (FMD) and nitrate-mediated endothelium-independent dilation (EID) were measured by ultrasonography on the right brachial artery of each subject. Baseline and final measurements were compared in each group and between the groups.**

Results: **One hundred and four subjects (50 atorvastatin and 54 rosuvastatin users) were enrolled in the study. Fifty-eight subjects were female. The groups were statistically similar in terms of age and body mass index, and haemoglobin, creatinine, total cholesterol, triglyceride, high-density lipoprotein and low-density lipoprotein cholesterol levels. In each group, the mean final FMD and EID values were higher compared to their respective baseline values, but the mean changes in FMD and EID were statistically similar in both groups (p = 0.958 for FMD and 0.827 for EID). There was no statistically significant difference between the atorvastatin and rosuvastatin groups in terms of final FMD and EID values (p = 0.122 and 0.115, respectively).**

Conclusion: **This study demonstrated that both one-year atorvastatin and rosuvastatin treatments significantly improved endothelial function, when assessed with FMD and EID and measured by ultrasonography. However, the amount of improvement in endothelial dysfunction was similar in the two treatments.**

Keywords: atorvastatin, endothelial function, flow-mediated vasodilatation, rosuvastatin

Correspondence to: Vahit Demir
Cardiology Department, Faculty of Medicine, Bozok University, Yozgat, Turkey
e-mail: dr.vdemir@hotmail.com

Hüseyin Ede
Cardiology Department, Faculty of Medicine, Bozok University, Yozgat, Turkey

Mehmet Tolga Doğru, Cağlar Alp, Yunus Celik, Nesligül Yıldırım
Cardiology Department, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey

Samet Yılmaz
Cardiology Department, Yozgat State Hospital, Yozgat, Turkey

Previously published in *Cardiovasc J Afr* 2018; **29**(3): 162–166

S Afr J Diabetes Vasc Dis 2018; **15**: 52–56

Hyperlipidaemia is an important risk factor for the development of atherosclerosis. Statins may reduce the risk of cardiovascular events and improve endothelial function.[1,2] The positive effect of statins on endothelial dysfunction is carried out via endothelial nitric oxide enzyme activation.[3] Pleiotropic effects of statins include improvement in endothelial function, anti-thrombosis, plaque stabilisation and anti-oxidative effects, and decreasing the duration of vascular inflammation.[4] However, differences in the effect of statins on endothelial dysfunction has not been researched sufficiently. Earlier studies demonstrated that improved endothelial dysfunction in different vascular beds started after a few days of treatment with statins.[5-8]

Endothelial dysfunction is the early sign of atherosclerosis and enhances the risk of cardiovascular events.9 Flow-mediated dilation (FMD) is a well-known method used for predicting the extent of atherosclerosis. FMD is measured on the brachial arteries and reflects the ability of an artery to enlarge after being compressed for a certain time. Nitric oxide (NO) is the most important vascular vasodilator and is produced by the endothelium in response to certain factors such as shear stress. Its production is impaired in the case of endothelial dysfunction. Increased production of NO after increased vascular blood flow is the underlying mechanism of FMD.[10]

Studies on primary and secondary prevention of cardiovascular disease and its complications by statins revealed that their effect occurs not only due to their lipid-lowering effect but also due to pleiotropic effects, the mechanism of which remains unclear. In this study we aimed to compare the effect of one-year rosuvastatin versus atorvastatin therapy on endothelial function in hyperlipidaemic patients, using FMD and endotheliumindependent dilation (EID), measured ultrasonographically on the brachial artery.

Methods

A total of 112 patients diagnosed with hyperlipidaemia and without a history of previous lipid-lowering medication for at least the previous two months, and with an indication for medical treatment despite a first-line, four-week, lipid-lowering diet, applied to the cardiology out-patient unit and were enrolled in the study between May 2010 and August 2011. Approval of the local ethics committee and informed consents of the participants were obtained accordingly.

A subject was considered treatment adherent when he/she took her/his prescribed statin regularly on a daily basis. A subject was considered complient if his/her baseline and post-treatment measurements were obtained as per the study protocol. Eight cases (four with compliance problems with follow up, one with lung cancer and three with non-adherence to medication) were excluded from the study.

The study was completed with 104 hyperlipidaemic patients, of whom 50 were assigned to atorvastatin 20 mg per day and 54 to rosuvastatin 10 mg per day. Patients under the age of 18 and over the age of 80 years, those with heart failure, uncontrolled hypertension, endocrine diseases, previous coronary artery disease, frequent and permanent cardiac dysrhythmia, malignancy, chronic obstructive pulmonary disease, and chronic liver, kidney, neurological or psychiatric diseases, which were likely to produce a compliance problem, were not included in the study.

Baseline demographic characteristics of the patients were recorded. Body mass index (BMI) was calculated as body weight (kg)/height^2 (m). Levels of fasting blood glucose, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), creatinine phosphokinase (CPK) and complete blood counts were measured in all patients after a 12-hour fasting period. In addition, the patients underwent transthoracic echocardiography.

Lipid levels indicated eligible patients, who were randomly assigned to receive either rosuvastatin 10 mg/day or atorvastatin 20 mg/day. The patients were followed for one year. Baseline measurements were repeated at the end of the 12-month treatment period. Change in LDL level (ΔLDL) was defined as the difference between baseline and post-treatment LDL values.

Endothelial function was measured ultrasonographically over the brachial artery using echocardiography (Ge-Vivid 7 Pro, General Electric, Florida, USA) with a 12-L probe.

All measurements were performed according to the method described elsewhere in the literature.[11] Brachial artery basal Doppler velocity (DV), basal diameter (BD), brachial artery hyperaemia velocity (HV), and post-flow brachial artery lumen diameter (hyperaemia diameter = HD flow-mediated dilation response = FMDR) were recorded. FMD was calculated from the following equation:

$$\% \text{ FMD} = \frac{\text{FMDR} - \text{BD}}{\text{BD}} \times 100$$

Baseline endothelium-independent dilation (EID) was measured 10 minutes after deflation of the cuff to obtain baseline conditions and was labelled as pre-nitrate BD. Thereafter, the patients received 400 µg of nitroglycerin sublingually; three to five minutes later, post-nitrate Doppler, post-nitrate velocity (NTGV) and post-nitrate arterial diameter (NTGD) were measured. Lumen diameter was measured three times and the arithmetic mean was calculated. Post-nitrate arterial diameter was named nitrate-mediated dilation response (NMDR). EID was calculated using the following equation:

$$\% \text{ EBG} = \frac{\text{NMDR} - \text{pre-nitrate BD}}{\text{Pre-nitrate BD}} \times 100$$

ΔFMD and ΔEID were defined as the difference between baseline and post-treatment FMD and EID values, respectively.

Statistical analyses

The SPSS (SPSS, Inc, Chicago, IL, USA) program was used to analyse the data. Mean and standard deviations (SD) were used for descriptive data. Student's *t*-test was used to compare normally distributed quantitative variables, whereas the Mann–Whitney *U*-test was used to compare independent non-normally distributed quantitative variables. Moreover, statistical comparison between continuous dependent variables was done by paired-samples *t*-test for normally distributed variables, whereas the Wilcoxon test was used for non-normally distributed variables. Relationships between the parameters were assessed with Pearson's correlation analysis for parametric variables and by Spearman's correlation analysis for non-parametric variables. The results were evaluated with a 95% confidence interval and at the significance level of $p < 0.05$.

Results

A total of 104 hyperlipidaemic cases were included in the study. The patients were randomly assigned to either atorvastatin (group 1, n = 50, 48.1%) or rosuvastatin (group 2, n = 54, 51.9%) therapy. Of the overall patients, 46 were male (53.7 ± 9.7 years) and 58 were female (54.3 ± 10.1 years). There was no statistically significant difference between the two groups in terms of baseline anthropometric characteristics of the subjects, haemoglobin, haematocrit, white blood cell count, thrombocyte count, and urea, creatinine, AST, ALT, CPK, total cholesterol, TG, HDL and LDL levels.

Mean ΔLDL at the end of 12 months was 71.0 ± 29.7 mg/dl (1.84 ± 0.77 mmol/l) and percentage ΔLDL was 42.2 ± 17.6% (n = 104) in the study population. ΔLDL was significantly correlated with ΔFMD (r = 0.367, $p < 0.005$) and ΔEID (r = 0.523, $p < 0.001$). Percentage ΔLDL was statistically correlated with ΔFMD (r = 0.412, $p < 0.005$) and ΔEID (r = 523, $p < 0.001$). In the atorvastatin group, a statistically significant reduction was shown in total cholesterol, LDL and TG levels compared to baseline values. LDL level showed a 52.5% decrease after 12 months compared to baseline value, whereas no decrease was observed in HDL level. FMD showed a statistically significant increase (Table 1).

In the rosuvastatin group, a statistically significant decrease was found in total cholesterol, LDL and TG levels compared to

Table 1. Post-treatment versus baseline values in the atorvastatin group

Atorvastatin	Baseline mean ± (SD)	12-month mean ± (SD)	*p*-value*
Basal diameter (mm)	4.0 ± 0.6	4.1 ± 0.6	0.045
Hyperaemia diameter (mm)	4.2 ± 0.6	4.3 ± 0.6	0.436
NTG diameter (mm)	4.5 ± 0.6	4.7 ± 0.6	0.002
FMD (%)	8.5 ± 3.3	10.4 ± 4.1	< 0.001
EID (%)	15.5 ± 5.1	16.3 ± 4.8	0.143
TC (mg/dl) (mmol/l)	261.3 ± 28.3 (6.77 ± 0.73)	174.3 ± 38.9 (4.51 ± 1.01)	< 0.001
TG (mg/dl) (mmol/l)	161.8 ± 66 (1.83 ± 0.75)	131.9 ± 50 (1.49 ± 0.57)	< 0.001
LDL-C (mg/dl) (mmol/l)	176.8 ± 23.5 (4.58 ± 0.61)	92.9 ± 28.1 (2.41 ± 0.73)	< 0.001
HDL-C (mg/dl) (mmol/l)	54.7 ± 12.1 (1.42 ± 0.31)	54.4 ± 12.4 (1.41 ± 0.32)	0.145
AST (U/l)	23.8 ± 9.1	21.9 ± 5.6	0.068
ALT (U/l)	23.6 ± 12.8	24.1 ± 13.1	0.746
CPK (U/l)	136.8 ± 74	113.4 ± 67	0.427

*Student's *t*-test, $p < 0.05$.

SD: standard deviation; NTG: post-nitrate; FMD: flow-mediated dilation; EID: endothelium-independent dilation; AST: aspartate transaminase; ALT: alanine transaminase; CPK: creatinine phosphokinase; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 2. Post-treatment versus baseline values in the rosuvastatin group

Rosuvastatin	Baseline	12 months	*p*-value*
Basal diameter (mm)	4.0 ± 0.5	4.2 ± 0.5	0.003
Hyperaemia diameter (mm)	4.4 ± 0.5	4.6 ± 0.5	< 0.001
NTG diameter (mm)	4.6 ± 0.5	4.7 ± 0.5	0.687
FMD (%)	9.7 ± 3.4	12.7 ± 3.7	< 0.001
EID (%)	16.8 ± 5.8	18.2 ± 5.8	0.105
TC (mg/dl)	271.2 ± 35.7	188.4 ± 44.8	< 0.001
(mmol/l)	(7.02 ± 0.92)	(4.88 ± 1.16)	
TG (mg/dl)	173.5 ± 55.2	143 ± 54.1	< 0.001
(mmol/l)	(1.96 ± 0.62)	(1.62 ± 0.61)	
LDL-C (mg/dl)	180.5 ± 26.1	105 ± 39.2	< 0.001
(mmol/l)	(4.67 ± 0.68)	(2.72 ± 1.02)	
HDL-C (mg/dl)	56.8 ± 13.6	54 ± 11.5	0.093
(mmol/l)	(1.47 ± 0.35)	(1.40 ± 0.30)	
AST (U/l)	22.8 ± 6.7	23.3 ± 6.5	0.819
ALT (U/l)	22.8 ± 9.7	23.6 ± 9.3	0.759
CPK (U/l)	94 ± 31.3	116 ± 73.8	0.007

*Student's *t*-test, $p < 0.05$.
SD: standard deviation; NTG: post-nitrate; FMD: flow-mediated dilation; EID: endothelium-independent dilation; AST: aspartate transaminase; ALT: alanine transaminase; CPK: creatinine phosphokinase; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

baseline values. LDL level showed a 58.5% decrease at the end of the 12 months compared to baseline value, whereas no change was observed in HDL levels. While a statistically significant increase was observed in the brachial artery basal diameter and hyperaemia diameter compared to baseline values, no change was observed in the post-nitrate diameter and EID values. FMD showed a statistically significant increase compared to baseline (Table 2).

No statistically significant difference was found between the atorvastatin and rosuvastatin groups in respect of baseline transthoracic echocardiographic and brachial artery endothelial function measurements (Table 3). Comparison between the two groups in terms of their effects on non-invasive ultrasonographic brachial artery measurements after one year revealed no statistically significant difference. However, a significant difference was observed in hyperaemia diameter in favour of rosuvastatin (Table 4).

Percentage changes in non-invasive brachial artery measurements after 12 months of treatment were compared between the two groups. A statistically significant difference was found in percentage change in the rosuvastatin group's brachial artery post-nitrate diameter ($p < 0.05$). Non-significant changes were found in the basal diameter and hyperaemia velocity in favour of the rosuvastatin group ($p = 0.089$ and $p = 0.088$, respectively) (Table 5).

Table 3. Statistical comparison between atorvastatin and rosuvastatin groups in terms of baseline brachial artery measurements

Baseline brachial artery measurements	Atorvastatin group	Rosuvastatin group	*p*-value*
BA basal diameter (mm)	4.01 ± 0.6	4.02 ± 0.5	0.850
BA basal velocity (cm/s)	71.95 ± 14.8	79.32 ± 16.9	0.240
BA hyperaemia diameter (mm)	4.34 ± 0.6	4.43 ± 0.5	0.404
BA hyperaemia velocity (cm/s)	72.21 ± 15.9	73.4 ± 16.3	0.713
BA NTG diameter (mm)	4.6 ± 0.6	4.69 ± 0.5	0.451
BA NTG velocity (cm/s)	68.92 ± 15.4	68.23 ± 15.5	0.833
BA FMD (%)	8.52 ± 3.3	9.71 ± 3.4	0.750
BA EID (%)	15.31 ± 5.1	16.84 ± 5.8	0.159

*Student's *t*-test, $p < 0.05$.
SD: standard deviation; BA: brachial artery; NTG: post-nitrate; FMD: flowmediated dilation; EID: endothelium-independent dilation.

Table 4. Rosuvastatin versus atorvastatin in terms of non-invasive test results after 12 months of statin therapy

Brachial artery measurements after therapy	Atorvastatin group ($n = 50$)	Rosuvastatin group ($n = 54$)	*p*-value*
BA basal diameter (mm)	4.01 ± 0.6	4.02 ± 0.5	0.850
BA basal velocity (cm/s)	71.95 ± 14.8	79.32 ± 16.9	0.240
BA hyperaemia diameter (mm)	4.34 ± 0.6	4.43 ± 0.5	0.404
BA hyperaemia velocity (cm/s)	72.21 ± 15.9	73.4 ± 16.3	0.713
BA NTG diameter (mm)	4.6 ± 0.6	4.69 ± 0.5	0.451
BA NTG velocity (cm/s)	68.92 ± 15.4	68.23 ± 15.5	0.833
BA FMD (%)	8.52 ± 3.3	9.71 ± 3.4	0.750
BA EID (%)	15.31 ± 5.1	16.84 ± 5.8	0.159

*Student's *t*-test, $p < 0.05$.
SD: standard deviation; BA: brachial artery; NTG: post-nitrate; FMD: flowmediated dilation; EID: endothelium-independent dilation.

Discussion

This study revealed that both atorvastatin and rosuvastatin had an effect on baseline lipid values, brachial artery basal diameter and hyperaemia diameter, and FMD and EID measurements. Comparing 12-month non-invasive measurements of atorvastatin and rosuvastatin groups, it was found that the statins had similar effects on endothelial function in the subjects with hyperlipidaemia.

Post-nitrate diameter in the rosuvastatin group was significantly improved at the end of the 12-month treatment compared to baseline values. Endothelial dysfunction is one of the early functional markers of atherosclerosis.[11,12] Preventative measurements should be taken before clinical manifestation of atherosclerotic events. For this reason, detection of early atherosclerotic changes is of great importance in reducing risk factors. Endothelial dysfunction can be detected via FMD, a non-invasive, easily applicable and repeatable method. Studies have demonstrated that FMD was correlated

Table 5. Changes in brachial artery measurements after 12 months of treatment in the atorvastatin versus rosuvastatin group

Change in brachial artery measurements after therapy	Atorvastatin group ($n = 50$) Median (25–75%)	Rosuvastatin group ($n = 54$) Median (25–75%)	*p*-value*
BA basal diameter (mm)	0.011 (–0.041–0.031)	0.010 (–0.007–0.045)	0.089
BA basal velocity (cm/s)	0.001 (–0.119–0.157)	–0.043 (–0.206–0.378)	0.120
BA hyperaemia diameter (mm)	0.018 (–0.034–0.060)	0.021 (0.011–0.048)	0.644
BA hyperaemia velocity (cm/s)	0.056 (–0.087–0.0347)	–0.012 (–0.168–0.116)	0.088
BA NTG diameter (mm)	0.028 (0.008–0.045)	0.020 (–0.028–0.036)	0.045
BA NTG velocity (cm/s)	–0.004 (–0.167–0.113)	–0.020 (0.0113–0.088)	0.982
BA FMD (%)	0.203 (0.008–0.441)	0.193 (0.049–0.0433)	0.958
BA EID (%)	0.110 (–0.115–0.225)	0.037 (–0.460–0.347)	0.827

*Mann–Whitney *U*-test, $p < 0.05$.
BA: brachial artery; NTG: post-nitrate; FMD: flow-mediated dilation; EID: endothelium-independent dilation.

with endothelial function, making it a good marker of endothelial function.[13,14]

In the MERCURY I trial, eight-week atorvastatin 20 mg/day and rosuvastinin 10 mg/day therapies were compared in terms of achieving target LDL-C values of NCEP ATPIII; 80% of the patients in the rosuvastatin group and 74% of those in the atorvastatin group achieved target LDL-C values.[15] In the SOLAR trial, either atorvastatin 10 mg/day, rosuvastatin 10 mg/day or simvastatin 20 mg/day was administered as the initial dose for six weeks in 1 634 high-risk patients. The dose was doubled in patients who failed to achieve target value at the end of six weeks. At the end of 12 weeks, target values were achieved with rosuvastatin in 76% of patients, with atorvastatin in 58%, and with simvastatin in 53%.[16] It is known that atorvastatin 20 mg is pharmacokinetically the same as rosuvastatin 10 mg.[17] In the present study, LDL cholesterol level decreased with both statins at the end of the 12th month versus baseline, but no statistically significant difference was found between the groups.

The effect of different doses of atorvastatin and rosuvastatin on HDL levels varies according to clinical setting and patient characteristics. The size of the increase is generally more signifcant with lower baseline values. Additionally, the effect is moderate compared to niacin or fibrates. The elevation of HDL level ranges from five to 13%.[18] In our study, the amount of elevation was not significant, which could have been due to low-dose statin usage or the relatively higher baseline HDL levels of the subjects.

Cardiovascular risk factors such as hyperlipidaemia contribute to endothelial dysfunction, which is the first step in atherogenesis. Although the concurrent presence of hyperlipidaemia and endothelial dysfunction is frequently encountered, the mechanism is unclear. However, oxidised LDL cholesterol is thought to cause endothelial injury. Many studies have demonstrated that endothelium-dependent (flow-mediated) dilation is enhanced with increased duration of the endothelium's exposure to oxidised LDL.[19-21]

Kawano *et al*. demonstrated impaired flow-mediated dilation in an experimental model of acute hyperglycaemia in healthy adults on a fatty diet.[22] Harrison *et al*. reported improvement in endothelial function due to decreased cholesterol in the diet.[23] In studies on statins, the time for endothelial function to improve ranged from hours to months. In earlier studies, improvement in endothelial function with increased NO levels due to statin therapy was observed at the end of a six-month treatment period.[24,25] On the other hand, Marchesi *et al*. observed remarkable improvement in endothelial function after a two-week atorvastatin therapy in postmenopausal women with hyperlipidaemia.[26]

In the present study, a 22.3 and 30.9% (p = 0.122) increase in FMD was observed in both atorvastatin and rosuvastatin groups, respectively, after 12 months of statin therapy. Improvement in FMD showed no correlation with post-treatment LDL levels. We found however that percentage ΔLDL was well correlated with ΔFMD and ΔEID, which may suggest that statins have a pleiotropic effect independent of their cholesterol-lowering effects. Similarly, ΔLDL was also found to be well correlated with ΔFMD and ΔEID values. In other words, endothelial function was statistically significantly improved at the end of 12-month statin therapy, in parallel with ΔLDL, among patients with hyperlipidaemia.

Although endothelium-independent dilation increased in both groups, the increase was not statistically significantly different. Increased brachial artery basal diameter after 12 months of treatment, which was more pronounced in the rosuvastatin group, reached a value close to the diameter obtained for baseline FMD, due probably to increased NO levels. More prominent increases in FMD and basal diameter in the rosuvastatin group suggest that the NO-secreting effect from the endothelium induced by rosuvastatin was more significant than that by atorvastatin.

There are some limitations of the present study, such as limited patient numbers, as well as not measuring blood NO and asymmetric di-methyl arginine levels due to technical issues. In addition, the technique for measuring FMD depends on the experience of the person carrying it out.

Conclusion

In this study, both atorvastatin 20 mg/day and rosuvastatin 10 mg/day therapies given to hyperlipidaemic patients for one year provided significant benefits on endothelial function. The data from non-invasive evaluations found that although the favourable effects of rosuvastatin on the endothelium may have been relatively more prominent compared to those of atorvastatin, there was no statistically significant difference.

References

1. Forte L, Cimmino G, Loffredo F, De Palma R, Abbate G, Calabrò P, *et al*. C-reactive protein is released in the coronary circulation and causes endothelial dysfunction in patients with acute coronary syndromes. *Int J Cardiol* 2011; **152**(1): 7–12.
2. Marzilli M. Pleiotropic effects of statins: evidence for benefits beyond LDL-cholesterol lowering. *Am J Cardiovasc Drugs* 2010; **10**(Suppl 1): 3–9.
3. Hermida N, Balligand JL. Low-density lipoprotein-cholesterol-induced endothelial dysfunction and oxidative stress: the role of statins. *Antioxid Redox Signal* 2014; **20**(8): 1216–1237.

4. Waters DD. Exploring new indications for statins beyond atherosclerosis: Successes and setbacks. *J Cardiol* 2010; **55**(2): 155–162
5. Dupuis J, Tardif JC, Cernacek P, Theroux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (Reduction of Cholesterol in Ischemia and Function of the Endothelium) trial. *Circulation* 1999; **99**(25): 3227–3233.
6. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**(9326): 7–22.
7. The HOPE (Heart Outcomes Prevention Evaluation) study: the design of a large, simple randomized trial of an angiotensin-converting enzyme inhibitor (ramipril) and vitamin E in patients at high risk of cardiovascular events. The HOPE study investigators. *Can J Cardiol* 1996; **12**(2): 127–137.
8. Hecker M, Bara AT, Busse R. Relaxation of isolated coronary arteries by angiotensin-converting enzyme inhibitors: role of endotheliumderived kinins. *J Vasc Res* 1993; **30**(5): 257–262.
9. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, *et al*. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2014; **15**: 736–746.
10. Faulx MD, Wright AT, Hoit BD. Detection of endothelial dysfunction with brachial artery ultrasound scanning. *Am Heart J* 2003; **145**(6): 943–951.
11. Gori T, Muxel S, Damaske A, Radmacher MC, Fasola F, Schaefer S, *et al*. Endothelial function assessment: flow-mediated dilation and constriction provide different and complementary information on the presence of coronary artery disease. *Eur Heart J* 2012; **33**(3): 363–371.
12. Manganaro A, Ciracì L, Andrè L, Trio O, Manganaro R, Saporito F, *et al*. Endothelial dysfunction in patients with coronary artery disease: insights from a flow-mediated dilation study. *Clin Appl Thromb Hemost* 2014; **20**(6): 583–588.
13. Liu Z, Zhao Y, Lu F, Zhang H, Diao Y. Day-by-day variability in selfmeasured blood pressure at home: effects on carotid artery atherosclerosis, brachial flow-mediated dilation, and endothelin-1 in normotensive and mild-moderate hypertensive individuals. *Blood Press Monit* 2013; **18**: 316–325.
14. Beyer AM, Zinkevich N, Miller B, Liu Y, Wittenburg AL, Mitchell M, *et al*. Transition in the mechanism of flow-mediated dilation with aging and development of coronary artery disease. *Basic Res Cardiol* 2017; **112**(1): 5.
15. Schuster H, Barter PJ, Stender S, Cheung RC, Bonnet J, Morrell JM, *et al*. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. *Am Heart J* 2004; **147**(4): 705–713.
16. Insull W Jr, Ghali JK, Hassman DR, Y As JW, Gandhi SK, Miller E. Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial. *Mayo Clin Proc* 2007; **82**(5): 543–550.
17. Meor Anuar Shuhaili MFR, Samsudin IN, Stanslas J, Hasan S, Thambiah SC. Effects of different types of statins on lipid profile: a perspective on Asians. *Int J Endocrinol Metab* 2017; **15**(2): e43319.
18. McTaggart F, Jones P. Effects of statins on high-density lipoproteins: a potential contribution to cardiovascular benefit. *Cardiovasc Drugs Ther* 2008; **22**(4): 321–338.
19. Zhou B, Ren C, Zu L, Zheng L, Guo L, Gao W. Elevated plasma migration inhibitory factor in hypertension-hyperlipidemia patients correlates with impaired endothelial function. *Medicine* (Baltimore) 2016; **95**(43): e5207.
20. Sawada T, Tsubata H, Hashimoto N, Takabe M, Miyata T, Aoki K, *et al*. Effects of 6-month eicosapentaenoic acid treatment on postprandial hyperglycemia, hyperlipidemia, insulin secretion ability, and concomitant endothelial dysfunction among newly-diagnosed impaired glucose metabolism patients with coronary artery disease. An open label, single blinded, prospective randomized controlled trial. *Cardiovasc Diabetol* 2016; **15**(1): 121.
21. Higashi Y, Sanada M, Sasaki S, Nakagawa K, Goto C, Matsuura H, *et al*. Effect of estrogen replacement therapy on endothelial function in peripheral resistance arteries in normotensive and hypertensive postmenopausal women. *Hypertension* 2001; **37**(2 Part 2): 651–657.
22. Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, *et al*. Hyperglycemia rapidly suppresses flow-mediated endotheliumdependent vasodilation of brachial artery. *J Am Coll Cardiol* 1999; **34**(1): 146–154.
23. Harrison DG, Armstrong ML, Freiman PC, Heistad DD. Restoration of endothelium-dependent relaxation by dietary treatment of atherosclerosis. *J Clin Invest* 1987; **80**(6): 1808–1811.
24. John S, Schlaich M, Langenfeld M, Weihprecht H, Schmitz G, Weidinger G, *et al*. Increased bioavailability of nitric oxide after lipid-lowering therapy in hypercholesterolemic patients: a randomized, placebocontrolled, double-blind study. *Circulation* 1998; **98**(3): 211–216.
25. Baspınar O, Bayram F, Korkmaz S, Aksu M, Kocer D, Dizdar OS, *et al*. The effects of statin treatment on adrenal and sexual function and nitric oxide levels in hypercholesterolemic male patients treated with a statin. *J Clin Lipidol* 2016; **10**(6): 1452–1461.
26. Marchesi S, Lupattelli G, Siepi D, Schillaci G, Vaudo G, Roscini AR, *et al*. Short-term atorvastatin treatment improves endothelial function in hypercholesterolemic women. *J Cardiovasc Pharmacol* 2000; **36**(5): 617–621.

Review assesses low-fat/high-carb and high-fat/low-carb diets

A strong US research review agreed that no specific fat-to-carbohydrate ratio is best and that an overall high-quality diet that is low in sugar and refined grains will help most people maintain a healthy weight and low chronic disease risk.

'This is a model for how we can transcend the diet wars,' said lead author David Ludwig, professor in the Department of Nutrition at Harvard Chan School and a physician at Boston Children's Hospital. 'Our goal was to assemble a team with different areas of expertise and contrasting views, and to identify areas of agreement without glossing over differences.'

The authors laid out the evidence for three contrasting positions on dietary guidelines for fat and carbohydrate consumption: high consumption of fat causes obesity, diabetes, heart disease, and possibly cancer, therefore low-fat diets are optimal; processed carbohydrates have negative effects on metabolism; lower-carbohydrate or ketogenic (very-low-carbohydrate) diets with high fat content are better for health; and the relative quantity of dietary fat and carbohydrate has little health significance – what's important is the type of fat or carbohydrate source consumed.

They agreed that by focusing on diet quality – replacing saturated or trans fats with unsaturated fats and replacing refined carbohydrates with whole grains and non-starchy vegetables – most people can maintain good health within a broad range of fat-to-carbohydrate ratios.

Within their areas of disagreement, the authors identified a list of questions that they said can form the basis of a new nutrition research agenda, including: do diets with various carbohydrate-to-fat ratios affect body composition (ratio of fat to lean tissue) regardless of caloric intake; do ketogenic diets provide metabolic benefits beyond those of moderate carbohydrate restriction, and especially for diabetes; and what are the optimal amounts of specific types of fat (including saturated fat) in a very-low-carbohydrate diet?

Finding the answers to these questions, the researchers said, will ultimately lead to more effective nutrition recommendations.

Source: Medical Brief 2018

Hypertension among newly diagnosed diabetic patients at Mulago National Referral Hospital in Uganda: a cross sectional study

MARTIN MUDDU, EDRISA MUTEBI, ISAAC SSINABULYA, SAMUEL KIZITO, CHARLES KIIZA MONDO

Abstract

Background: **The prevalence of hypertension in patients with diabetes is approximately two-fold higher than in age-matched subjects without the disease and, conversely, individuals with hypertension are at increased risk of developing diabetes compared with normotensive persons. Up to 75% of cases of cardiovascular disease (CVD) in patients with diabetes are attributed to hypertension. Diabetics who have hypertension are more likely to develop complications and die, and appropriate blood pressure control in these individuals reduces the risk. This study sought to determine the prevalence and factors associated with hypertension among newly diagnosed adult diabetic patients in a national referral hospital in Uganda.**

Methods: **In this cross-sectional study, conducted between June 2014 and January 2015, we recruited 201 newly diagnosed adult diabetic patients. Information on patients' socio-demographics was obtained using a pre-tested questionnaire, while biophysical profile, blood pressure measurement, biochemical testing and echocardiographic findings were obtained by the research team for all the participants. Bivariate and multivariate logistic regression analyses were used to investigate the association of several factors with hypertension.**

Results: **Of the 201 patients recruited, 102 were male (50.8%) and the mean age was 46 ± 15 years. The majority of patients (159) had type 2 diabetes mellitus (DM) (79.1%) with a mean HbA_{1c} level of 13.9 ± 5.3%. The prevalence of hypertension was 61.9% (95% CI: 54.8–68.6%). Knowledge of hypertension status was at 56 (27.7%) patients, 24 (44.4%) hypertensives were on treatment, and 19 (33.9%) were using ACE inhibitors/angiotensin receptor blockers. The independent factors associated with hypertension were being employed (OR 0.37, 95% CI: 0.16–0.90, $p = 0.029$) and being overweight or obese (OR 11.6, 95% CI: 4.29–31.2, $p < 0.0001$).**

Conclusion: **The prevalence of hypertension was high in this population of newly diagnosed diabetics, few patients had knowledge of their hypertension status and few were on appropriate treatment. Both modifiable and non-modifiable risk factors were associated with hypertension in this group. Therefore routine assessment, treatment and control of hypertension among diabetics is necessary to prevent cardiovascular complications and death. There is also a need to address the modifiable risk factors.**

Keywords: hypertension, newly diagnosed, diabetes, Uganda

Correspondence to: Martin Muddu
Department of Medicine, College of Health Sciences, Makerere University, Mulago Hospital Complex, Mulago, Uganda
e-mail: muddu.martin@gmail.com

Edrisa Mutebi, Isaac Ssinabulya, Charles Kiiza Mondo
Department of Medicine, College of Health Sciences, Makerere University, Mulago Hospital Complex, Mulago, Uganda

Samuel Kizito
Clinical Epidemiology Unit, College of Health Sciences, Makerere University, Mulago, Uganda

Previously published in *Cardiovasc J Afr* 2018; **29**(4): 218–224

S Afr J Diabetes Vasc Dis 2018; **15**: 57–63

The burden of non-communicable diseases (NCDs) is increasing rapidly in sub-Saharan Africa.[1] It is anticipated that NCDs may account for 46% of deaths in sub-Saharan Africa by 2030, compared to 28% in 2008.[1] Hypertension and diabetes mellitus (DM) are of particular concern; however, precise epidemiological data are rare.[1-4] One of the commonest NCDs experienced during this early stage of the epidemiological transition is hypertension. It is predicted that more than 125 million adults in sub-Saharan Africa alone will have hypertension by 2025,[5,6] and in Uganda, hypertension is the most reported NCD.[7-10]

Increasing urbanisation and associated lifestyle changes as well as improvements in life expectancy have contributed to a surge in NCDs, including hypertension.[1,5] Likewise, the prevalence of DM is on a rise in sub-Saharan Africa and will more than double by 2025.[11]

The prevalence of hypertension in patients with diabetes is approximately two-fold higher than in age-matched subjects without the disease,[12-14] and conversely, individuals with hypertension are at increased risk of developing diabetes compared with normotensive persons. Furthermore, up to 75% of cases of cardiovascular disease (CVD) in patients with diabetes can be attributed to hypertension.[15] CVD, especially stroke, accounts for up to 80% of all deaths in the diabetic population and three-quarters of these deaths occur in sub-Saharan Africa.[16,17]

The high burden of hypertension in diabetics has led to an increase in the risk and prevalence of cardiac abnormalities in diabetes.[18] Also, life expectancy in sub-Saharan Africa has risen in the past 50 years. Many more people living with diabetes are therefore exposed to the risk of hypertension for long periods for the complications to develop and for them to experience the clinical syndromes of CVD.[19]

Diabetics who have hypertension are more likely to develop complications and die, and appropriate blood pressure control in these individuals reduces the risk. The lower the systolic blood pressure, the lower the risk of complications.[12] There is an additional risk reduction with angiotensin converting enzyme inhibitors (ACE inhibitors) and β-blockers over and above that associated with lowering of blood pressure.[12]

In patients with type 2 DM, hypertension is associated with left ventricular hypertrophy (LVH),[20,21] which is an independent predictor of cardiovascular events in hypertensive patients with diabetes.[22] Hypertension is also a major risk factor for myocardial infarction and stroke,[12,23,24] and indeed hypertension is the leading risk factor for mortality worldwide.[5,25-28] Additionally, hypertension is a major causal factor of end-stage kidney failure, blindness and non-traumatic amputation in people with diabetes, where attributable risks are 50, 35 and 35%, respectively.[16]

Unfortunately the majority of people with hypertension in sub-Saharan Africa do not know they have it, and most are not on treatment. This reflects the low level of knowledge of the dangers of untreated hypertension in this population.[10]

In sub-Saharan Africa there is still a lack of awareness about the growing problem of NCDs, which, unfortunately, is often coupled with the absence of a clear policy framework for prevention and management.[7] Given the long-term decreased productivity associated with hypertension among diabetics, identifying and treating a large proportion of patients has the potential to generate tremendous social and economic benefits in this region.[5,29-31]

In this study we sought to determine the prevalence and factors associated with hypertension among newly diagnosed adult diabetic patients in a national referral hospital in Uganda. These findings are not only necessary, but also contribute to the diagnosis and management of DM and hypertension in sub-Saharan Africa.

Methods

This study was carried out in the diabetes out-patient clinic, the medical endocrine ward and the medical emergency ward of Mulago National Referral Hospital. It is the only national referral hospital for Uganda and is the teaching hospital for Makerere University, with a bed capacity of 1 500. Mulago Hospital receives referrals from all parts of the country including from neighbouring countries such as Southern Sudan, the Democratic Republic of Congo and Rwanda. The study population is representative of the Ugandan diabetic population.

This was a cross-sectional study among 201 newly diagnosed diabetic patients at Mulago Hospital in Uganda, conducted between June 2014 and January 2015. All newly diagnosed diabetic patients aged 18 years and above attending the diabetes clinic or admitted to the medical wards of Mulago Hospital during the study period, who met the inclusion criteria and provided informed consent, were recruited consecutively. We excluded patients with urinary tract infection in order to avoid confounding in microalbuminuria, and those who were unable to provide the necessary information. Fig. 1 illustrates the patient recruitment flow.

Institutional consent was sought from the Department of Medicine, Makerere University, Mulago National Referral Hospital and the School of Medicine research and ethics committee of Makerere University College of Health Sciences. All study participants provided written informed consent for involvement in the study. Enrolment was totally free and voluntary, and participants were free to withdraw at any time without any consequences. The patients' records/information was anonymised and de-identified prior to analysis.

We took a focused history and performed a specific physical examination to determine biophysical measurements. Information gathered was entered into a pre-tested questionnaire. We assessed the following factors: patients' demographic data, history of hypertension, age, physical exercise at work and leisure, marital status, date of diagnosis of DM, drug history, occupation, education level and last normal menstrual period.

Body mass was measured to the nearest kilogram using a Secco weighing scale, height was measured in metres using a non-stretchable tape, and these were used to compute body mass index (BMI). Waist and hip circumferences were measured and waist-to-hip ratios were determined for all patients.

Glycated haemoglobin (HbA_{1c}) was measured by automated high-performance liquid chromatography. Other investigations included urinalysis and microalbuminuria using albumin-tocreatinine ratio.

Echocardiography parameters were acquired using a commercially available machine, Phillips HD11XE (Eindhoven, the Netherlands), with two-dimensional, M-mode and Doppler capabilities. It was used according to the American Society of Echocardiography guidelines.[32]

Blood pressure was measured using a mercury sphygmomanometer, according to the American Heart Association guidelines for the auscultatory method of blood pressure assessment.[33] The degree of precision of blood pressure measurement in this study was ± 2 mmHg.[33] Hypertension was defined as present if subjects were on anti-hypertensive medication, had a history of hypertension and/or evidence of hypertension (blood pressure ≥ 140/90 mmHg).

Statistical analysis

Data were double entered in a database developed with Epidata version 3.1, validated, and inconsistences were cleared. The data were then exported to Stata 13 for analysis. Continuous data were summarised using measures of central tendency while categorical data were summarised as frequencies and percentages and presented in tables. Prevalence was presented as percentages with their confidence intervals. Comparisons were made using the Student's *t*-test for continuous data and chi-squared or Fisher's exact test for categorical data.

The outcome was dichotomised as patients having hypertension or not, then logistic regression was used to determine the association between the predictors and hypertension. This was presented as

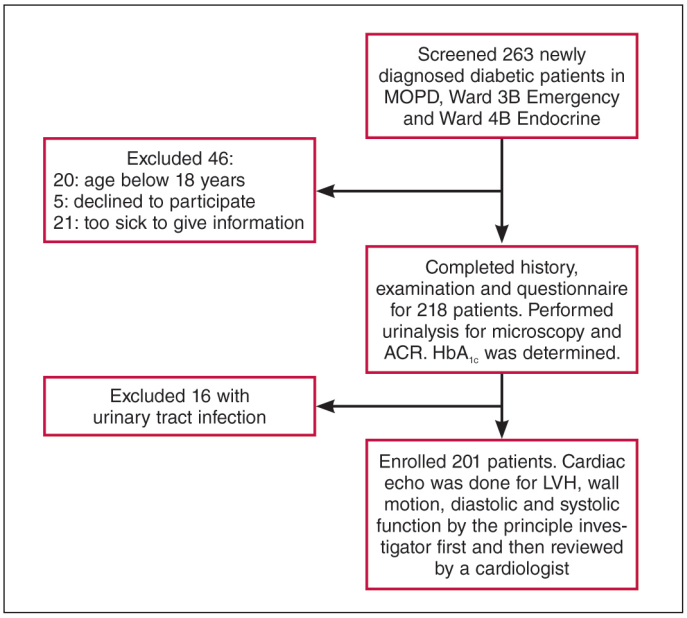


Fig. 1. Patient flow chart.

odds ratio (OR) and their 95% confidence interval (CI). Only factors with a *p*-value < 0.2 at bivariate analysis were considered for multivariate analysis. Multivariate logistic regression was performed and interaction was assessed for with the Chunk test. Confounding was assessed for using a 10% difference between the crude and adjusted models. Significance was at $p \leq 0.05$.

Results

This study recruited 201 newly diagnosed diabetic patients between June 2014 and January 2015. Of these, 102 (50.8%) were males. The mean age of the participants was 46 ± 15 years (Table 1). Patients with type 1 and type 2 DM had mean ages of 25.6 (18–42) and 51.9 (26–90) years, respectively. The majority of patients had type 2 DM (*n* = 159, 79.1%) and the rest had type 1 DM (*n* = 42, 20.9%) (Table 2). The mean HbA_{1c} was 13.9 ± 5.3%. Mean duration of diabetes was two months. The majority of patients (124, 62.0%) were unemployed.

Blood pressure assessment was performed on all 201participants and the results are shown in Table 3. Prevalence of hypertension was 61.9% (95% CI: 54.8–68.6%). Systolic hypertension was present in 104 (51.5%) participants (95% CI: 45.3–59.2%) while diastolic hypertension was present in 92 (45.5%) (95% CI: 39.3–53.2%). Among those who were hypertensive, only 56 (27.7%) knew that they were hypertensive, and among these, only 24 (44.4%) were on treatment for hypertension. The use of either ACE inhibitors or angiotensin receptor blockers (ARBs) among those who knew their hypertension status was only 19 (33.9%) subjects.

For participants who knew their hypertension status, the majority 44 (77.2) had been hypertensive for less than five years. The number who had been hypertensive for durations between five and 10 years and more than 10 years were eight (4.3%) and five (8.8%), respectively.

In bivariate analysis, the factors associated with hypertension included: female gender, age above 40 years, participants who were employed, participants who were never married and those who were currently married, overweight and obesity, increase in waist:hip ratio, LVH and diastolic dysfunction (Table 4). After adjusting for the patients' gender, age, employment, marital status, BMI, waist:hip ratio, LVH and diastolic dysfunction, the only significant factors associated with hypertension were being employed (OR 0.37, 95% CI: 0.16–0.90, $p = 0.029$), and overweight and obesity (OR 11.6, 95% CI: 4.29–31.2, $p < 0.0001$).

Table 1. Social demographics of 201 newly diagnosed diabetic patients at Mulago National Referral Hospital who participated in the study

Characteristics	Total (*n*)	Total (%)	Hypertensive *n* (%)	Normotensive *n* (%)
Age				
< 40 years	58	28.9	21 (36.2)	37 (63.8)
> 40 years	143	71.1	105 (73.4)	38 (26.6)
Gender				
Male	102	50.8	54 (52.9)	48 (47.1)
Female	99	49.3	72 (72.7)	27 (27.3)
Employment				
Employed	76	38.0	41 (53.9)	35 (46.1)
Unemployed	124	62.0	85 (68.6)	39 (31.4)
Pregnancy				
Yes	6	5.4 3	(50.0)	3 (50.0)
No	105	94.6	74 (70.5)	31 (29.5)
Education				
None	17	8.5	10 (58.8)	7 (41.2)
Primary	78	38.8	50 (64.1)	28 (35.9)
Secondary	75	37.3	45 (60.0)	30 (40.0)
Tertiary	31	15.4	21 (67.7)	10 (32.3)
Marital status				
Never married	29	14.4	7 (24.1)	22 (75.9)
Currently married	119	59.2	83 (69.8)	36 (30.3)
No longer married	53	26.4	36 (67.9)	17 (32.1)

Table 2. Characteristics of 201 newly diagnosed diabetic patients at Mulago National Referral Hospital who participated in the study

Characteristics	Total (*n*)	Total (%)	Hypertensive *n* (%)	Normotensive *n* (%)
Physical activity at work				
Sedentary	25	12.4	16 (69.6)	7 (30.4)
Mild	51	25.3	33 (64.7)	18 (35.3)
Moderate	82	40.6	54 (66.7)	27 (33.3)
Strenuous			22 (50.0)	22 (50.0)
Does not work	44	21.8	1 (50.0)	1 (50.0)
Physical activity at leisure				
Sedentary	142	71.0	96 (67.6)	46 (32.4)
Moderate	58	29.0	29 (50.0)	29 (50.0)
DM type				
Type 1	42	20.9	11 (26.2)	31 (73.8)
Type 2	159	79.1	115 (72.3)	44 (27.7)
Microalbumin in urine				
Absent	79	44.9	50 (62.5)	30 (37.5)
Present	97	55.1	58 (61.1)	37 (38.3)
BMI				
Underweight	39	19.4	10 (25.6)	29 (74.4)
Normal weight	75	37.3	40 (53.3)	35 (46.7)
Over weight	3	1.5	1 (33.3)	2 (66.7)
Obesity	84	41.8	75 (89.3)	9 (10.7)
Waist:hip ratio				
Normal	141	69.8	81 (57.9)	59 (42.1)
Abnormal	61	30.2	45 (73.8)	16 (26.2)
HbA1c (%)				
< 7%	15	8.4	11 (73.3)	4 (26.7)
> 7%	164	91.6	101 (61.9)	62 (38.0)
Ejection fraction (%)				
> 50%	158	78.2	102 (64.6)	56 (35.4)
< 50%	44	21.8	24 (55.8)	19 (44.2)
LVH				
Present	39	19.3	89 (77.4)	26 (26.5)
Absent	163	80.7	37 (43.0)	49 (56.9)
Diastolic function				
Normal	91	45.1	44 (48.9)	46 (51.1)
Impaired	111	54.9	82 (73.9)	29 (26.1)
Wall motion				
Normal	193	96.5	120 (62.2)	73 (37.8)
Abnormal	7	3.5	5 (71.4)	2 (28.6)

Table 3. Prevalence, knowledge and treatment of hypertension among 201 newly diagnosed diabetic patients at Mulago Hospital

Parameters	Number	Prevalence (%)	95% CI
Hypertension	125	61.9	54.8–68.6
Systolic BP > 140 mmHg	104	51.5	45.3–59.2
Diastolic BP > 90 mmHg	92	45.5	39.3–53.2
Knowledge of hypertension	56	27.7	22.1–34.6
HTN newly diagnosed	69	34.2	27.6–39.8
ACEI/ARB use in known HTN	19	33.9	26.7–39.2
Known HTN on drugs	24	44.4	38.9–52.4
Known HTN not on drugs	30	55.6	47.2–62.1

HTN: hypertension, ACEI: ace inhibitor, ARB: angiotensin receptor blocker.

Discussion

The prevalence of hypertension among newly diagnosed diabetics was high in this group, with more than six patients out of 10 having hypertension. This is in keeping with earlier studies, which found that the prevalence of hypertension in patients with diabetes was approximately two-fold higher than in age-matched subjects without the disease,[12-14] and conversely, individuals with hypertension were at increased risk of developing diabetes compared with normotensive persons.[15]

In Uganda, the prevalence of hypertension among non-diabetics ranges between 20 and 35%, with a higher prevalence in the urban areas.[10,34-37] This is consistent with evidence from other parts of sub-Saharan Africa that indicated the prevalence of hypertension was between 20 and 50%.[7,35,37-40] Therefore, the prevalence we found of 62% in diabetic subjects is approximately twice the current prevalence of hypertension in non-diabetic patients in Uganda.

Unfortunately only one-quarter of all those who are hypertensive know their status, and this is evident from other studies in the region, which found that the majority of patients with hypertension in sub-Saharan Africa did not know they were hypertensive and very few were on treatment, yet hypertension is the leading cause of stroke in Africa. In another cross-sectional study in Uganda, awareness of hypertension was low, at less than 30%.[7]

This low awareness could be explained by the fact that only 27.8% of the population ever has their blood pressure measured in Uganda. Awareness of hypertension largely depends on the capacity of the health system to provide diagnostic services for hypertension to the general population.[40] Unfortunately, the healthcare system in Uganda is largely constrained by communicable diseases and NCDs have not received the attention they deserve.[7] In order to increase awareness, there is a need to screen all adults at an appropriate opportunity when they come into contact with the health system. This could even be done through outreaches and community programmes.[7,41,42]

Furthermore, among those who knew they had hypertension, less than half were on treatment. This is similar to what earlier studies found, and this carries a great risk for the complications of diabetes, especially CVDs such as stroke, LVH, myocardial infarction, as reported by the United Kingdom Prospective Diabetes Study (UKPDS). In one cross-sectional study among people with hypertension in Uganda, less than 10% were controlled. In another retrospective study conducted in an urban diabetes clinic in Kampala, optimal blood pressure control, defined as ≤ 140/80 mmHg, was noted in 56% of the patients.[43]

This corroborates the notion that blood pressure control among adult diabetic patients in Uganda is sub-optimal. This calls for the

Table 4. Logistic regression for factors associated with hypertension among 201 newly diagnosed diabetic patients at Mulago Hospital

	Hypertension					
Factors	**Absent, *n* (%)**	**Present, *n* (%)**	**Crude OR (95% CI)**	***p*-value**	**Adjusted OR (95%)**	***p*-value**
Gender						
Male	48 (47.1)	54 (52.9)	1			
Female	27 (27.3)	72 (72.7)	2.37 (1.32–4.27)	0.004		
Age						
< 40 years	37 (63.8)	21 (36.2)	1		1	
> 40 years	38 (26.6)	105 (73.4)	4.87 (2.54–9.34)	< 0.0001	2.49 (0.62–9.95)	0.197
Employment						
Unemployed	39 (31.5)	85 (68.6)	1		1	
Employed	35 (46.1)	41 (53.9)	0.54 (0.30–0.97)	0.039	0.37 (0.16–0.90)	0.029
Marital status						
No longer married	17 (32.1)	36 (67.9)	1		1	
Never married	22 (75.9)	7 (24.1)	7.25 (2.84–18.5)	< 0.0001	2.86 (0.69–11.9)	0.149
Currently married	36 (30.3)	83 (69.8)	6.66 (2.38–18.6)	< 0.0001	1.37 (0.28–6.63)	0.703
HbA_{1c}						
Normal	4 (26.7)	11 (73.3)	1			
Abnormal	62 (38.0)	101 (61.9)	0.59 (0.18-1.94)	0.387		
Microalbuminuria						
Normal	30 (37.5)	50 (62.5)	1			
Abnormal	37 (38.3)	58 (61.1)	0.94 (0.51-1.74)	0.844		
BMI						
Normal weight	66 (56.4)	51 (43.6)	1		1	
Overweight, obesity	9 (10.7)	75 (89.3)	10.8 (4.9–23.6)	< 0.0001	11.6 (4.29–31.2)	< 0.0001
Waist:hip ratio						
Normal	59 (42.1)	81 (57.9)	1		1	
Abnormal	16 (26.2)	45 (73.8)	2.05 (1.06–3.97)	0.034	1.03 (0.39–2.73)	0.949
Ejection fraction						
> 50%	56 (35.4)	102 (64.6)	1			
< 50%	19 (44.2)	24 (55.8)	0.69 (0.35–1.38)	0.295		
LVH						
Absent	49 (56.9)	37 (43.0)	1		1	
Present	26 (26.5)	89 (77.4)	4.53 (2.46–8.35)	< 0.0001	1.97 (0.88–4.38)	0.098
Diastolic function						
Normal	46 (51.1)	44 (48.9)	1		1	
Impaired	29 (26.1)	82 (73.9)	2.96 (1.64–5.34)	< 0.0001	0.94 (0.40–2.18)	0.885

HbA_{1c}: glycated haemoglobin, BMI: body mass index, LVH: left ventricular hypertrophy

development and implementation of local guidelines to improve diabetes care and minimise complications due to hypertension.[43]

Possible reasons for this very low level of control may be that the majority of people with hypertension are not aware they have the condition, and even among those who are aware, less than half are receiving treatment. However, even among those receiving treatment, only one in three achieve blood pressure control. A worrying global trend is that low levels for the control of hypertension are widespread in both low- and high-income countries.[7,40,44,45]

There is an additional risk reduction with ACE inhibitors and β-blockers over and above that associated with lowering of blood pressure among diabetics.[12] However, the use of ACE inhibitors/ARBs among those who knew their status was in only one-third of all participants, yet we know that ACE inhibitors reduce the risk for nephropathy and other complications of diabetes, such as LVH. For this reason, the JNC 7 and JNC 8 recommend that every diabetic who has hypertension must be started on ACE inhibitors/ARBs among other treatment options.[46]

In patients with type 2 DM, hypertension is associated with LVH.[20,21] According to the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, LVH is an independent predictor of cardiovascular events in hypertensive patients with diabetes.[22] Hypertension is also a major risk factor for myocardial infarction and stroke,[12,23,24] and indeed it is the leading risk factor for mortality worldwide.[5,25-27] Therefore prevention and control of hypertension are critical in reducing morbidity and mortality attributable to cardiovascular diseases among diabetics.

According to the UKPDS, the incidence of clinical complications among diabetics is significantly associated with systolic blood pressure, except for cataract extraction. Each 10 mmHg decrease in updated mean systolic blood pressure is associated with risk reductions of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction and 13% for microvascular complications. Any reduction in blood pressure is likely to reduce the risk of complications, with the lowest risk being in those with systolic blood pressure less than 120 mmHg.[12]

An upcoming comprehensive review of global publications on NCD costs from low- and middle-income countries confirms that primary prevention of CVD, stroke and diabetes is far less expensive and has lower unit costs than treatment interventions for these conditions. One way to achieve this is to control hypertension.[34]

The following factors were associated with hypertension among the newly diagnosed diabetics in the bivariate model: age above 40 years, female gender, unemployment, lack of physical exercise, overweight and obesity, increased waist:hip ratios, LVH and diastolic dysfunction. However after adjusting for possible confounders, only unemployment, gender and increasing BMI were independently associated with hypertension in this model. Among these factors, unemployment and BMI are modifiable, while gender is the non-modifiable factor associated with hypertension.

Attaining and maintaining a healthy weight improves blood pressure and diabetes management, and reduces cholesterol levels. The Trials of Hypertension Prevention (TOHP) study showed that a decrease of 4.4 kg can lead to a blood pressure reduction of 4/3 mmHg.[16]

In a study to determine the prevalence and factors associated with hypertension among residents of the rural district of Rukungiri, Uganda, some of the factors found to be associated with hypertension included: being overweight or obese, female gender and older age.[37] However all these factors, apart from obesity and being overweight, had no significance in our study in the multivariate model. The reason could be that Wamala *et al*.[37] in the earlier study had a bigger sample size compared to ours and enrolled community members, while our population was for newly diagnosed diabetics.

Similar findings have been reported by Wamala and co-workers[37] and Musinguzi *et al*.[7] in other cross-sectional studies. These observations suggest that demographic transition, urbanisation and increasing life expectancy are major determinants of prevalence of hypertension among diabetics.[7,47-49]

In a population-based, cross-sectional survey, Baziel *et al*.[1] found further evidence to show that increasing BMI and a waist circumference above the normal range were associated with hypertension. In the same study, sociodemographic factors associated with hypertension included increasing age, male gender, overweight and obesity.

With the substantial burden of hypertension in Uganda coupled with low awareness and limited treatment of hypertension, especially among diabetics, enhanced communitybased education and prevention efforts tailored to addressing modifiable factors are needed.[5] In our study, participants who were employed were 63% less likely to have hypertension compared to their unemployed counterparts. One possible explanation would be the lack of physical exercise among the unemployed participants, whereas those who are working often do manual labour in most parts of sub-Saharan Africa.

As observed elsewhere, the prevalence of hypertension increases with increasing age, and the increase is more marked among women than men.[33,50] We found age above 40 years to be associated with hypertension in the bivariate model, however this level of significance was lost in the multivariate model. With increasing life expectancy, the risk of hypertension becomes very important in sub-Saharan Africa, a region undergoing an epidemiological transition.

In addition patients who had LVH and/diastolic dysfunction were more likely to have hypertension compared to their counterparts without these heart problems. However this was no longer significant at multivariate level. One of the possible explanations could be that hypertension among diabetics caused LVH and diastolic dysfunction, as cited in the ABCD trial and other studies.[22] Therefore treating hypertension would be one way to prevent these complications because 75% of all CVD in diabetics can be attributed to hypertension.

Microalbuminuria was not associated with hypertension in this study, despite the fact that it is one of the major CVD risk factors. Okpere *et al*., in a cross-sectional study among young people in the community, found contradictory evidence,[51] but the population they studied was not diabetic.

Type 2 DM and hypertension share several common risk factors, such as physical inactivity and unhealthy diet. Overweight and obesity are potentially amenable to behavioural modification. The benefits of prevention and care extend beyond cardiovascular disease to related conditions of public health importance. They are the focus of efforts to ensure greater prioritisation of NCDs on the global research agenda as well as of development agencies and in the health and development policies of low-income countries.

Limitations

In the diagnosis of hypertension, we did not perform ambulatory blood pressure monitoring, which is the gold standard, according to guidelines for the diagnosis of hypertension.[29] This was due

to lack of capacity. A non-diabetic control group would have provided better comparison, however in this study we assessed the prevalence and associated factors of hypertension but not its risk factors among diabetics. The recruitment time between June 2014 and January 2015 was relatively short due to limitations in logistics. This could have obscured seasonal differences.

Conclusion

The prevalence of hypertension was high in this population of newly diagnosed diabetics, who had little knowledge of hypertension, and very few patients were on appropriate treatment. Both modifiable and non-modifiable risk factors were associated with hypertension in this group. Therefore, routine assessment, treatment and control of hypertension among diabetics is necessary to prevent CVD complications and death. Pharmacotherapy should be combined with lifestyle changes to address the modifiable risk factors.

Research reported in this manuscript was supported by the Fogarty International Center of the National Institutes of Health under award number R24TW008861. Dr Mudda was also supported by the Fogarty International Center and the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health under the Global Health Equity Scholars Consortium at Yale University (D43TW010540). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors are grateful to the following persons for their invaluable support: Professors Nelson Sewankambo and Moses R Kamya, the staff of Ward 4B Endocrine, Diabetic Clinic, and the echocardiography and clinical laboratory of Mulago Hospital.

References

1. Kavishe B, Biraro S, Baisley K, Vanobberghen F, Kapiga S, *et al*. High prevalence of hypertension and of risk factors for non-communicable diseases (NCDs): a population based cross-sectional survey of NCDS and HIV infection in Northwestern Tanzania and Southern Uganda. *BMC Med* 2015; **13**(126): 126.
2. Twagirumukiza M, de Bacquer D, Kips JG, de Backer G, Stichele RV, van Bortel LM. Current and projected prevalence of arterial hypertension in sub-Saharan Africa by sex, age and habitat: an estimate from population studies. *J Hypertens* 2011; **29**: 1243–1252.
3. Bloomfield GS, Barasa FA, Doll JA, Velazquez EJ. Heart failure in sub-Saharan Africa. *Curr Cardiol Rev* 2013; **9**: 157–173.
4. Moran AE, Tzong KY, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, *et al*. Variations in ischemic heart disease burden by age, country, and income: the Global Burden of Diseases, Injuries, and Risk Factors 2010 study. *Glob Heart* 2014; **9**: 91–99.
5. Kotwani P, Kwarisiima D, Clark TD, Kabami J, *et al*. Epidemiology and awareness of hypertension in a rural Ugandan community: a crosssectional study. *BMC Public Health* 2013; **13**: 1151.
6. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**: 217–223.
7. Musinguzi G, Nuwaha F. Prevalence, awareness and control of hypertension in Uganda. *PloS One* 2013; **8**(4): 62236.
8. Maher D, Waswa L, Baisley K, Karabarinde A, Unwin N. Epidemiology of hypertension in low-income countries: a cross-sectional populationbased survey in rural Uganda. *J Hypertens* 2011; **29**: 1061–1068.
9. Maher D, Waswa L, Baisley K, Karabarinde A, Unwin N, *et al*. Distribution of hyperglycaemia and related cardiovascular disease risk factors in low-income countries: a cross-sectional population-based survey in rural Uganda. *Int J Epidemiol* 2011; **40**: 160–171.
10. Mondo CK, Otim MA, Akol G, Musoke R, Orem J. The prevalence and distribution of non-communicable diseases and their risk factors in Kasese district, Uganda. *Cardiovasc J Afr* 2013; **24**(3): 31–36
11. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047–1053.
12. Adler AI, Stratton IM, HAW Neil, Yudkin JS. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *Br Med J* 2000; **321**: 412–419.
13. Cutler JA. High blood pressure and endorgan damage. *J Hypertens* 1996; **14**(Suppl): 36.
14. Tuomilehto J, Rastenyte D, Birkenhäger WH, Thijs L, Antikainen R, Bulpitt CJ, *et al*. Effect of calcium channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 1999; **320**: 67784.
15. Sowers J. Recommendations for special populations: diabetes mellitus and the metabolic syndrome. *Am J Hypertens* 2003; **16**(11 pt 2): 41S–45S.
16. Makowsky M, Ally PH, Prebtani A, Gelfer M, Manohar A, Jones C. Management of hypertension in people with diabetes mellitus: translating the 2012 Canadian Hypertension Education Program recommendations into practice. *Can J Diabetes* 2012; **36**: 345–353.
17. Dinh W, Lankisch M, Nickl W, Scheyer D, Scheffold T, *et al*. Insulin resistance and glycemic abnormalities are associated with deterioration of left ventricular diastolic function: a cross-sectional study. *Cardiovasc Diabetol* 2010; **9**: 63.
18. Cooper R, Rotimi C, Ataman S, McGee D, *et al*. The prevalence of hypertension in seven populations of west African origin. *Am J Public Health* 1997; **87**: 160–168.
19. Kengne AP, Amoah AG, Mbanya J-C. Cardiovascular complications of diabetes mellitus in sub-Saharan Africa. *Circulation* 2005; **112**: 3592–3601.
20. Baba MM, Balogun MO, Akintomide AO, Adebayo RA, Talle MA, *et al*. Left ventricular geometry in Nigerians with type II diabetes mellitus. *Nig Q J Hosp Med* 2012; **22**(3): 152–157.
21. Somaratne JB, Whalley GA, Poppe KK, ter Bals MM, Wadams G, *et al*. Screening for left ventricular hypertrophy in patients with type 2 diabetes mellitus in the community. *Cardiovasc Diabetol* 2011; **10**: 29.
22. Havranek E, Esler A, Estacio RO, Mehler PS, Schrier RW. Differential effects of antihypertensive agents on electrocardiographic voltage: results from the Appropriate Blood Pressure Control in Diabetes (ABCD) trial. *Am Heart J* 2003; **145**(6): 993–998.
23. Keil JE, Sutherland SE, Knapp RG, Lackland DT, Gazes PG, Tyroler HA. Mortality rates and risk factors for coronary disease in black as compared with white men and women. *N Engl J Med* 1993; **329**: 738.
24. Collins R, Peto R, MacMahon S, Herbert P, Fiebach N, Eberlein K, *et al*. Blood pressure, stroke, and coronary heart disease. *Lancet* 1990; **335**: 827–838.
25. Lawes CM, van der Hoorn S, Rodgers A. Global burden of bloodpressure related disease, 2001. *Lancet* 2008; **371**: 1513–1518.

26. Yach D, Hawkes C, Gould CL, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. *J Am Med Assoc* 2004; **291**: 2616–2622.
27. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2224–2260.
28. Daskalopoulou SS, Rabi DM, Prebtani A, *et al*. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2015; **31**: 549–568.
29. Mensah GA. Epidemiology of stroke and high blood pressure in Africa. *Heart* 2008; **94**: 697–705.
30. Opie LH, Seedat YK. Hypertension in sub-Saharan African populations. *Circulation* 2005; **112**: 3562–3568.
31. Addo J, Smeeth L, Leon DA. Hypertension in sub-Saharan Africa: a systematic review *Hypertension* 2007; **50**: 1012–1018.
32. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, *et al*. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440–1463.
33. Drawz PE, Abdalla M, Rahman M. Blood pressure measurement: clinic, home, ambulatory, and beyond. *Am J Kidney Dis* 2012; **60**(3): 449–462.
34. Schwartz JI, Guwatudde D, Nugent R, Kiiza KM. Looking at noncommunicable diseases in Uganda through a local lens: an analysis using locally derived data. *Glob Health* 2014; **10**: 77.
35. Mayega RW, Makumbi F, Rutebemberwa E, Peterson S, Ostenson CG, Tomson G, *et al*. Modifiable socio-behavioural factors associated with overweight and hypertension among persons aged 35 to 60 years in eastern Uganda. *PLoS One* 2012; **7**: e47632.
36. Mayega RW, Guwatudde D, Makumbi FE, Nakwagala FN, Peterson S, Tomson G, *et al*. Comparison of fasting plasma glucose and haemoglobin A_{1c} point-of-care tests in screening for diabetes and abnormal glucose regulation in a rural low income setting. *Diabetes Res Clin Pract* 2014; **104**: 112–120.
37. Wamala J, Karyabakabo Z, Ndungutse D, Guwatudde D. Prevalence factors associated with hypertension in Rukungiri District, Uganda – A community-based study. *Afr Health Sci* 2009; **9**: 153–160.
38. Damasceno A, Azevedo A, Siva matos C, Prista A, Diogo D, *et al*. Hypertension prevalence, awareness, treatment, and control in Mozambique (urban/rural gap during epidemiological transition). *Hypertension* 2009; **54**: 77–83.
39. Agyemang C, Bruijnzeels MA, Owusu-Dabo E. Factors associated with hypertension awareness, treatment, and control in Ghana, West Africa. *J Hum Hypertens* 2005; **20**: 67–71.
40. Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens* 2009; **27**: 963–975.
41. Tumwesigye E, Wana G, Kasasa S, Muganzi E, Nuwaha F. High uptake of home-based, district-wide, HIV counseling and testing in Uganda. *AIDS Patient Care STDS* 2010; **24**: 735–741.
42. Menzies N, Abang B, Wanyeze R, Nuwaha F, Mugisha B, *et al*. The costs and effectiveness of four HIV counselling and testing strategies in Uganda. *AIDS Patient Care STDS* 2009; **23**: 395–401.
43. Kibirige D, Atuhe D, Sebunya R, Mwebaze R. Suboptimal glycaemic and blood pressure control and screening for diabetic complications in adult ambulatory diabetic patients in Uganda: a retrospective study from a developing country. *J Diabetes Metab Dis* 2014; **13**: 40.
44. Psaltopoulou T, Orfanos P, Naska A, Lenas D, Trichopoulos D, *et al*. Prevalence, awareness, treatment and control of hypertension in a general population sample of 26 913 adults in the Greek EPIC study. *Int J Epidemiol* 2004; **33**: 1345–1352.
45. Dzudie A, Kengne AP, Muna WF, Ba H, Menanga A, *et al*. Prevalence, awareness, treatment and control of hypertension in a self-selected sub-Saharan Africa urban population: a cross-sectional study. *Br Med J Open* 2012; **2**: 2012–001217.
46. Reisin E, Harris RC, Rahman M. Commentary on the 2014 BP guidelines from the panel appointed to the Eighth Joint National Committee (JNC 8). *J Am Soc Nephrol* 2014: ASN. 2014040371.
47. Walker R, Whiting D, Unwin N, Mugusi F, Swai M, *et al*. Stroke incidence in rural and urban Tanzania: a prospective, community-based study. *Lancet Neurol* 2010; **9**: 786–792.
48. Walker RW, McLarty DG, Kitange HM, Whiting D, Masuki G, *et al*. Stroke mortality in urban and rural Tanzania. *Lancet* 2000; **355**: 1684–1687.
49. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. *Global Burden of Disease and Risk Factors*. New York: The World Bank and Oxford University Press, 2006.
50. Wild S, Roglic G, Green A, Sicree R. King. Global prevalence of diabetes: estimates for 2000 and projections for 2030. *Diabetes Care* 2004; **20**: 1047–1053.
51. Okpere AN, Anochie IC, Eke FU. Prevalence of microalbuminuria among secondary school children. *Afr Health Sci* 2012; **12**(2): 140–147.

Artificial sweeteners found to be toxic to gut microbes

FDA-approved artificial sweeteners and sport supplements were found to be toxic to digestive gut microbes, according to a study by researchers at Ben-Gurion University of the Negev (BGU) in Israel and Nanyang Technological University in Singapore.

The collaborative study indicated relative toxicity of six artificial sweeteners (aspartame, sucralose, saccharine, neotame, advantame, and acesulfame potassium-k) and 10 sport supplements containing these artificial sweeteners. The bacteria found in the digestive system became toxic when exposed to concentrations of only one mg/ml of the artificial sweeteners.

'We modified bioluminescent *E coli* bacteria, which luminesce when they detect toxicants and act as a sensing model representative of the complex microbial system,' says Professor Ariel Kushmaro, John A Ungar chair in biotechnology in the Avram and Stella Goldstein-Goren department of biotechnology engineering, and member of the Ilse Katz Institute for Nanoscale Science and Technology and the National Institute for Biotechnology in the Negev. 'This is further evidence that consumption of artificial sweeteners adversely affects gut microbial activity which can cause a wide range of health issues.'

Artificial sweeteners are used in countless food products and soft drinks with reduced sugar content. Many people consume this added ingredient without their knowledge. Moreover, artificial sweeteners have been identified as emerging environmental pollutants, and can be found in drinking and surface water, and groundwater aquifers.

'The results of this study might help in understanding the relative toxicity of artificial sweeteners and the potential of negative effects on the gut microbial community as well as the environment. Furthermore, the tested bio-luminescent bacterial panel can potentially be used for detecting artificial sweeteners in the environment,' says Kushmaro.

Source: Medical Brief 2018

Association of microalbuminuria with left ventricular dysfunction in Nigerian normotensive type 2 diabetes patients

TT SHOGADE, IO ESSIEN, UE EKRIKPO, IO UMOH, CT UTIN, BC UNADIKE, JJ ANDY

Abstract

Background: **Diabetes mellitus (DM) is a risk factor for left ventricular (LV) dysfunction, and microalbuminuria is frequently associated with DM. This study aimed to compare LV function among normotensive type 2 diabetes (T2DM) patients with normoalbuminuria, those with microalbuminuria, and healthy controls.**

Methods: **This was a cross-sectional study conducted at the diabetes and cardiology clinics of the University of Uyo Teaching Hospital, Uyo, Akwa-Ibom State, Nigeria, from January 2013 to March 2014. Microalbuminuria was tested for using Micral test strips, and echocardiography-derived indices of LV function were compared among the three groups.**

Results: **Sixty-three normoalbuminuric, 71 microalbuminuric T2DM patients and 59 healthy controls were recruited. Mean age of participants was 50 ± 8 years and the three groups were age and gender matched (p = 0.23, p = 0.36, respectively). LV diastolic dysfunction (LVDD) showed a stepwise increase from the healthy controls to the normoalbuminuric to the microalbuminuric T2DM patients (16.9 vs 61.9 vs 78.9%, respectively) (p < 0.001), while E/A ratio and fractional shortening showed a significant stepwise decrease (both p < 0.001). LV systolic dysfunction was rare among the three groups. Microalbuminuria showed a strong direct association with LVDD (OR 3.58, 95% CI: 1.99–6.82, p < 0.001). Age remained independently associated with LVDD (OR 1.10, 95% CI: 1.03–1.17, p = 0.003).**

Conclusions: **LV diastolic function was altered in Nigerian normotensive T2DM patients, and the presence of microalbuminuria with DM had additional effects on this abnormality. Early screening for DM and microalbuminuria could identify individuals with high cardiovascular risk and possibly abnormal LV function.**

Keywords: diabetes mellitus, microalbuminuria, left ventricle, diastolic dysfunction

Correspondence to: TT Shogade
Department of Medicine, College of Health Sciences, University of Uyo, and University of Uyo Teaching Hospital, Uyo, Akwa-Ibom, Nigeria
e-mail: docttaiwo@yahoo.com

IO Essien, UE Ekrikpo, IO Umoh, BC Unadike (deceased), JJ Andy
Department of Medicine, College of Health Sciences, University of Uyo, and University of Uyo Teaching Hospital, Uyo, Akwa-Ibom, Nigeria

CT Utin
Cleno Health Ultrasound Institute, Uyo, and University of Uyo Teaching Hospital, Akwa-Ibom, Nigeria

Previously published in *Cardiovasc J Afr* 2018; **29**(5): 283–288

S Afr J Diabetes Vasc Dis 2018; **15**: 64–68

Diabetes mellitus (DM) is associated with diverse cardiovascular conditions such as myocardial infarction, heart failure (HF), stroke and diabetic cardiomyopathy (DMCMP), which are the leading causes of diabetes-related morbidity and mortality.[1,2] Previous studies elsewhere[3,4] and in Nigeria[5] have demonstrated left ventricular diastolic dysfunction (LVDD) in normotensive diabetics, supporting the existence of DMCMP.

The Framingham Heart Study showed that the frequency of HF is twice as high in diabetic men and five times higher in diabetic women compared with age-matched controls, and that this increased incidence of HF persisted despite correction for age, hypertension, obesity, hypercholesterolaemia and coronary artery disease (CAD).[6] An increased risk for developing HF in prospective analyses after correction for confounding variables has also been reported.[7] Therefore screening for the presence of DMCMP at the earliest stage is appropriate for the early detection and prevention of HF.

The most sensitive non-invasive test for detection of LV dysfunction is a two-dimensional echocardiogram with pulsedwave Doppler.[8] As the cost of echocardiography is high, a less expensive pre-screening test for monitoring further deterioration in cardiac function in normotensive type 2 diabetes (T2DM) patients is needed. Microalbuminuria (MCA), a known marker of glomerular endothelial dysfunction, is also associated with microangiopathy in T2DM patients.[9] It is suggested here that detection of MCA may also serve as an inexpensive pre-screening test for monitoring further deterioration in cardiac function in normotensive T2DM Nigerian patients. This study was designed to determine whether the presence of MCA in T2DM Nigerian subjects could demonstrate further deterioration in cardiac function in these patients.

Methods

The study was done in accordance with the Declaration of Helsinki and the protocol was approved by the University of Uyo Teaching Hospital, Uyo Institutional Health Ethical Research Committee (IHREC) reference number UUTH/AD/S/96/VOL.XII/38. The study was conducted in the diabetes and cardiology clinics of UUTH between January 2013 and March 2014. Two hundred participants were recruited; 134 consecutive diabetic patients, diagnosed according to the American Diabetes Association,[10] or who were

on oral antidiabetic drugs, and 59 non-diabetic age- and gender-matched controls completed the study.

Exclusion criteria were hypertension (blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs), age above 65 years, macroalbuminuria, serum creatinine of ≥ 1.5 mg/dl, chest deformity or long-standing chest disease evidenced on chest X-ray, sickle cell disease, urinary tract infection, pregnancy, cardiac conditions such as arrhythmia, heart failure, valvular heart disease, pericardial disease, congenital heart disease, and ischaemic heart disease as evidenced by clinical,electrocardiographic and echocardiographic features.

Age, gender and duration of diabetes were recorded for each subject. Weight was determined in kilograms (kg) using a weighing scale, height using a stadiometer, and waist and hip circumferences (WC and HC) were measured in centimetres (cm) using a tape measure. Body mass index (BMI), body surface area (BSA) and waist:hip ratio (WHR) were calculated.

Blood pressure was measured using an Accosson mercury sphygmomanometer with appropriate sized cuff at the brachial artery, Korotkoff phase 1 was used for systolic (SBP) and phase 5 for diastolic blood pressure (DBP) after at least 15 minutes of rest in a sitting position. Pulse rate (PR) was measured at the radial artery. The mean of three consecutive measurements, taken at five-minute intervals, was recorded. An overnight fasting venous blood sample was collected for measurement of levels of plasma glucose, creatinine and urea, and lipid profile using standard protocols.

A two-step microalbuminuria screening process was conducted. Combur 10 test strip (Roche Diagnostics, Mannheim, Germany), a visual colorimetric semi-quantitative urine test strip, was used to test for protein, blood, nitrite and leucocyte levels. If all were absent then detection of microalbuminuria was performed on the same urine sample.

Microalbuminuria was determined using Micral test strips, an optically read semi-quantitative immunoassay method (Roche Diagnostics, Australia) with a sensitivity and specificity of 80 and 88%, respectively.[11] There are four colour blocks on the test strip corresponding to negative (or 0), 20, 50 and 100 mg/l of albumin. The test was done on two occasions; the first was random urine samples (RUS) and the second was first morning void (FMV) urine samples of the subjects.

Microalbuminuria was considered to be present when the two urine samples produced a reaction colour corresponding to 20 mg/l or more. The result from the FMV urine sample was recorded as the MCA status of the subject. It has been suggested that MCA detected in the FMV urine sample corresponds better with 24-hour urinary albumin excretion (UAE) than microalbuminuria measured in a RUS, because it is less influenced by physical exercise and diet.[12]

Echocardiographic examination was performed with the patient in the left lateral decubitus position using a Hewlett- Packard Sonos 4500 echocardiography machine with a 3.5-MHz transducer. Measurements were taken under two-dimensional guided M-mode, as recommended by the American Society of Echocardiography (ASE).[13]

Endocardial fractional shortening (FS) was calculated automatically by the echocardiography machine using the formula:[14]

$$FS = \frac{LVIDd - LVIDs}{LVIDd} \times 100$$

where LVIDd is left ventricular internal dimension in diastole and and LVIDs is left ventricular internal dimension in systole Left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV) were calculated automatically by the echocardiography machine from M-mode-derived LV dimensions, using Teicholz's formula:

$$LVEDV \text{ or } LVESV = \frac{7.0 \times LVID^3}{2.4 + LVID}$$

Ejection fraction (EF) was calculated using the formula:

$$EF = \frac{EDV - ESV}{EDV} \times 100$$

The LV systolic function was considered normal if the EF was greater than 50% and/or FS was greater than 25%.[14] The LV diastolic function was assessed using Doppler modalities. Early (E) and atrial (A) velocities as well as deceleration time (DT) were measured using pulsed-wave Doppler by placing the sample volume at the tips of the mitral leaflets in apical four-chamber view. Isovolumic relaxation time (IVRT) was measured as the time interval from the end of LV outflow and start of LV inflow, as indicated by simultaneous registration of outflow and inflow signals by high-frequency pulsed-wave Doppler.

Pulmonary venous flow (PVF), systolic (S), diastolic (D) and atrial reversal (Ar) velocities were obtained by placing a pulsedwave Doppler sample volume 1–2 cm into the pulmonary vein, proximal to its insertion into the left atrium. E/A and S/D were calculated.

Diastolic function (DF) was categorised into grades according to its progression to diastolic dysfunction (DD):

- normal DF: E/A between 1 and 2, IVRT 60–100 ms and DT 160–240 ms
- grade 1 DD: E/A < 1, IVRT > 100 ms, DT > 240 ms
- grade 2 DD: E/A 1– 2, IVRT 60–100 ms, DT 150–220 ms, PVFS/D < 1
- grade 3 DD: E/A > 2, IVRT < 60 ms, DT < 160 ms.15 where DT is deceleration time and PVFS is pulmonary venous flow S velocity.

Pulmonary artery systolic pressure (PASP) was estimated from peak tricuspid regurgitant flow using continuous-wave Doppler. Tissue Doppler echocardiography was not used because, at the time the study was conducted, the echo machine used did not have the facility.

Statistical analysis

Data obtained were analysed using STATA 10. Continous variables are expressed as mean (± standard deviation) and categorical variables as percentages. Categorical variables were analysed using the chi-squared test. Student's *t*-test and analysis of variance (ANOVA) were used to analyse continuous variables. Correlates of LV function were determined using Pearson's rank correlation and predictors were assessed using logistic regressions. A p-value ≤ 0.05 was considered statistically significant.

Results

One hundred and ninety-three participants comprising 63 T2DM patients with normoalbuminuria, 71 T2DM with microalbuminuria and 59 controls were studied. The mean age for all participants was 50 years and the three groups were age and gender matched. Table 1 shows the clinical characteristics of the three study groups. The duration since diagnosis of DM was significantly longer in the microalbuminuric than in the normoalbuminuric diabetics (p = 0.02). WC, SBP and PR showed a significant stepwise increase from control to microalbuminuric group ($p < 0.001$, $p = 0.03$, $p = 0.03$, respectively). Weight, BMI, WHR, DBP and PP were comparable among the three groups.

Renal function, as assessed by estimated glomerular filtration rate (eGFR) using the Cockcroft Gault formula, was reasonably preserved among the three groups. It was highest in the control group but not statistically significantly different.

The mean values of all lipid components were normal and comparable, except for the low-density lipoprotein (LDL) cholesterol level and atherogenic ratio, which showed a significant stepwise increase from control to microalbuminric group (p = 0.0008 and p = 0.01, respectively). FBS was also significantly higher in the diabetic groups compared to the controls (p = 0.001).

Table 2 shows the echocardiographic parameters of LV function among the three groups. Mean values of EF and FS were normal in the three groups, but FS showed a significant stepwise decrease from control to microalbuminuric group (p = 0.0002).

Doppler echocardiographic parameters showed some degree of LV diastolic dysfunction, which was more pronounced in the diabetic groups. A velocity (p = 0.0034), IVRT (p = 0.0001) and PASP (p = 0.02) showed a significant stepwise increase from control to microalbuminuric group, with a reverse trend for E velocity (p < 0.001) and E/A ratio (p < 0.001).

Fig. 1 shows the prevalence and pattern of LVDD among the three groups. The prevalence of LVDD showed a stepwise increase from 16.9% in the control to 78.9% in the microalbuminuric group. The most common grade of DD was grade 1, which occurred in 70.4 and 55.5% of microalbuminuric and normoalbuminuric groups, respectively, compared to 16.9% in the controls. Grade 1 was the only type of DD found in the control group; 3.2% of the normoalbuminuric group and 8.5% of the microalbuminuric group

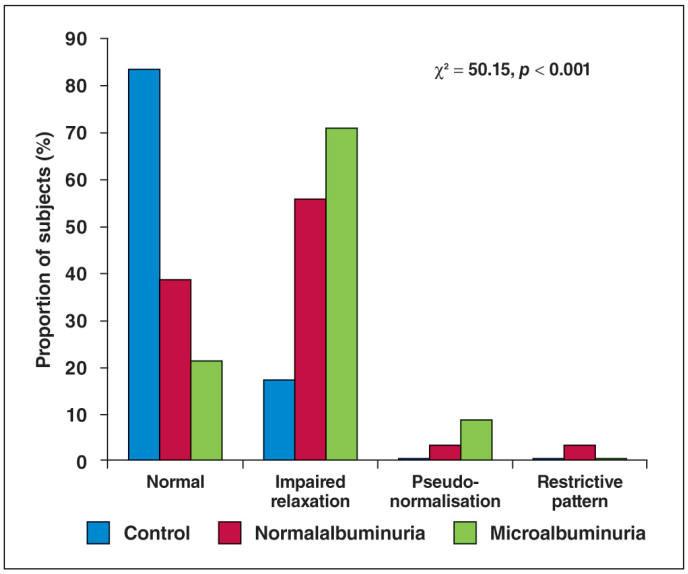


Fig. 1. Composite bar chart showing the prevalence and pattern of left ventricular diastolic dysfunction among the three groups.

Table 1. Sociodemographic, anthropometric and laboratory data (mean ± SD) variations among healthy controls, and normotensive diabetics with normoalbuminuria or microalbuminuria

Characteristics	Controls (n = 59)	Normo-albuminuric No = 63	Micro-albuminuric (n = 71)	F-test	p-value
Age (years)	47 ± 10.0	50 ± 7.5	51 ± 7.0	0.87	0.43
Gender (% male)	49	51	45	2.05	0.36
DMdur (years)	0	4.7 ± 2.8	6.1 ± 4.1	2.38	0.02
Weight (kg)	66 ± 11	68 ± 13	69 ± 12	1.00	0.37
Height (cm)	162 ± 8	162 ± 8	161 ± 9	0.62	0.54
BMI (kg/m²)	24.93 ± 4.4	26.4 ± 5.2	26.5 ± 3.8	2.14	0.12
BSA (m²)	1.71 ± 0.17	1.74 ± 0.18	1.75 ± 0.18	0.64	0.53
Waist (cm)	83 ± 10*†	89 ± 10	91 ± 10	11.19	< 0.001
WHR	0.89 ± 0.08	0.93 ± 0.07	0.93 ± 0.13	2.96	0.05
SBP (mmHg)	116 ± 11†	118 ± 9	120 ± 8	3.51	0.03
DBP (mmHg)	74 ± 8	74 ± 6	76 ± 6	2.62	0.08
PP (mmHg)	42 ± 9	42 ± 6	43 ± 7	1.42	0.25
PR (beats/min)	79 ± 12*	83 ± 10	83 ± 8	3.55	0.03
Creatinine (mg/dl)	0.9 ± 0.19	1.0 ± 0.31	1.01 ± 0.24	2.64	0.08
Urea (mmol/l)	2.6 ± 0.8*†	4.2 ± 1.7	4.0 ± 1.7	4.3	0.02
eGFR (ml/min)	102 ± 20	79 ± 31	86 ± 30	2.38	0.10
TC (mmol/l)	4.0 ± 0.6	4.6 ± 1.1	4.5 ± 1.2	1.17	0.32
TG (mmol/l)	0.9 ± 0.4	1.3 ± 0.8	1.1 ± 0.5	2.33	0.10
HDL-C (mmol/l)	1.73 ± 0.3	1.45 ± 0.5	1.37 ± 0.5	2.81	0.07
LDL-C (mmol/l)	1.74 ± 0.6†	2.38 ± 1	2.64 ± 0.8	5.14	0.008
AR	2.3 ± 0.4*†	3.5 ± 1.6	3.6 ± 1.0	4.67	0.01
FBS (mmol/l)	5.0 ± 0.5*†	8.1 ± 4	9.3 ± 4	3.72	0.001

F-test for ANOVA or student's t-test.
*p < 0.05 compared to normoalbuminuria by ANOVA.
†p < 0.05 compared to microalbuminuria by ANOVA.
BMI: body mass index, BSA: body surface area, DMdur: duration of diabetes mellitus, WHR: waist:hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, PR: pulse rate, PP: pulse pressure, AR: atherogenic ratio, eGFR: estimated glomerular filtration rate, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, FBS: fasting blood sugar level.

Table 2. Comparison of echocardiographic parameters (mean ± SD) of left ventricular systolic and diastolic function among healthy controls, and normotensive diabetics with normoalbuminuria or microalbuminuria

Echo parameters	Control (n = 59)	Normo-albuminuric (n = 63)	Micro-albuminuric (n = 71)	F-test	p-value
LVIDd (mm)	42 ± 4.4†	40 ± 4.9	38 ± 4.3	7.84	.0006
LVIDs (mm)	27 ± 3.2	26 ± 2.8	26 ± 3.2	0.81	0.45
EDV (ml)	82 ± 19†	76 ± 20	68 ± 16	8.13	0.0004
ESV (ml)	27 ± 8	26 ± 8	25 ± 7	0.82	0.44
Stroke volume (ml)	54 ± 20†	51 ± 19†	45 ± 17	9.28	0.0002
Cardiac output (l)	4.3 ± 0.9†	4.2 ± 1.1†	3.6 ± 1.0	10.05	0.0002
Ejection fraction (%)	62 ± 7.3	63 ± 8	60 ± 6.2	1.99	0.14
FS (%)	36 ± 5.5†	34 ± 6.1†	31 ± 4.1	11.39	< 0.001
Mitral E velocity (m/s)	77 ± 21*†	65 ± 18	61 ± 12	20.65	< 0.001
Mitral A velocity (m/s)	67 ± 17†	69 ± 13	74 ± 13	5.9	0.0034
E/A ratio	1.2 ± 0.3†	1.0 ± 0.3	0.8 ± 0.2	31.51	< 0.001
IVRT (s)	79 ± 13†	84 ± 16	90 ± 18	9.65	0.0001
Deceleration time (s)	199 ± 29	192 ± 42	192 ± 33	0.03	0.9658
PVF S velocity (m/s)	56 ± 11†	47 ± 14	52 ± 11	4.57	0.0123
PVF D velocity (m/s)	49 ± 8*	42 ± 7	47 ± 11	5.11	0.0074
S/D ratio	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.3	0.38	0.685
PVF Ar velocity (m/s)	31 ± 4.4	33 ± 4.0	34 ± 3.0	2.72	0.069
PASP (mmHg)	30 ± 8	30 ± 7†	33 ± 9	4.22	0.0165
LADs (mm)	35 ± 3.3	34 ± 3.5†	36 ± 3.6	4.5	0.0125

*p < 0.05 compared to normoalbuminuria by ANOVA followed by Bonferroni *post hoc* test.
†p < 0.05 compared to microalbuminuria by ANOVA followed by Bonferroni *post hoc* test.
F-test for ANOVA.
PVF: pulmonary venous flow, LADs: left atrial end-systolic dimension, IVRT: isovolumic relaxation time, E: transmitral early-to-late inflow velocity ratio, A: transmitral late atrial velocity, PASP: pulmonary artery systolic pressure.

Table 3. Correlation coefficient of clinical and biochemical variables compared with E/A ratio and IVRT in normotensive diabetic subjects ($p < 0.05$)

	E/A ratio		IVRT	
Parameters	**Rho**	***p*-value**	**Rho**	***p*-value**
Age (years)	–0.45	< 0.001	0.06	0.55
DM duration (years)	–0.06	0.51	0.14	0.15
Weight (kg)	0.11	0.24	0.08	0.39
Body surface area (m^2)	0.13	0.16	0.09	0.34
Body mass index (kg/m^2)	0.06	0.49	–0.03	0.77
Waist circumference (cm)	–0.03	0.77	0.15	0.12
Hip circumference (cm)	0.004	0.97	0.06	0.55
Waist:hip ratio	–0.09	0.35	0.05	0.61
Systolic BP (mmHg)	–0.04	0.65	–0.01	0.91
Diastolic BP (mmHg)	0.14	0.15	–0.06	0.53
Pulse pressure	–0.14	0.12	0.02	0.86
Pulse rate (beat/min)	–0.11	0.22	–0.26	0.005
Creatinine (mg/dl)	–0.32	0.009	0.19	0.13
eGFR (ml/min)	0.33	0.008	–0.09	0.47
Total cholesterol (mmol/l)	–0.16	0.25	–0.13	0.36
Trigylcerides (mmol/l)	0.01	0.91	0.32	0.01
HDL-C (mmol/l)	0.02	0.87	–0.08	0.57
LDL-C (mmol/l)	–0.07	0.60	–0.04	0.76

Rho: correlation coefficient, DM: diabetes mellitus, eGFR: estimated glomerular filtration rate, HDL-C: high-density lipoprotein cholesterol, LD-C: low density lipoprotein cholesterol.

had grade 2 pattern of DD. None of the microalbuminuric group had grade 3 but 3.2% of the normoalbuminuric group did. These observed differences were statistically significantly different (χ^2 = 50.05, $p < 0.01$).

Table 3 shows clinical and biochemical parameters that correlated significantly with indices of LV diastolic function (E/A ratio and IVRT) among the normotensive diabetics. The strongest correlate of E/A ratio in the model was age ($p < 0.001$). Serum creatinine level (p = 0.009) and eGFR (p = 0.009) also correlated significantly with E/A, but the other parameters did not.

Table 4 shows univariate and multivariate regression models used to determine predictors of LVDD in the normotensive diabetics. At the univariate level, age and MCA status were significantly associated with the occurrence of LVDD. Those with microalbuminuria had about a four-fold increased risk of developing LVDD compared to those with normoalbuminuria (95% CI: 1.99–6.82, $p < 0.001$).

Table 4. Logistic regression model to determine predictors of left ventricular diastolic dysfunction in the normotensive diabetic subjects

	Univariate analysis		Multivariate analysis	
Variable	**Odds ratio (95% CI)**	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
Age	1.11 (1.04–1.17)	< 0.001*	1.10 (1.03–1.17)	0.003*
Microalbuminuria	3.58 (1.99–6.82)	< 0.001*	1.81 (0.70–4.68)	0.222
Gender	0.69 (0.31–1.55)	0.309	0.56 (0.21–1.48)	0.240
BMI	0.98 (0.90–1.07)	0.719	0.91 (0.79–1.06)	0.227
Waist	1.01 (0.98–1.06)	0.452	1.04 (0.97–1.12)	0.263
DM duration	1.10 (0.96–1.24)	0.142	1.04 (0.90–1.19)	0.599
Systolic BP	1.01 (0.95–1.05)	0.824	0.98 (0.91–1.06)	0.694
Diastolic BP	0.96 (0.89–1.03)	0.234	0.97 (0.87–1.08)	0.598

Receiver operating curve 0.76, CI: confidence interval, DM: diabetes mellitus, BP: blood pressure.

Also, for every one year increase in age, the risk of developing DD increased by 11% (95% CI: 4–17%, $p \leq 0.001$).

After adjusting for all the other factors in the multivariate model, only age remained an independent predictor of DD. The model shows that for every one year increase in age, there was a 10% increased risk of developing DD (OR = 1.10, 95% CI: 1.03–1.17, p = 0.003). The area under the receiver operating curve of this model was 0.76, suggesting a good model.

Discussion

In this study, LVDD occurred significantly more frequently in the diabetic groups with or without MCA compared with the controls ($p < 0.001$) and the prevalence of LVDD in both diabetic groups were within the range of 40 to 75% reported by studies done on normotensive diabetics within[16] and outside the country.[17]

Grade 1 LVDD was the commonest, which was significantly more in the microalbuminuric than the normoalbuminuric group and was the only grade seen in the controls ($p < 0.01$). Aigbe *et al*.[16] and Patil *et al*.[17] reported similar findings. Higher grades (2 and 3), although rare, were commoner in the microalbuminuric (8.5%) than the normoalbuminuric group (6.4%).

Lower rates of LVDD were reported by Liu *et al*.[18] among American Indians with T2DM, 16% in normo-, 26% in micro- and 31% in the macroalbuminuric groups, because diastolic function assessment was based on only transmitral flow parameters, with no distinctions made between normal and grade 2 DD. Therefore, patients with a pseudo-normalised pattern were not included in their analysis.

Systolic dysfunction was rare among the normotensive T2DM patients, which is similar to a previous report.[3] A higher value of 15.56% reported by Dodiyi-Manuel *et al*.[5] may be due to the higher EF cut-off value of 55% used to define systolic dysfunction, thus suggesting that systolic dysfunction detected by conventional echocardiography is not an early feature of DMCMP. This supports the assumption that alteration of both relaxation and filling usually precede marked changes in chamber systolic function, although more sophisticated imaging technology such as speckle-tracking imaging (STI), used to assess myocardial strain and strain rate, have permitted the detection of subtle systolic dysfunction in the diabetic myocardium.[19]

The significant correlation of E/A ratio with age ($p < 0.001$), creatinine level (p = 0.009) and eGFR (p = 0.008) in the normotensive T2DM patient suggests a worsening of LVDD as the patient grows older and serum creatinine level rises as a result of decline in renal function. Danbauchi *et al*.[20] reported a significant correlation of LVDD with age, fasting blood glucose and two-hour postprandial glucose level in T2DM patients. Likewise, Yazici *et al*.[21] in their study on 76 T2DM patients of Turkish origin documented that E/A ratio correlated significantly with age, glycated haemoglobin (HbA_{1c}) level and duration of diabetes. These observations suggest that aging and impairment of renal function correlate with LVDD in normotensive diabetics.

The relationship between microalbuminuria and asymptomatic LVDD in T2DM patients has been a subject of much debate. In this study, a worsening of diastolic function as evidenced by significantly higher A velocity, lower E velocity and E/A ratio, larger left atrial dimension and longer IVRT were observed in the microalbuminuric compared to normoalbuminuric group. Baykan *et al*.[22] also reported significantly longer deceleration time

and IVRT in the microalbuminuric than the normoalbuminuric group.

Liu *et al.*[18] was the first to report that albuminuria status was independently associated with systolic and diastolic dysfunction in patients with T2DM. Akiyama *et al*.[23] reported that the odds of having LVDD in Japanese T2DM patients with albuminuria was about eight times more than those without albuminuria (OR 7.95, 95% CI: 1.74–21.6, $p = 0.005$). By contrast, Alwis *et al*.[4] noted in their study on 28 T2DM patients without any cardiovascular disease that 73.7% of those without microalbuminuria and 66.7% of those with microalbuminuria had LVDD. Likewise, Yildirimturk *et al*.[24] found among 50 diabetics, no significant differences in LV systolic and diastolic function between patients with or without MCA. The relatively smaller sample sizes may explain the lack of significant difference in diastolic function between diabetic patients with or without MCA in these studies.

In our study, the univariate model showed a strong direct association of LVDD with microalbuminuria (OR 3.58, 95% CI: 1.99–6.82, $p < 0.001$) and age (OR 1.1, 95% CI: 1.04–1.17, $p < 0.001$), which is similar to a previous study.[22] Only age remained as an independent predictor of LVDD (OR 1.10, 95% CI: 1.03–1.17, $p < 0.003$) after controlling for other confounders, including microalbuminuria.

It is commonly believed that grade 1 LVDD in patients above 65 years may represent a relaxation abnormality associated with the aging process. However patients younger than 65 years may represent impaired relaxation due to other conditions, which may be a precursor to more advanced diastolic impairment if not treated. In our study, subjects older than 65 years were excluded. The negative prevalence of grade 2 and 3 LVDD in the control group and the fact that pseudo-normal and restrictive LV filling patterns are usually pathological phenomenona[25] suggest that the higher proportion of LVDD seen in the diabetic groups was linked not only to aging but also to DM with or without MCA.

We included both micro- and macroalbuminuric patients in our study, as this increased the chances of detecting albuminuria as an independent predictor of LVDD, as reported by Liu *et al*.[18] in their study. Although the association between MCA and LVDD in normotensive T2DM patients was weak, it was stronger than the association of T2DM without albuminuria with LVDD.

The limitation in this study was lack of glycated haemoglobin values of the subjects studied.

Conclusion

Our study showed that the prevalence of LVDD was significantly higher in normotensive T2DM patients with or without microalbuminuria. This study was also confirmatory of the strong direct association of microalbuminuria with LVDD and the direct and independent association of age with LVDD in normotensive diabetic patients. Therefore periodic screening for microalbuminuria, especially in patients with risk factors such as hypertension or diabetes, could allow early identification of cardiovascular disease and help in stratifying overall cardiovascular risk.

References

1. Bos M, Agyemang C. Prevalence and complications of diabetes mellitus in Northern Africa, a systematic review. *BMC Public Health* 2013; **13**: 387–344.
2. Chinenye S, Uloko A, Ogbera A, *et al*. Profile of Nigerians with diabetes mellitus –Diabcare Nigeria study group (2008): Results of a multicenter study. *Indian J Endocrinol Metab* 2012; **16**(4): 558–564.
3. Booman-De Winter L, Rutten F, Cramer M. High prevalence of diastolic dysfunction in patients with type 2 diabetes. *Eur J Hear Fail Suppl* 2011; **10**: 205–210.
4. Alwi I, Harun S, Waspadji S, Rahman A, Ismail D. Left ventricular diastolic dysfunction in type 2 diabetes mellitus patient without cardiovascular disease: the association with microalbuminuria. *Med J Indones* 2005; **14**(3): 169–173.
5. Dodiyi-Manuel S, Akpa M, Odia O. Left ventricular dysfunction in normotensive type II diabetic patients in Port Harcourt, Nigeria. *Vasc Health Risk Manag* 2013; **3**(9): 529–533.
6. Kannel W, Mc Gee D. Diabetes and Cardiovascular Risk Factors: The Framingham Study. *Circulation* 1979; **59**: 8–13.
7. Aaron M, Scott C, Chen H. The development of heart failure in patients with diabetes mellitus and preclinical diastolic dysfunction: A population based study. *J Am Coll Cardiol* 2010; **55**(4): 1–12.
8. Nagueh S, Appleton C, Gillebert T, *et al*. Recommendation for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009; **22**(2): 107–133.
9. Kalaitzidis R, Bakris G. Pathogenesis and treatment of microalbuminuria in patients with diabetes: The road ahead. *J Clin Hypertens* 2009; **11**(11): 636–643.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011; **34**(1): 62–69.
11. Parikh C, Fischer M, Estacio R, Schrier R. Rapid microalbuminuria screening in type 2 diabetes mellitus: simplified approach with Micral test strips and specific gravity. *Nephrol Dial Transpl* 2004; **19**(7): 1881–1885.
12. Chavan V, Durgawale P, Sayyed A, *et al*. A comparative study of clinical utility of spot urine samples with 24-h urine albumin excretion for screening of microalbuminuria in type 2 diabetic patients. *Indian J Clin Biochem* 2011; **26**(3): 283–289.
13. Sahn D, De Mario A, Kisslo J, Weyman A. The committee on M-mode standardization of the American Society of Echocardiography: recommendations regarding quantitation in M-mode echocardiography, results of a survey of echocardiography method. *Circulation* 1978; **58**: 1072–1083.
14. Lang R, Bierig M, Devereux R. Recommendation for chamber quantification. *Eur J Echocardiogr* 2006; **7**(2): 79–108.
15. Oh J, Park S, Nagueh S. Advances in cardiovascular imaging: established and novel clinical applications of diastolic function assessment by echocardiography. *Circ Imaging* 2011; **4**: 444–455.
16. Aigbe I, Kolo P, Omotoso A. Left ventricular structure and function in black normotensive type 2AAM diabetes mellitus patients. *Ann Afr Med* 2012; **11**(2): 84–89.
17. Patil V, Patil H, Shah K, Vasani J, Shetty P. Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function. *Cardiovasc Dis Res* 2011; **2**(4): 213–222.
18. Liu J, Robbins D, Palmieri V. Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes. *J Am Coll Cardiol* 2003; **41**(11): 2022–2028.
19. Aneja A, Tang W, Bansilal S, Garcia M, Me F. Diabetic cardiomyopathy: insight into pathogenesis, diagnostic challenges, and therapeutic options. *Am J Med* 2008; **121**(9): 748–757.
20. Danbauchi S, Anumah F, Alhassan M, David S, Onyemelukwe G, Oyati I. Left ventricular function in type 2 diabetic patients without cardiac symptoms in Zaria Nigeria. *Ethn Dis* 2005; **15**(4): 635–640.
21. Yazici M, Ozdemir K, Gonen M *et al*. Is there any relationship between metabolic parameters and left ventricular functions in type 2 diabetic patients without evident heart disease? *Echocardiography* 2008; **25**(7): 675–682.
22. Baykan M, Erdogan T, Erem C, *et al*. The relationship between flowmediated dilatation and left ventricular function in type 2 diabetic patients with microalbuminuria. *Endocrine* 2006; **30**(2): 197–202.
23. Akiyama T, Eto Y, Matsuda H, Kimura Y, Yanagawa T. Albuminuria and left ventricular mass index are associated with left ventricular diastolic dysfunction in type 2 diabetes mellitus patients. *Diabetol Int* 2014; **5**(2): 129–133.
24. Yildirimturk O, Kilicgedik M, Tugcu A, Aytekin V, Aytekin S. The relationship of microalbuminuria with left ventricular functions and silent myocardial ischaemia in asymptomatic patients with type 2 diabetes. *Arch Turk S* 2009; **37**: 91–97.
25. Khali S, Kamal A, Hashim F, Olaish M. Study of left ventricular diastolic function in patients with diabetes mellitus. *Sudan J Med Sci* 2007; **2**(2): 85–90.

SGLT-2 inhibitors in type 2 diabetes

Protecting the kidney (and heart) beyond glucose control

BRIAN RAYNER

Background

Longstanding diabetes is associated with both macrovascular (myocardial infarction, stroke and peripheral vascular disease) and microvascular disease (retinopathy, nephropathy and neuropathy). Nephropathy affects approximately 40% of patients with diabetes and follows a long natural history (Fig. 1), initially manifesting with an elevated glomerular filtration rate (GFR) due to poor glucose control.[1] In time there is a progressive and inexorable decline in renal function to end-stage renal disease. However, because many diabetics remain undiagnosed for many years, chronic kidney disease (CKD) may be present at diagnosis.

Nephropathy is predicted by small amounts of albumin in the urine (below dipsticks detection) or microalbuminuria that progressively increases to overt albuminuria associated with loss of kidney function. In the United Kingdom Prospective Diabetes Study (UKPDS) the progression rate from normoalbuminuria to microalbuminuria was 2% per year, to macroalbuminuria 2.8%, and macroalbuminuria to elevated serum creatinine 2.3%.[2]

The importance of diabetic kidney disease (DKD) is two-fold. Firstly, it heralds a markedly increased mortality rate with advancing kidney disease, mainly due to cardiovascular (CV) disease. The annual death rate for normoalbuminuria is 0.7%, microalbuminuria 2%, macroalbuminuria 3.5% and elevated creatinine 12.1%.[2,3] If nephropathy develops at age 30 years, life expectancy is reduced by 14.8 years in men and 16.9 years in woman.[4] The reasons for the increased CV risk are complex and involve both traditional risk factors, especially worsening of hypertension, and non-traditional risk factors such as vascular calcification, which is beyond the scope of this article.

Secondly, DKD is now the commonest cause of end-stage CKD in most countries in the world and South Africa is no exception.[5] Currently 47.2% of dialysis patients in the private sector are diabetics and the vast majority type 2. In the state sector the figure is 11.2% and the implication of this is that the majority of diabetics in the public sector are sent home to die of end-stage CKD. The cost of dialysis in the private sector is in excess of R200 000 per annum per patient and accounts for one of the single biggest expenditures by medical aids in South Africa.

It is abundantly clear that CV disease and DKD are inextricably linked, and both need to be addressed to reduce the burden of kidney and associated CV disease.

Correspondence to: Brian Rayner
Division of Nephrology and Hypertension University of Cape Town
e-mail: brian.rayner@uct.ac.za

Previously published by *deNovo Medica,* September 2018

S Afr J Diabetes Vasc Dis 2018; **15**: 69–73

Current knowledge of prevention and treatment of DKD

There are many challenges in the treatment of DKD. Firstly, it is silent and insidious with signs and symptoms only developing in CKD stages 4 and 5; so late diagnosis is common. There is lack of public awareness and failure to implement regular screening. The major modifiable risk factors for DKD are the presence of microalbuminuria (or incipient nephropathy), hypertension, smoking, obesity, dyslipidaemia and dietary factors.

It is also critical to understand that small improvements in the trajectory of GFR can translate into long-term benefits. For example, by changing the trajectory of loss of GFR from 3 ml/min/year to 2 ml/min/year, the time to end-stage CKD can be increased by up to 10 years or more.[6]

All diabetics should have their creatinine, estimated GFR (eGFR), urine dipsticks, and urine albumin/creatinine ratio performed at diagnosis and annually. If abnormal, these need to be performed more regularly. Dipsticks positive for albumin, macroalbuminuria, and/or eGFR < 60 ml/min are very suggestive of DKD. Microalbuminuria signifies incipient nephropathy and a very elevated eGFR > 120 ml/min is also a risk factor because of the long-term harmful effects of hyperfiltration.

Correct performance and interpretation of urinary albumin/creatinine ratio are essential. Firstly, the urine should be a first voided overnight specimen to standardise testing. Spot urines significantly overestimate the presence of albuminuria. Ideally three specimens need to be obtained, but in practice testing is usually performed using only one. Normoalbuminuria is an albumin creatinine ratio < 3 mg/mmol, microalbuminuria 3–30 mg/mmol and macroalbuminuria > 30 mg/mmol (Table 1). Unfortunately several laboratories report in gm of albumin to gm of creatinine,

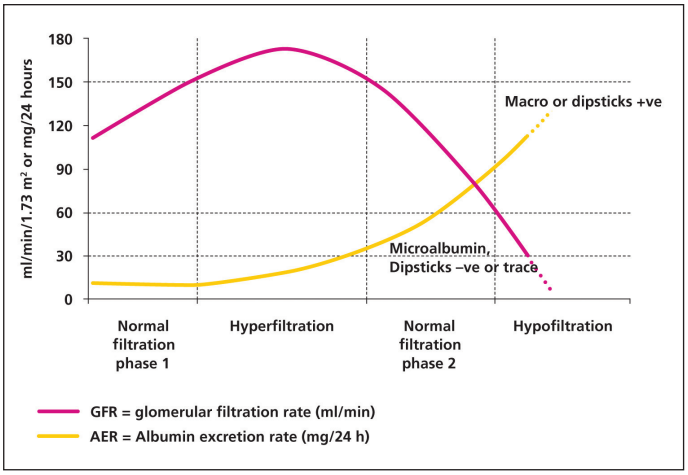


Fig. 1. Change in kidney function (GFR and albumin excretion) as diabetic nephropathy progresses.

Table 1. Interpretation of urinary albumin/creatinine ratio* (ACR) in mg/mmol

Stage	ACR
Normoalbuminuria	< 3
Microalbuminuria	
Macroalbuminuria	> 30

* For conversion of ACR to gm/gm multiply by 10.

which results in problems with interpretation. To obtain ranges for gm/gm multiply the above ranges by 10.

Treatment and prevention of DKD and CV events require a multifaceted approach. Healthy lifestyle remains crucial. For example, in early DKD, physical inactivity increases mortality by 50%, smoking by 40%, excess alcohol intake by 21% and obesity by 68%.[4] Blood pressure (BP) should be targeted to < 140/90 mmHg and ideally < 130/80 mmHg if well tolerated. All patients with micro- and macroalbuminuria must receive an ACE inhibitor or angiotensin receptor antagonist, even if normotensive, as this prevents progression of microalbuminuria to macroalbuminuria, the doubling of serum creatinine level and reduces end-stage CKD.[7] All patients should receive statin treatment almost regardless of serum cholesterol,[8] but aspirin is not routinely indicated unless for secondary prevention of CV disease. In the early phases, tight glucose control is recommended (HbA_{1c} < 6.5 mmol/l) as it prevents the onset of early DKD and other microvascular complications.[9] In late DKD, tight glucose control has little impact and may be harmful because of the risk of hypoglycaemia.

In the STENO-2 study this type of multifaceted approach resulted in a 46% risk reduction in death, 59% in CV events, 61% in nephropathy and 58% in retinopathy. Importantly, these benefits accrued only after five years of treatment.[10]

Importance of Na^+–glucose co-transport (SGLT) in the kidney

The normal kidney filters 180 litres of plasma, approximately 24 000 mmol of Na^+ and 180 g or 1 000 mmol of glucose. The sodium–glucose co-transporters (SGLT-1 and -2) completely reabsorb glucose linked to Na^+ in the proximal tubule. Glucose is reabsorbed one-to-one with Na^+ by SGLT-2 and one-to-two by SGLT-1. SGLT-2 is responsible for 90% and SGLT-1 10% of reabsorption.[11] Any defect in SGLT-2 results in renal glycosuria that has no long-term harmful effects on the kidney. In diabetes, particularly if it is suboptimally controlled, the filtration of glucose increases and the SGLT is upregulated to counteract the increased filtration.[12] However, once its threshold is exceeded, glycosuria occurs, causing an osmotic diuresis, resulting in the typical manifestations of uncontrolled diabetes, namely polyuria and polydipsia.

Relationship between heart failure and DKD

These changes have a profound effect on renal autoregulation, which potentially lies at the heart of the pathophysiology of DKD and heart failure (HF). (Many physicians are not aware that HF is more common than myocardial infarction in longstanding type 2 diabetics.)[13] Because the SGLT is upregulated by the increased glucose load in diabetics there is both increased Na^+ (and glucose) reabsorption. The resultant reduction in Na^+ delivery to the juxta glomerular apparatus results in tubular glomerular feedback (TGF) and activation of the intrarenal renin–angiotensin system (RAS).[14] The net result is a dilated afferent and constricted efferent arteriole, causing increased intraglomerular pressure, hyperfiltration and loss of autoregulation (Fig. 2). The position is compounded by the increased systemic Na^+ reabsorption that stimulates atrial natriuretic peptides, which increases renal blood flow, further exacerbating the hyperfiltration. The glomerulus is particularly sensitive to the effects of glomerular hypertension, hyperfiltration and loss of autoregulation,[15] and is seen as a fundamental pathophysiological mechanism for the development of nephropathy and the raised GFR seen in early diabetes (Fig. 1). It also exposes the glomerulus to systemic BP, and it is for this reason that both BP control and RAS inhibitors are renoprotective. RAS inhibitors, in addition to lowering BP, dilate the efferent arteriole and reduce glomerular pressure, but do not fully restore autoregulation as the afferent remains dilated[16] (Fig. 2). Longstanding increased Na^+ reabsorption by the kidney may also be plausibly linked to development of HF due to Na^+ overload and exacerbation of hypertension.

SGLT-2 inhibitors

Highly specific inhibitors of SGLT-2 have been developed by several pharmaceutical companies. The best known are empagliflozin, dapagliflozin and canagliflozin. Briefly, inhibition of the co-transporter results in glucose wasting through the kidney, resulting in insulin-independent improvement in HbA_{1c} similar to that seen with metformin, sustained weight loss due to calorie loss and significant reduction in BP due to natriuresis. These drugs are now widely registered in many countries for the treatment of type 2 diabetes.

In the kidney, SGLT-2 inhibitors increase natriuresis by blocking glucose-mediated Na^+ uptake in the proximal tubule. The resultant increased Na^+ delivery to the juxta glomerular apparatus brings about constriction of the afferent arteriole through TGF, resulting in restoration of renal autoregulation and reduction in hyperfiltration. These effects reduce the GFR in the short term by 2–3 ml/min[14] but are likely to protect the kidney in the long term in a manner similar to the effects of RAS inhibitors. Addition of SGLT-2 inhibitors to RAS inhibitors is likely to fully restore renal autoregulation (Fig. 2).

CV and kidney outcome studies with SGLT-2 inhibitors

Historically, although improving glycaemic control is associated with reduction in microvascular events, the effects on improving CV outcomes have generally been inconclusive.[17] It also became apparent that some hypoglycaemia, for example rosiglitazone, may be associated with CV harm.[18] For this reason in 2008 the FDA required companies to demonstrate empirically that a developmental drug for diabetes does not appear to increase the rate of CV disease. As a result, a plethora of CV outcome studies were launched. Most notably the DPP-4 inhibitors lowered glucose, but did not improve CV outcomes.[19]

This nihilism regarding prevention of CV outcomes was dramatically changed when the EMPA-REG OUTCOME study was presented at the European Association for the Study of Diabetes congress in Stockholm in 2015.[20] Empagliflozin 10 and 25 mg was compared to placebo in patients with uncontrolled diabetes in patients with established CV disease or at very high risk for CV disease, treated with standard of care. Both doses of

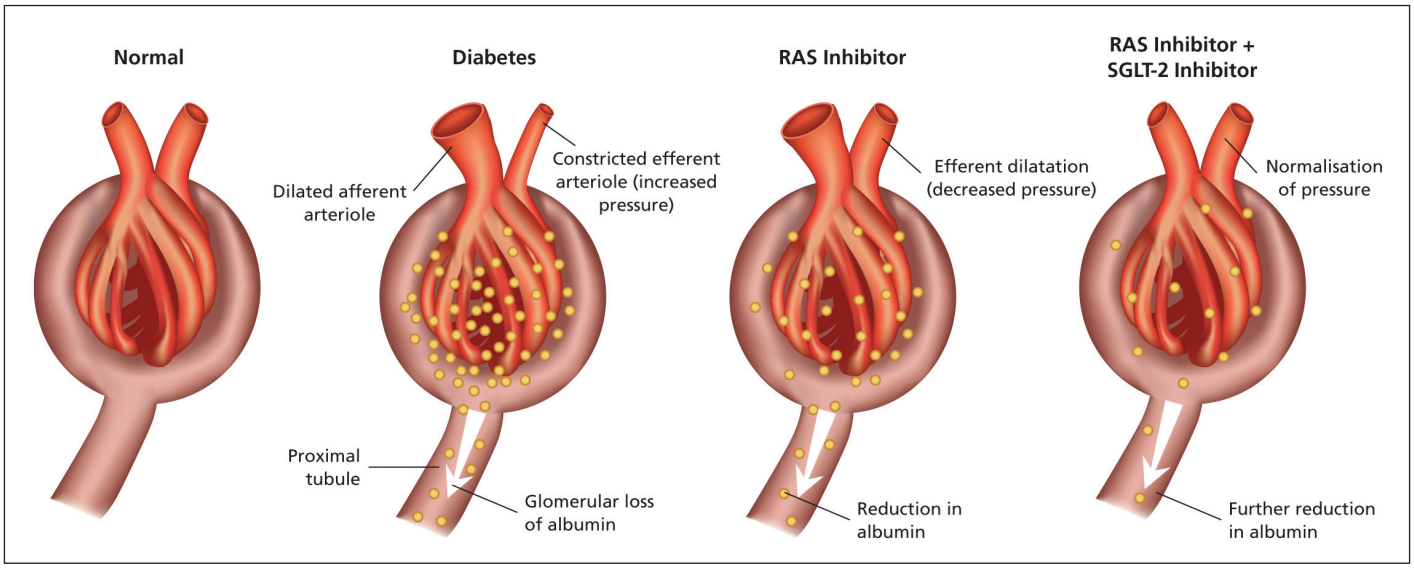
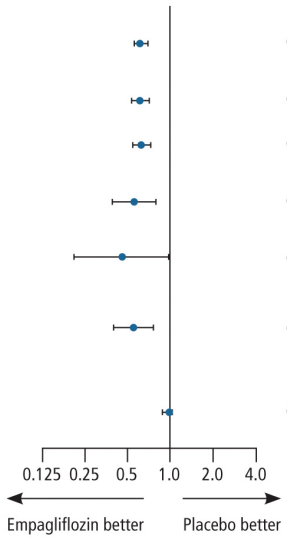


Fig. 2. Nephron changes in diabetes and after administration of RAS inhibitor + SGLT2 inhibitor.

empagliflozin lowered HbA_{1c} and body weight, and improved BP control, but more importantly there was a 38% reduction in CV death ($p < 0.0001$) and a 35% reduction in hospitalisation for HF ($p = 0.0017$). From the kidney perspective, there was a 39% reduction in new or worsening nephropathy ($p < 0.001$) and 46% in hard renal end-points namely doubling in serum creatinine level, initiation of renal-replacement therapy and death from end-stage CKD) ($p < 0.001$).[21] The benefits were also seen in patients where the estimated GFR was < 45 ml/min where there was a 44% reduction in doubling of serum creatinine level ($p = 0.0009$) (Fig. 3).

There was strong support that benefits accrued primarily due to the underlying mechanism of action of empagliflozin and not through glucose-lowering per se. Hospitalisation for HF separated very early, suggesting that increased natriuresis was the primary reason. Kidney benefit appeared after six months of treatment and analysis of the eGFR showed early reduction in GFR in both empagliflozin arms followed by a stable trend thereafter.[21] In the placebo arm, there was no initial drop in eGFR, but this was followed by an inexorable decline with the lines crossing at about 52 weeks. This supports the concept that reducing hyperfiltration

Renal Outcome Measure	Empagliflozin		Placebo		Hazard Ratio (95% CI)	p Value
	no. with event/ no. analyzed (%)	*rate/1000 patient yr*	*no. with event/ no. analyzed (%)*	*rate/1000 patient yr*		
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2101 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45ml/min/1.73m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45ml/min/1.73m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



All the analyses shown were performed with the use of Cox regression in patients who received at least one dose of either empagliflozin or placebo. All the analyses were prespecified except for the composite outcome of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease. The abbreviation eGFR denotes estimated glomerular filtration rate.

Fig. 3. Risk compression for seven renal outcomes. *From EMPA-REG OUTCOME renal trial.*

as described above is the primary mechanism for renal protection, with reduction in BP having a lesser role.

The CANVAS programme using canagliflozin compared to placebo reported similar reductions in CV and kidney events.[22] More recently a dedicated trial (CREDENCE) using canagliflozin vs placebo in patients with DKD was stopped prematurely due to the superior effects of canagliflozin on kidney end-points (https://www.jnj.com/). This study is not published and further details are awaited. Outcomes studies with dapagliflozin have not been reported to date.

Although the place of SGLT-2 inhibitors in the treatment of type 2 diabetes is not formally established, they should undoubtedly be used in overweight patients with established CV or at high risk of CV disease based on the EMPA-REG OUTCOME study and the CANVAS programme, provided there are no contra-indications, and taking into account the side-effect profile of the SGLT-2 inhibitors.

In addition, they should be considered in patients with signs of CKD (albuminuria and/or reduced eGFR but not below 30 ml/min), although this not a registered indication in South Africa. There is also no reason, except for immediate drug costs, why these drugs should not also be considered as second line after metformin in the diabetic algorithm of care; they can also be combined with most other antidiabetic medications, including insulin.

The future of these drugs looks very exciting as further CV and kidney outcome studies are nearing completion. Additionally, studies are being extended to CV and kidney protection in non-diabetic subjects. In patients with CKD, there is increased single-nephron GFR due to increased glomerular pressure and hyperfiltration to compensate for loss of GFR, which in the long term is deleterious to the kidney. SGLT-2 inhibitors may indeed benefit patients with non-diabetic CKD by reducing glomerular pressure and hyperfiltration.

Cautions and side effects of SGLT-2 inhibitors

The prescriber should refer to the full package insert before selecting a SGLT-2 inhibitor for treatment of type 2 diabetes, but there are a few important contra-indications and cautions to be considered.[23] Firstly it should not be given to type 1 diabetics due to risk of 'normoglycaemic' ketoacidosis and used with caution in thin type 2 diabetics as they may potentially be mislabelled and have type 1 diabetes. Normoglycaemic ketoacidosis can occur very rarely in type 2 diabetics, usually during periods of prolonged fasting. The SGLT-2 inhibitor should be stopped in these circumstances or carefully monitored. They should also be avoided in patient > 75 years, where risks of dehydration may outweigh benefits.

The most common side effect is genital candidiasis due to glycosuria, and is mainly seen in females. This is easily treated with local antifungal creams and seldom recurs. There may be a slight increase in urinary tract infection, but this is seldom severe.

Initial reports suggested a possible increase in fracture risk with SGLT-2 inhibitors, but this was not borne out by a recent meta-analysis.[24] Initial reports suggested an association between bladder cancer and dapagliflozin, but further analysis suggested these cases were pre-existing.[25] Canagliflozin was linked to increased risk of amputation in the CANVAS programme,[22] and further study is required to establish if this is a causal link.

Conclusions

The publication of the EMPA-REG OUTCOME study in 2015 was a major milestone in development of safer and more effective drugs for type 2 diabetes. It broke the nihilism expressed by many in relation to prevention of CV disease in type 2 diabetics. For the first time in decades an antidiabetic drug was found to safely lower blood glucose and show unequivocal evidence for prevention of CV and renal disease that can be explained by the underlying mechanism of action. It is important that a pharmaco-economic analysis be undertaken with regard to these drugs, especially in relation to prevention and the prohibitive costs of treatment of end-stage CKD.

Acknowledgement

This report was made possible by an unrestricted educational grant from Boehringer Ingelheim. The content of the report is independent of the sponsor.

References

1. Palatini P. Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. *Nephrology, Dialysis, Transplantation* 2012; **27**(5): 1708–1714.
2. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney International* 2003; **63**(1): 225–232.
3. Ritz E, Schmieder RE, Pollock CA. Renal protection in diabetes: lessons from ONTARGET. *Cardiovascular Diabetology* 2010; **9**: 60.
4. Wen CP, Chang CH, Tsai MK, Lee JH, Lu PJ, Tsai SP, *et al.* Diabetes with early kidney involvement may shorten life expectancy by 16 years. *Kidney Int* 2017; **92**(2): 388–396.
5. South African Renal Registry. Annual Report, 2015.

6. Hebert LA, Wilmer WA, Falkenhain ME, Ladson-Wofford SE, Nahman NS, Jr, Rovin BH. Renoprotection: one or many therapies? *Kidney Int* 2001; **59**(4): 1211–1226.
7. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**(12): 861–869.
8. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**(9435): 685–696.
9. Ruospo M, Saglimbene VM, Palmer SC, De Cosmo S, Pacilli A, Lamacchia O, *et al.* Glucose targets for preventing diabetic kidney disease and its progression. *Cochrane Syst Rev* 2017; **6**: Cd010137.
10. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**(6): 580–591.
11. Harada N, Inagaki N. Role of sodium-glucose transporters in glucose uptake of the intestine and kidney. *J Diabetes Invest* 2012; **3**(4): 352–353.
12. Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. *J Clin Endocrinol Metab* 2010; **95**(1): 34–42.
13. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol* 2014; **2**(10): 843–851.
14. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, *et al.* Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014; **129**(5): 587–597.
15. Staruschenko A. Hypertension and diabetes mellitus: the chicken and egg problem. *Hypertension* 2017; **69**(5): 787–788.
16. Sochett EB, Cherney DZ, Curtis JR, Dekker MG, Scholey JW, Miller JA. Impact of renin angiotensin system modulation on the hyperfiltration state in type 1 diabetes. *J Am Soc Nephrol* 2006; **17**(6): 1703-1709.
17. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Br Med J Clin Res Ed* 2000; **321**(7258): 405–412.
18. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**(24): 2457–2471.
19. Gupta P, White WB. Cardiovascular safety of therapies for type 2 diabetes. *Exp Opin Drug Safety* 2017; **16**(1): 13–25.
20. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**(22): 2117–2128.
21. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, *et al.* Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; **375**(4): 323–334.
22. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**(7): 644–657.
23. Naidoo P, Ho K, Rambiritch V, Butkow N. Sodium-glucose co-transporter inhibitor (SGLT): a novel class of antidiabetic drugs. *S Afr J Diabetes Vasc Dis* 2015; **11**: 145–148.
24. Ruanpeng D, Ungprasert P, Sangtian J, Harindhanavudhi T. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: A meta-analysis. *Diabetes Metab Res Rev* 2017; **33**(6). Epub 2017 Jun 16.
25. Ptaszynska A, Cohen SM, Messing EM, Reilly TP, Johnsson E, Johnsson K. Assessing bladder cancer risk in type 2 diabetes clinical trials: the Dapagliflozin Drug Development Program as a 'case study'. *Diabetes Ther* 2015; **6**(3): 357–375.

Statins don't reduce cardiovascular disease risk in healthy older people

Statins are not associated with a reduction in cardiovascular disease (CVD) or death in healthy people aged over 75 years, finds a recent study. However, in those with type 2 diabetes, statins were related to a reduction in cardiovascular disease and death from any cause up to the age of 85 years.

The results of the study, led by the University Institute for Primary Care Research Jordi Gol (IDIAPJGol) and Girona Biomedical Research Institute (IDIBGI), do not support the widespread use of statins in old and very old people, but they do support treatment in selected people, such as those aged 75 to 84 years with type 2 diabetes, say the researchers.

Cardiovascular disease is the leading cause of death globally, especially for those aged 75 years and over. Statin prescriptions to elderly patients have increased in recent decades, and trial evidence supports statin treatment for people aged 75 years or older with existing heart disease (known as secondary prevention).

Evidence on the effects of statins for older people without heart disease (known as primary prevention) is lacking, particularly in those aged 85 years or older and those with diabetes. So, researchers based in Spain set out to assess whether statin treatment is associated with a reduction in cardiovascular disease and death in old (75–84 years) and very old (85 years and over) adults with and without type 2 diabetes.

Using data from the Catalan primary care system database (SIDIAP), they identified 46 864 people aged 75 years or more with no history of cardiovascular disease between 2006 and 2015. Participants were grouped into those with and without type 2 diabetes and as statin non-users or new users (anyone starting statins for the first time during the study enrolment period). Primary care and hospital records were then used to track cases of CVD (including coronary heart disease, angina, heart attack and stroke) and death from any cause (all-cause mortality) over an average of 5.6 years.

In participants without diabetes, statin treatment was not associated with a reduction in CVD or all-cause mortality in both old and very old age groups, even though the risk of CVD in both groups was higher than the risk thresholds proposed for statin use in guidelines. In participants with diabetes, however, statins were associated with significantly reduced levels of CVD (24%) and all-cause mortality (16%) in those aged 75–84 years. But this protective effect declined after age 85 and disappeared by age 90.

This was an observational study, so no firm conclusions can be drawn about cause and effect, and the authors cannot not rule out the possibility that some of their results may be due to unmeasured (confounding) factors.

But they point out that this was a high-quality study with a large sample size, reflecting real-life clinical conditions. Therefore they concluded that their results do not support the widespread use of statins in old and very old populations, but they do support treatment in those with type 2 diabetes younger than 85 years.

In a linked editorial, Aidan Ryan at University Hospital Southampton and colleagues, say the biggest challenge for clinicians is how to stratify risk among those aged more than 75 years to inform shared decision making. These observational findings should be tested further in randomised trials, they write. In the meantime, they say 'patient preference remains the guiding principle while we wait for better evidence.'

Source: Medical Brief 2018

Roadmap to achieve 25% hypertension control in Africa by 2025

ANASTASE DZUDIE, BRIAN RAYNER, DIKE OJJI, ALETTA E SCHUTTE, MARC TWAGIRUMUKIZA, ALBERTINO DAMASCENO, SERINGE ABDOU BA, ABDOUL KANE, EULOGE KRAMOH, JEAN BAPTISTE ANZOUAN KACOU, BASDEN ONWUBERE, RUTH CORNICK, KAREN SLIWA, BENEDICT ANISIUBA, ANA OLGA MOCUMBI, ELIJAH OGOLA, MOHAMED AWAD, GEORGE NEL, HARUN OTIENO, ALI IBRAHIM TOURE, SAMUEL KINGUE, ANDRE PASCAL KENGNE, PABLO PEREL, ALMA ADLER, NEIL POULTER, BONGANI MAYOSI, ON BEHALF OF THE PASCAR TASK FORCE ON HYPERTENSION

Correspondence to: Anastase Dzudie
Department of Internal Medicine, Yaoundé Faculty of Medicine and Biomedical Sciences, Yaoundé, Cameroon
e-mail: aitdzudie@yahoo.com

Samuel Kingue
Department of Internal Medicine, Yaoundé Faculty of Medicine and Biomedical Sciences, Yaoundé, Cameroon

Anastase Dzudie, Karen Sliwa, Bongani Mayosi
Department of Medicine, University of Cape Town, Cape Town, South Africa

Anastase Dzudie, Karen Sliwa
Hatter Institute for Cardiovascular Research in Africa, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

Brian Rayner
Division of Nephrology and Hypertension, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

Dike Ojji
Department of Medicine, Faculty of Health Sciences, University of Abuja; Cardiology Unit, Department of Medicine, University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria

Aletta E Schutte
Hypertension in Africa Research Team (HART); MRC Unit for Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa

Marc Twagirumukiza
College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda and African Society of Hypertension (AfSoH) Initiative, Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

Albertino Damasceno
Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique

Seringe Abdou Ba
Le Dantec University Teaching Hospital, Dakar, Senegal

Abdoul Kane
Service de cardiologie, Hôpital Général de Grand Yolf, Dakar, Senegal

Euloge Kramoh, Jean Baptiste Anzouan Kacou
Institut cardiologique d'Abidjan, Abidjan, Cote d'Ivoire

Basden Onwubere
Department of Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria

Ruth Cornick
Knowledge Translation Unit, University of Cape Town Lung Institute and Department of Medicine, University of Cape Town, Cape Town, South Africa

Benedict Anisiuba
Department of Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria

Ana Olga Mocumbi
National Health Institute, Mozambique and University Eduardo Mondlane, Maputo, Mozambique

Elijah Ogola
Department of Clinical Medicine and Therapeutics, University of Nairobi, Kenya

Mohamed Awad
Division of Cardiology, University of Khartoum, Khartoum, Sudan

George Nel
Pan-African Society of Cardiology (PASCAR), Cape Town, South Africa

Harun Otieno
Section of Cardiology, Department of Medicine, Aga Khan University Hospital, Nairobi, Kenya

Ali Ibrahim Toure
Division of Cardiology, University of Khartoum, Sudan

Andre Pascal Kengne
Medical Research Council, Cape Town, South Africa

Pablo Perel, Alma Adler
Science Advisory Unit, World Heart Federation, Geneva, Switzerland and London School of Hygiene and Tropical Medicine, London, UK

Neil Poulter
International Centre for Circulatory Health, Imperial College, London, UK

Previously published in *Cardiovasc J Afr* 2017; **28**(4): 261–272

Co-published in *Global Heart* 2017

S Afr J Diabetes Vasc Dis 2018; **15**: 74–85

Abstract

Background and aim: **The Pan-African Society of Cardiology (PASCAR) has identified hypertension as the highest area of priority for action to reduce heart disease and stroke on the continent. The aim of this PASCAR roadmap on hypertension was to develop practical guidance on how to implement strategies that translate existing knowledge into effective action and improve detection, treatment and control of hypertension and cardiovascular health in sub-Saharan Africa (SSA) by the year 2025.**

Methods: **Development of this roadmap started with the creation of a consortium of experts with leadership skills in hypertension. In 2014, experts in different fields, including physicians and non-physicians, were invited to join. Via face-to-face meetings and teleconferences, the consortium made a situation analysis, set a goal, identified roadblocks and solutions to the management of hypertension and customised the World Heart Federation roadmap to Africa.**

Results: **Hypertension is a major crisis on the continent but very few randomised, controlled trials have been conducted on its management. Also, only 25.8% of the countries have developed or adopted guidelines for the management of hypertension. Other major roadblocks are either government and health-system related or healthcare professional or patient related. The PASCAR hypertension task force identified a 10-point action plan to be implemented by African ministries of health to achieve 25% control of hypertension in Africa by 2025.**

Conclusions: **Hypertension affects millions of people in SSA and if left untreated, is a major cause of heart disease and stroke. Very few SSA countries have a clear hypertension policy. This PASCAR roadmap identifies practical and effective solutions that would improve detection, treatment and control of hypertension on the continent and could be implemented as is or adapted to specific national settings.**

Keywords: hypertension, roadmap, Africa, prevalence, control, blood pressure, action

Executive summary

The Word Health Organisation (WHO) estimated that the number of people affected by hypertension is highest in Africa, at about 46% of adults aged 25 years and older, compared to 35 to 40% elsewhere in the world. Many hypertensive Africans are unaware of their status, and are rarely treated or poorly controlled, making them at highest risk for stroke, and heart and renal disease.

African Union member states at the 2004 Addis Ababa meeting described hypertension as one of the continent's greatest health challenges after HIV/AIDS. An urgency was recognised to develop and share best practices, including affordable and effective community-based programmes to screen and treat hypertension.

The WHO's 2013–2020 global action plan calls upon the United Nations (UN) member states to take immediate action in preventing and controlling non-communicable diseases (NCDs). Target six of the action plan aims to achieve a 25% relative reduction in the prevalence of raised blood pressure or to contain this by 2020, according to national circumstances. State and government heads in the UN Political Declaration are committed to preventing and controlling NCDs through the establishment and strengthening of multi-sectoral national policies and plans.

The Pan-African Society of Cardiology (PASCAR) met several times to identify key actions for a hypertension roadmap on the continent. The PASCAR coalition identified several roadblocks hampering the control of hypertension on the continent, which exist at government/health-system, physician and patient levels and include the following.

Government- and health system-related roadblocks

- lack of established policies for controlling hypertension
- poor political willingness to implement policies on NCDs
- poor universal health insurance coverage, leading to out-of-pocket payment by most patients, which leads to poor access and adherence to treatment
- lack of policies on antihypertensive medication procurement and distribution, resulting in stock shortages
- lack of *ad hoc* screening and proper referral systems for patients identified at routine screening
- inability of governments to effectively work with the private sector, non-governmental organisations (NGOs) and academia in a coordinated plan to tackle the burden of hypertension.

Healthcare professional-related roadblocks

- lack of appropriate evidence-based guidelines for healthcare professionals in individual countries
- hypertension treatment guidelines are poorly implemented because of a lack of continuing medical education
- a dearth of healthcare professionals (physicians, nurses and trained health workers) at primary care level with very low physician/patient ratio
- lack of quality and affordable antihypertension medications.

Patient-related roadblocks

- poor awareness about hypertension and its consequences
- poor adherence to drug therapy because of limited access to medication
- difficulty in changing lifestyles, and false health beliefs that hypertension is curable, due to poor patient education.

PASCAR 10-point action plan

The PASCAR hypertension task force identified a 10-point action plan, to be implemented by African ministries of health to achieve 25% control of hypertension in Africa by 2025.

1. All NCD national programmes should additionally contain a plan for the detection of hypertension.
2. Allocate appropriate funding and resources for the early detection, efficient treatment and control of hypertension.
3. Create or adopt simple and practical clinical evidence-based hypertension management guidelines.
4. Annually monitor and report the detection, treatment and control rates of hypertension, with a clear target of improvement by 2025, using the WHO STEPwise surveillance in all countries.
5. Integrate hypertension detection, treatment and control within existing health services, such as vertical programmes (e.g. HIV, TB).
6. Promote a task-sharing approach with adequately trained community health workers (shift-paradigm).
7. Ensure the availability of essential equipment and medicines for managing hypertension at all levels of care.
8. Provide universal access and coverage for detecting, treating and controlling hypertension.

9. Support high-quality research to produce evidence that will guide interventions.
10. Invest in population-level interventions for preventing hypertension, such as reducing high levels of salt intake and obesity, increasing fruit and vegetable intake and promoting physical activity.

African ministries of health, in their leadership roles, are called to adopt the 10-point action plan and customise it at a country level using a multi-sectoral approach. PASCAR calls on NGOs, all fraternal organisations, healthcare leaders and other members of the international community to join in this ambitious endeavour to support efforts by African ministries of health in reducing the burden of hypertension in Africa. Effective advocacy towards policy makers and politicians in national governments is particularly encouraged.

Hypertension definitions

There is a graded relationship between blood pressure (BP) levels, as low as 115/75 mmHg, and cardiovascular disease (CVD) risk.[1] However, hypertension is defined as the BP level above which treatments have been shown to reduce clinical events in randomised trials, which is accepted as ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic BP. The classification of BP levels used for defining hypertension is presented in Table 1.

Table 1. Definitions of classes of raised blood pressure

Category	SBP (mmHg)		DBP (mmHg)
Optimal	< 120		< 80
Normal	120–129		80–84
High normal	130–139	or	85–89
Grade 1 hypertension (mild)	140–159	or	90–99
Grade 2 hypertension (moderate)	160–179	or	100–109
Grade 3 hypertension (severe)	≥ 180	or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

SBP, systolic blood pressure; DBP, diastolic blood pressure

Hypertension burden in Africa

Hypertension has progressively become a major threat to the well-being of people in sub-Saharan Africa (SSA). During the past four decades, the highest levels of BP worldwide have shifted from high-income countries (HIC) to low- and middle-income countries (LMIC) in South Asia and SSA.[2] The WHO estimates that the prevalence of hypertension is highest in the African region, with about 46% of adults aged 25 years and older being hypertensive.[3] This compares to 35% in the Americas and other HIC and 40% elsewhere in the world.[3]

High hypertension rates, ranging from 19.3% in Eritrea to 39.6% in the Seychelles, were reported for 20 African countries in WHO STEPS (STEPwise approach to surveillance) surveys conducted between 2003 and 2009.[4] In a systematic review, the pooled prevalence in over 110 414 participants aged ± 40 years in 33 surveys was 30% (95% confidence interval: 27–34%).[5] In Africa, the number of people with hypertension increased from 54.6 million in 1990 to 92.3 million in 2000, and 130.2 million in 2010. Under prevailing circumstances, this could increase to 216.8 million by 2030.[6]

Gap in the care versus opportunity to control hypertension

The PASCAR task force recommends key steps for appropriate office measurement (Fig. 1). BP-lowering strategies that have shown their efficacy in HIC are likely to succeed in Africa. In Table 2, a synopsis is provided of currently published treatment guidelines differing regarding treatment thresholds.

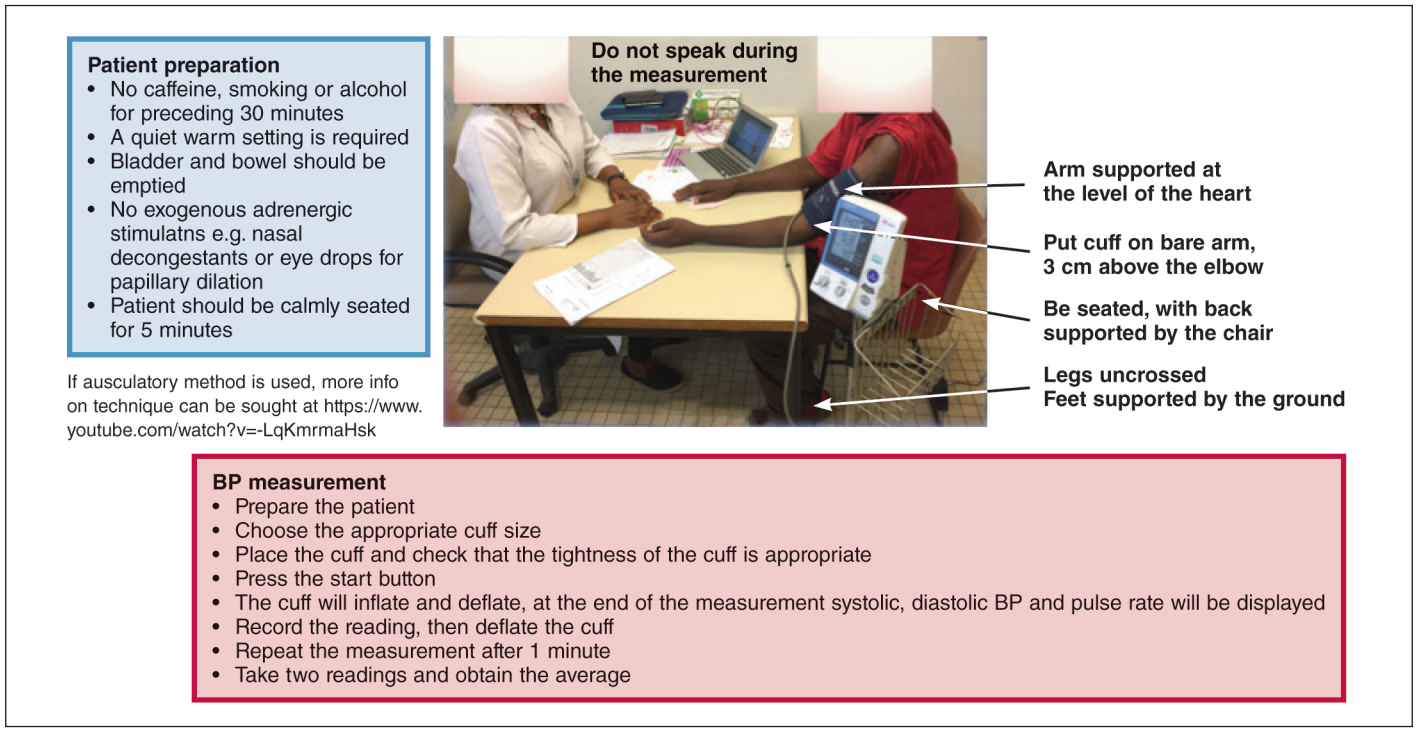


Fig. 1. PASCAR recommendations for blood pressure measurement, thresholds and action required following appropriate office measurement.

A simple and practical treatment algorithm using these thresholds is recommended (Fig. 2). Our schedule should consider patient costs (including transport and loss of wages because of time off to attend clinic visits), which affect treatment adherence and burden to the healthcare system.

Because of the asymptomatic nature of hypertension, long-term medication adherence is poor. Patients and healthcare practitioners must be educated on non-pharmacological BP control methods (see Fig. 2). We encourage patient education using text messages, e-mails or social media (WhatsApp or Facebook), all of which are

Table 2. Blood pressure guidelines

	WHO PEN[1]	NICE 2011[2]	ESH/ESC 2013[3]	ASH/ISH 2014[4]	AHA/ACC/ CDC 2013[5]	US JNC 8 2014[6]	South Africa 2015[7]	Egypt 2013[8]
Definition of hypertension (mmHg)	≥ 140/90	≥ 140/90 and daytime ABPM (or home BP) ≥ 135/85	≥ 140/90	≥ 140/90	≥ 140/90	Not addressed	≥ 140/90	≥ 140/90 (high risk) – 150/95 (low risk) and daytime ABPM (or home BP) ≥ 135/85
Drug therapy in low-risk patients after non-pharmacological treatment (mmHg)	> 160/100	≥ 160/100 or daytime ABPM ≥ 150/95	≥ 140/90	≥ 140/90	≥ 140/90	< 60 years, ≥140/90; ≥ 60 years, ≥ 150/90	≥140/90	≥ 140/90 for high risk and ≥ 160/100 for low risk
First-line therapy ≥ 60 years,	< 55 years, low-dose thiazide diuretic and/or ACE inhibitor; ≥ 55 years, CCB and/or low-dose thiazide diuretic	< 55 years, ACE inhibitor or ARB; ≥ 55 years or African ancestry, CCB	ACE inhibitor or ARB; beta-blocker; CCB; diuretic	Low-dose diuretic		ACE inhibitor or ARB; CCB; diuretic CCB/diuretic in people of African ancestry	ACE inhibitor or ARB; CCB; diuretic CCB/diuretic in people of African ancestry	Any of diuretics, betablockers, CCB, ACEIs or ARBs. preferably a thiazide diuretic. In elderly (> 65 years) or in blacks, start with diuretic or CCB.
Beta-blockers as first-line drug	No	No (step 4) subgroups)	Yes (in specific	No (step 4)	No (step 3)	No (step 4)	No (step 4)	Yes, in specific e.g. young, particularly those with tachycardia
Diuretic	Thiazides,	Chlortalidone, indapamide	Thiazides, chlortalidone, indapamide	Thiazides, chlortalidone, indapamide	Thiazides	Thiazides, chlortalidone, indapamide	Thiazide or thiazide-like (indapamide)	Thiazides, chlorthalidone, amiloride or spironolactone
Initiate drug therapy with two drugs (mmHg)	Not mentioned	Not mentioned	In patients with markedly elevated BP or patients with high overall CV risk	≥ 160/100	≥ 160/100	≥ 160/100	≥ 160/100	Diuretic + beta-blockers/ CCB/ACEIs/ARBs if BP > 170/105
Blood pressure target (mmHg)	< 140/90	< 140/90; ≥ 80 years, < 150/90	< 140/90; elderly < 80 years, SBP 140–150, SBP < 140 in fit patients; elderly ≥ 80 years, SBP 140–150	< 140/90; ≥ 80 years, < 150/90	< 140/90; lower targets may be appropriate in some patients, including the elderly	< 60 years, < 140/90; ≥ 60 years < 150/90	< 140/90	< 150/95 in low-risk patients and in elderly (> 65 years). < 140/90: ≥ 2 risk factors, CKD, TOD < 130/80: HF or CKD when associated with proteinuria > 1 g/24 hours.
Blood pressure target in patients with diabetes mellitus (mmHg)	< 130/80	Not addressed	< 140/85	< 140/90	< 140/90; lower targets may be considered	< 60 years, < 140/90; ≥ 60 years, < 150/90	< 140/90	< 140/90 mmHg or < 130/80 if associated with proteinuria > 1 g/24 hours

ABPM, ambulatory blood pressure monitoring; ACC, American College of Cardiology; ACE inhibitor, angiotensin converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ASH, American Society of Hypertension; BP, blood pressure; CCB, calcium channel blocker; CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; CV, cardiovascular; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISH, International Society of Hypertension; NICE, National Institute for Health and Care Excellence; SBP, systolic blood pressure; TOD, target-organ damage; US JNC 8, Eighth US Joint National Committee; WHO PEN, World Health Organisation Package of Essential Non-communicable disease interventions.

[1]World Health Organisation. Implementation tools: package of essential non-communicable (PEN) disease interventions for primary healthcare in low-resource settings. Available at: http://apps.who.int/iris/bitstream/10665/133525/1/9789241506557_eng.pdf. Accessed April 8, 2015.
[2]National Institute for Health and Care Excellence. NICE guidelines [CG127]. Hypertension: clinical management of primary hypertension in adults. Available at: www.nice.org.uk/guidance/cg127/chapter/guidance. Accessed April 8, 2015.
[3]Mancia G, Fagard R, Narkiewicz K, *et al*. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; **34**: 2159–2169.
[4]Weber MA, Schiffrin EL, White WB, *et al*. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens* 2014; **32**: 3–15.
[5]Go AS, Bauman MA, Coleman King SM, *et al*. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *J Am Coll Cardiol* 2014; **63**: 1230–1238.
[6]James PA, Oparil S, Carter BL, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *J Am Med Assoc* 2014; **311**: 507–520.
[7]Seedat Y, Rayner B, Veriava Y. South African hypertension practice guideline 2014. *Cardiovasc J Afr* 2014; **25**(6): 288–194.
[8]The Egyptian Hypertension Society: Egyptian hypertension guidelines. *Egypt Heart J* 2014; **66**(2): 79–132.

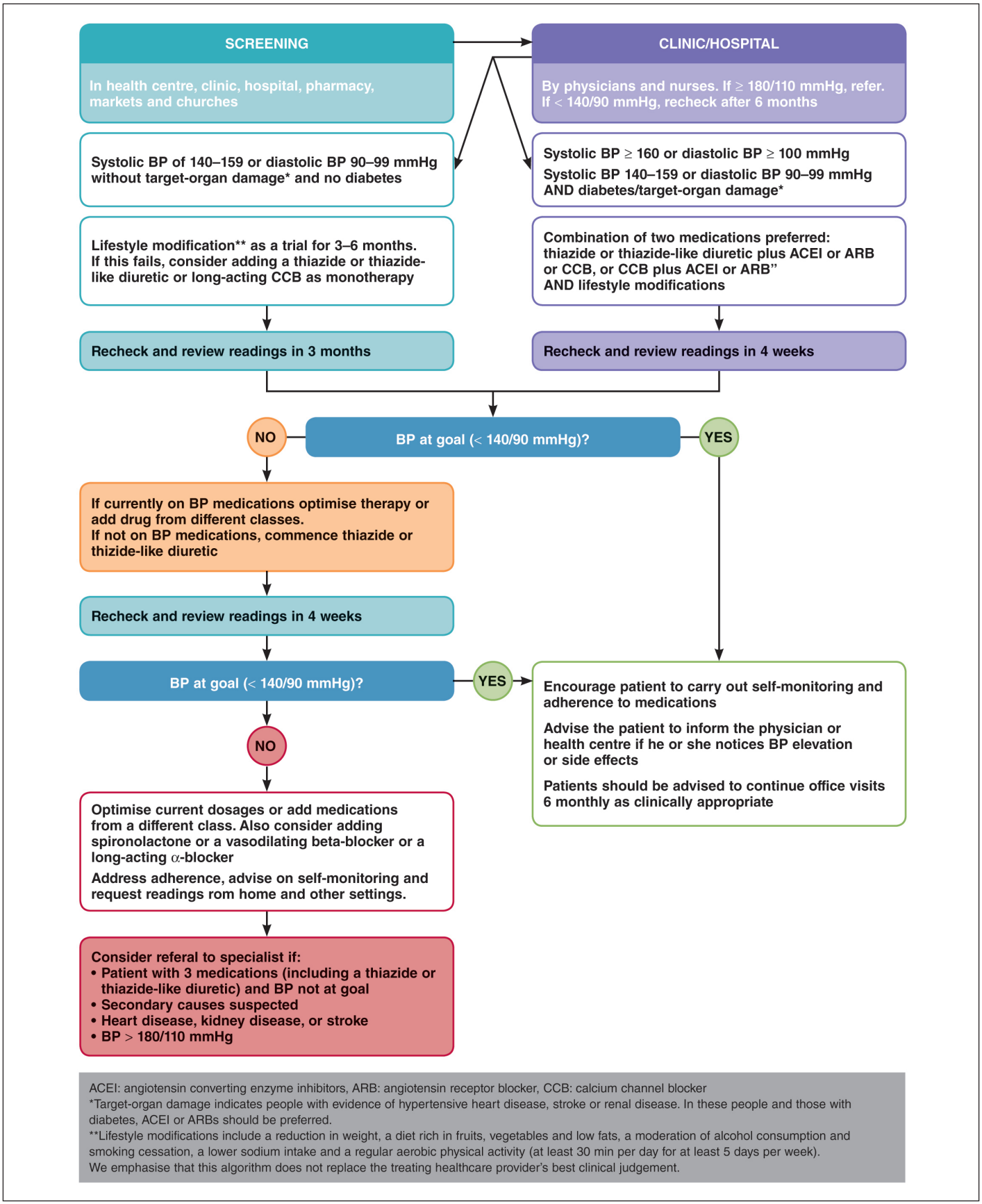


Fig. 2. PASCAR hypertension treatment algorithm

progressively available and affordable in Africa. We also encourage face-to-face education by traditional and religious leaders.

The discrepancy between best practice (based on highquality evidence) and the care provided in routine clinical practice is called the 'care gap'. This includes situations in which interventions with proven efficacy are under-utilised. This description is most marked in Africa, where it is favoured by poverty and inadequate utilisation of existing resources. Despite strong evidence of the management benefit, this can reflect as poor awareness and control of CVD rates or risk factors.

Current data on awareness and hypertension control rates in SSA are from a wide range of studies differing in methodology and limiting the opportunity for reliable comparisons. However, available data show that the high prevalence of hypertension in Africa, as in other LMICs, is coupled with low awareness and control rates (Fig. 3), a reflection of a maximal care gap.[5-8]

In 2011, UN member states acknowledged at the highest international level that premature deaths from NCDs reduce productivity and curtail economic growth, causing significant social challenges in most countries.[9] In 2015, the previous target of 25% reduction in rate of premature mortality from NCDs by 2025 was extended to a reduction of 33% by 2030, through prevention, treatment and promotion of mental health and wellbeing.[10]

Since 2004, the African Union, in a pro-active approach, named hypertension one of the continent's greatest health challenges after HIV/AIDS. After more than a decade, this political enthusiasm, which is crucial for the development and implementation of any healthcare policy, has yet to be translated into public health action. The role of hypertension experts is key to facilitate the states' action to adequately contain this threat. In a simple and practical hypertension policy, the PASCAR approach emphasises working in collaboration with all other stakeholders to set clear goals and define priority actions and minimum standards of African healthcare systems.

The World Heart Federation roadmap and other relevant initiatives

As part of the WHO's target in reducing heart attacks and stroke by 2025, the World Heart Federation (WHF) launched a roadmap focusing on raised BP during the 2015 World Health Assembly in Geneva.[11] Herein the routes are described towards reducing premature cardiovascular mortality rate by 25%,[11] focusing on presenting practical steps for hypertension control. For effective hypertension control, four population groups were identified: people who are unaware of their BP status; those who are aware of having raised BP but it is uncontrolled; those who are aware of their raised BP, which is under control; and those who are aware of having normal BP.

After identifying the target population, practical steps are provided for improving hypertension management. These include opportunistic screening for awareness of BP status and effective drug treatment for high BP.

The use of generic antihypertensive medications rather than proprietary medications is encouraged, to substantially reduce the cost of care, but with a caveat for the need to ensure quality generic medications. Bearing in mind the holistic nature of healthcare delivery, this initiative identified health-system requirements to achieve BP management targets and include human, physical and intellectual resources, healthcare delivery, healthcare recipients, financing, and governance and information systems.

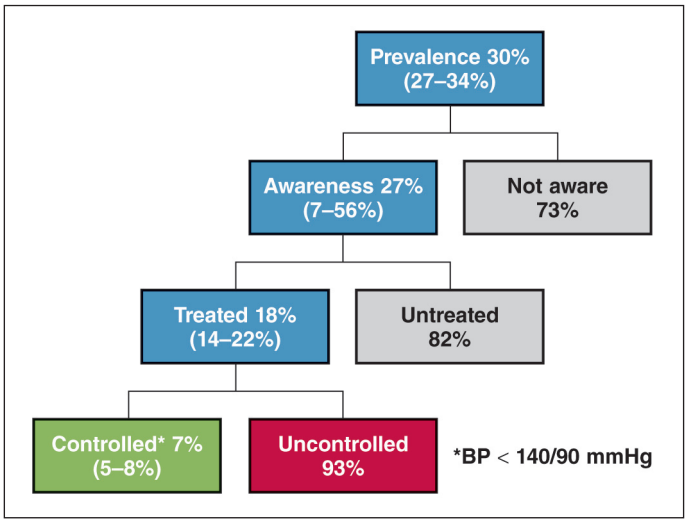


Fig. 3. Prevalence, awareness, treatment and control of hypertension in Africa. Numbers are from Ataklte *et al*. Burden of undiagnosed hypertension in sub-Saharan Africa: A systematic review and meta-analysis.[5]

With global information technology tools available, the suggestion of using e-health, particularly m-health, for patient education is a very feasible approach in the guidelines. If well applied, this could be a useful tool in hypertension control. This roadmap is anticipated to substantially bridge the gap between HIC and LMIC in terms of hypertension management and control policy. The WHO Package of Essential Non-communicable (PEN) Disease Interventions for Primary Healthcare in Low-Resource Settings is an integrated approach to NCDs focusing exclusively on primary healthcare in low-resource settings.[12]

The WHF roadmap provides a global framework to reduce CVD mortality, focusing on evidence-based interventions. Strong emphasis is placed on health systems, cost-effectiveness and subsequent evaluation of programmes. Hypertension as a single risk factor, and an entry point to prevent CVD rather than the absolute-risk approach, provides a framework to identify roadblocks in implementing evidence-based interventions. Hypertension seldom occurs in isolation, co-existing with other CVD risk factors, contributing to the absolute-risk status.

The PASCAR roadmap strongly emphasises hypertension as a global health crisis and major threat. We hope that hypertension screening will increase in the next eight years, resulting in a paradoxical increase in the prevalence of hypertension. For this reason, the task force's target is to increase treatment and control rates among the treated subjects by 25% in the SSA region by 2025.

We identified roadblocks to the control of hypertension in the African region and proposed solutions to these roadblocks, thus defining the best strategy to achieve this in SSA. Because the epidemic of NCDs is driven by globalisation, urbanisation, demographic trends and socio-economic conditions,[13] interventions to reach our targets are required from the health sector and other governmental sectors, along with civil society and the private sector.

Therefore, guidance is provided for policy makers, healthcare professionals (nurses, general practitioners, family doctors, internists, cardiologists, nephrologists and other hypertension specialists), patients, the private sector and the public, including civil society, on controlling hypertension to reduce premature mortality from CVD. To guide the action of stakeholders, we also highlight the

importance of reaching minimum standards (Table 3) for the health systems of countries to achieve the 25% hypertension control target. Implementation of these solutions and suggestions on customising the overall strategy at a country level are discussed.

The WHF roadmap provides a general framework that could be useful for LMICs, however, to be implemented it should be customised according to the local context. With PASCAR's leadership and the contribution of other professional organisations, this approach seems to be at the right time to turn the many hypertension challenges in Africa into immense opportunities. Although population-based strategies for lowering BP may be cost-effective, they are not the focus of this roadmap, but we recognise these would be beneficial.

Methods

In January 2014, panel members who were appointed to develop the PASCAR roadmap were invited to join the PASCAR task force on hypertension. Based on their expertise and leadership in hypertension, 41 nominees from 21 countries received invitations, with 95% responding positively. These experts included cardiologists, nephrologists, public health physicians, researchers (including clinical trialists), nurses, pharmacologists, evidence-based medicine specialists and guideline developers.

During the first face-to-face meeting held in Nairobi on 27 October 2014,[14] the group acknowledged the lack of a continental strategy to address the hypertension crisis. A decision was taken to develop a roadmap for the prevention and management of hypertension in Africa as a matter of urgency under the auspices of the WHF.

To customise the WHF BP roadmap for Africa, the core group performed a comprehensive literature search and communicated with the WHF from November 2014 to July 2015 via teleconference and e-mail. After receiving and comprehending the WHF roadmap document, task force members held a second face-to-face meeting in London on 30 August 2015, to make suggestions on its relevance and customisation. A detailed presentation of this roadmap was reviewed and discussed by PASCAR task force members, hypertension experts and leaders of hypertension societies via e-mail, with WHF feedback.

Development of a warehouse for African guidelines and clinical trials on hypertension was also reviewed. Finally, the steps in developing the African roadmap for reducing CVD mortality rates through BP control was planned.

The first draft of the PASCAR roadmap for hypertension management and control was presented in Mauritius on 4 October 2015. Attendees were 13 presidents of national cardiac societies or representatives, the president of the International Forum for Hypertension Control and Cardiovascular Disease Prevention in Africa and representative of the International Society of Hypertension, a representative of the African Heart Network, members of the PASCAR task force on hypertension, and scientists from the WHF. The draft was reviewed and oral and e-mail comments were received from participants. The WHO PEN programme[12] was compared with the PASCAR hypertension roadmap to ensure complementarity between the two documents.

The second version of the roadmap draft was submitted to a core group for internal review from October to December 2015. In March 2016, a selected group of hypertension experts from 12 French-speaking countries met in Yaoundé to discuss the algorithm

Table 3. Minimum care for hypertension management at each healthcare level in Africa

	Level of care		
	Primary	Secondary	Tertiary
Basic staff, equipment, test and medication	**Trained health worker or nurse**	**Medical Practitioner**	**Specialist**
Basic equipment			
Automated blood pressure devices, or calibrated sphygmomanometer, either mercury or oscillometric plus appropriate cuffs	+++	+++	+++
Home blood pressure devices		+	+++
Ambulatory blood pressure devices		+/–	+++
Tape measure for waist circumference	+++	+++	+++
Scale for weight	+++	+++	+++
Stadiometer for height	+++	+++	+++
Standard 12-lead ECG		++	+++
Glucometer	+	+++	+++
Funduscope		++	+++
Stethoscope	+++	+++	+++
Basic tests			
Urine dipsticks for protein, blood and glucose	+++	+++	+++
Standard 12-lead ECG recording		++	+++
Glucometer strips for testing glucose + +++ +++			
Na+, K+ and creatinine with calculation of eGFR	+	++	+++
Cholesterol		+	+++
Glycated haemoglobin (HbA_{1c})	+	++	+++
Chest radiograph		+/–	+++
Basic medication classes with examples*			
Thiazide or thiazide-like diuretic (hydrochlorothiazide, indapamide, chlorthalidone)	+++	+++	+++
Calcium channel blockers (amlodipine, nicardipine, long-acting nifedipine)	+++	+++	+++
Angiotensin converting enzyme inhibitor (enalapril, lisinopril, perindopril, ramipril)	+	+++	+++
Angiotensin receptor blockers (candesartan, valsartan, losartan)		+++	+++
Vasodilating beta-blockers (nebivolol, bisoprolol, carvedilol)		+++	+++
Spironolactone		+++	+++
Long-acting α-blocker (doxazocin)		+	+
Combinations of blood pressure-lowering medications	+	+++	+++

+++: strongly recommended; ++ moderately recommended, +: recommended; –: not done; +/–: done if facilities are available.
*Availability of drugs at each level of care has been indicated and recommended here for initiation only, all drugs can be used once initiated by a medical practitioner.
A trained healthcare worker may initiate and follow up some medication.

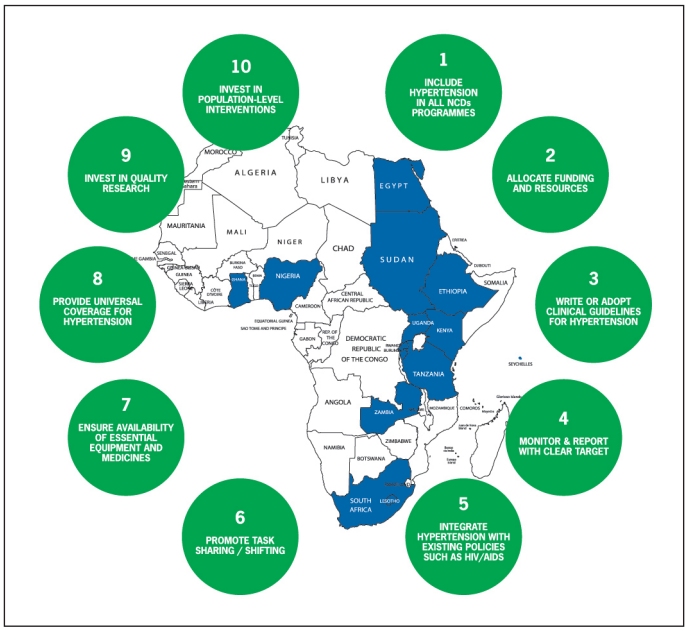


Fig. 4. 2015 map of African countries with evidence of existing clinical practice guidelines for hypertension management and 10 actions to reduce the hypertension burden in Africa

and the draft.[15] Comments were received and the draft was amended.

The task force reviewed the final draft of the roadmap in Mexico in June 2016, which was then submitted for external peer-review by three independent experts in hypertension and policy development. The subsequent review was done by a group of experts in cardiology, nephrology, primary care and research (including clinical trials). Comments were reviewed and discussed by the panel and incorporated into a revised and final document.

PASCAR searches and surveys on the status of hypertension policy programmes and clinical practice guidelines

From May to July 2015, an internal PASCAR survey was conducted, aiming to determine which African countries ran hypertension control programmes focusing on policy. Using the Survey Monkey software tool,[16] national hypertension experts from 40 countries were asked whether a hypertension policy programme was operating in their country and could be judged as being 'dormant', 'not much active', 'active', or 'very much active'.

Among the responders (n = 127) representing 27 SSA countries, we noticed that up to 63.7% did not have a hypertension policy programme or that it was dormant or not very active. This regrettable situation highlights the importance of a continental initiative to develop a hypertension policy to address BP control from a population-wide and high-risk approach.

Evidence has shown that explicit clinical practice guidelines (CPGs) do improve the care gap by providing practitioners and health-service users with synthesised quality evidence regarding decision-making.[17] In another PASCAR study, we assessed the existence, development and use of national guidelines for the detection and management of hypertension in the African region, regardless of quality.

Between May and July 2015, CPGs for hypertension were searched, using a scientifically developed search strategy. Searches were done using Google and PubMed. Search terms included (country name) AND (hypertension OR HTN OR high blood pressure) AND (clinical practice guidelines OR treatment guide). French, Portuguese and Spanish translations were included in the search strategy.

Websites of ministries of health, national medical associations and the WHO were hand-searched, authors were e-mailed, and requests were sent on Afronets to obtain copies of CPGs for hypertension. To be included in the search, the CPGs had to be available and provided in full-text versions for assessment by the review team, comprising three independent authors. CPGs from Europe or South America or those that could not be obtained were considered non-existent. Two national hypertension experts were contacted for confirmation on countries for which we could not find CPGs on hypertension. CPGs published in peerreviewed journals needed to be readily accessed by end-users. E-mail messages were used for further clarification.

In Fig. 4, the 2015 map is presented of countries with clear evidence of the existence of national guidelines for detection and management of BP across Africa. Only 16 (25.8%) out of 62 countries had CPGs complying with our search criteria. No evidence of CPGs on hypertension management could be found for the other 46 (74.2%) countries. Given that the only existing multinational expert recommendations for the management of hypertension in Africa dates back to 2003 and has not been updated since,[18] we concluded that there is a legitimate, pressing need to support African ministries of health with a clear hypertension roadmap.

PASCAR roadmap to decrease the burden of hypertension in Africa

To reduce the incidence of CVD through treating hypertension in the African region, it will be necessary to increase the rates of detection, treatment and control of the disease. The 10 actions that need to be undertaken by African ministries of health to achieve a 25% control of hypertension in Africa by 2025 (Fig. 4) are listed below and we include an explanation as to why (bullets) and how (dashes) this needs to be done.

1. All NCD national programmes should additionally contain a plan for the detection of hypertension.
   - The hypertension crisis has yet to receive an appropriate response in SSA.[19]
   - Incidence of hypertension increased by 67% since 1990 and was estimated to cause more than 500 000 deaths and 10 million years of life lost in 2010 in SSA.[20,21]
   - Hypertension is the main cause of stroke, heart failure and renal disease in SSA.
   - Stroke, which is a major complication of uncontrolled hypertension, has increased to 46% since 1990 and essentially affects breadwinners.[20]
   - Failure to control hypertension and its economic repercussions through revising health policies and services endangers the economic prosperity of all African nations.[22]
     - All SSA countries should have adopted and should follow the WHO global agenda of reducing NCDs by 2020.
     - When reporting to the Ministry of Health and the WHO, stakeholders should report specifically on hypertension.
     - National cardiac and hypertension societies should monitor the prevalence, awareness and control rates of hypertension and report to PASCAR.
     - Government, private sector, academia and community

organisations should pay attention to this report and work together for a reduction in hypertension prevalence.

2. Allocate appropriate funding and resources for the early detection, efficient treatment and control of hypertension.
   - The costs of priority interventions for NCDs, including hypertension, have been shown to be small and countries are receiving global funds.
   - No new global funding is needed to implement the 10 actions for controlling hypertension.
   - Comprehensive implementation to control hypertension and reduce salt intake is affordable in all countries.
   - The current increasing burden of uncontrolled hypertension is a barrier to the development of all African nations.
   - Funding to support civil society and health organisations will contribute to developing and implementing appropriate health policies to control hypertension.
   - Funding is needed to support dissemination of best practices to detect, manage and control NCDs within Africa.
     – Increase healthcare budgets in Africa to align with the WHO global action plan of 2013–2020, which has already been adopted by all SSA countries.
     – Realign existing funding with the emerging hypertension threat that SSA populations are experiencing.
     – Dedicate a clear percentage of the health budget to hypertension policy.
     – Use existing resources more efficiently.
     – Develop innovative funding mechanisms, including additional alcohol and tobacco taxes.
     – National cardiac and hypertension societies should monitor the hypertension/NCD-related budget every two years and advocate otherwise for improvement.
3. Create or adopt simple and practical clinical evidence-based hypertension management guidelines.
   - The role of simple and practical guidelines is crucial for managing NCDs at large, and hypertension specifically.
   - In 2015, only 25% of SSA countries had developed or adopted clinical guidelines for managing hypertension (Fig. 4).
   - New scientific knowledge guides implementation and efficiency in developing guidelines according to the best actual practices.
     – PASCAR will develop and regularly update continental guidelines with a simple care algorithm (Fig. 2) for detecting, treating and controlling hypertension. National cardiac societies are called upon to adopt or adapt to the country's circumstances where appropriate.
     – Alternatively, the WHO HEARTS technical package for CVD management in primary healthcare overtakes WHO PEN12 and provides a comprehensive CVD control approach,[23] with the possibility of integrating hypertension as a risk factor.
     – PASCAR has defined and will regularly update the minimum standards (Table 3) to control hypertension, which need to be achieved by each SSA country. Countries are called upon to adopt and implement these.
4. Annually monitor and report the detection, treatment and control rates of hypertension, with a clear target of improvement by 2025, using the WHO STEPwise surveillance in all countries.
   - The success of all NCD interventions, including hypertension policy, will depend on how specific, measurable, achievable, realistic and time-bound the objectives are.
   - A framework for national and continental monitoring, reporting and accountability will ensure that the returns on investments in hypertension and other NCDs meet the expectations of all partners.
     – The WHO STEPwise approach to NCD risk-factor surveillance should be strengthened in all African countries to report on detecting, treating and controlling hypertension annually.
     – BP to be measured at all relevant clinical encounters.
     – Regular representative population surveys are effective in monitoring trends of key risk factors and the uptake of priority interventions, such as the WHO STEPS approach to monitor NCD risk factors.
     – National cardiac and/or hypertension societies should measure the level of coverage for some sentinel sites (communities, industries, primary healthcare centres, etc.) and report to PASCAR.
     – National cardiac and/or hypertension societies should take responsibility for reporting progress in hypertension control, mobilising resources, developing policy and identifying best practices.
     – The monitoring and reporting team in sentinel sites will ensure that people know their BP, hypertensives receive appropriate treatment, BP is controlled and they remain on treatment.
5. Integrate hypertension detection, treatment and control within existing health services, such as vertical programmes (e.g. HIV, TB).
   - What the medical community learned from the large-scale management of TB and HIV/AIDS should be successful in managing hypertension.
     – The government, private sector, academia and community organisations should work together to align plans for detecting, treating and controlling hypertension with other ongoing programmes.
     – Emphasis should be placed on (1) standardised treatment protocols, (2) identification and availability of affordable and effective drugs, and (3) service delivery, as with TB and HIV programmes.
6. Promote a task-sharing approach with adequately trained community health workers (shift-paradigm).
   - SSA carries 11% of the world population, 25% of the global burden of disease, with only 3% of the world's health labour force, and has a global health expenditure of less than 1%.[24]
   - These health-worker shortages are a major barrier to controlling hypertension in Africa.
   - Clear evidence exists that health staff without formal professional training can be adequately trained to effectively detect people with severe hypertension.[25]
   - Using trained community health workers (CHW) to detect hypertension would free health professionals in Africa to treat and control the condition.
   - Well-trained nurses, general and family physicians can adequately manage uncomplicated hypertension, freeing specialists for more severe cases.
     – Design a course to train CHW in detecting hypertension, providing information and educating the community.
     – Train 250 000 CHW to detect hypertension by 2025.

  - Design special courses reinforcing health staff capacity to manage hypertension.
  - Use an online system to train at least 50 000 certified nurses and 25 000 certified general physicians to take appropriate decisions regarding detecting, treating and controlling hypertension by 2025.
  - PASCAR and national cardiac societies will design the course, and national recertification may be required after training.
7. Ensure the availability of essential equipment and medicines for managing hypertension at all levels of care.
   - Target 8 of the global action plan acknowledges the need to improve the availability of affordable BP machines and medicines for the poor.[26]
   - Target 9 of the global action plan is an 80% availability of affordable basic technologies and essential medicines, including generics, required to treat major NCDs in public and private facilities.[26]
   - Access to affordable and good-quality drugs for hypertension is important for all LMICs, and especially SSA.[26]
     - Governments and societies should be willing to prioritise hypertension control and provide low-cost BP machines and medications.
     - PASCAR and national cardiac and hypertension societies have adopted a hypertension treatment algorithm, suggesting the use of high-quality antihypertensive medications (Fig. 2).
     - The ongoing randomised clinical trial, Comparing Three Combination Therapies in Lowering Blood Pressure in Black Africans (Creole), will provide more evidence-based information on the most efficacious of three 'free' combinations of two antihypertensive agents on 24-hour ambulatory systolic BP.[27]
     - PASCAR has defined minimum standards for BP machines and drug availability and affordability to control hypertension in Africa (Table 3).
     - PASCAR and national cardiac and hypertension societies should strongly advocate making antihypertensive medica-tions available and more affordable to patients.
     - Governments should encourage adding to and periodically updating the hypertension medications on their national essential medicine list.
     - Governments should subsidise the cost of and remove import duties on these essential medications.
     - Governments should put in place an efficient, highquality monitoring process of medicines.
     - Donor organisations and pharmaceuticals should be engaged in making these medications affordable.
     - PASCAR will regularly measure the proportion of the population with access to affordable, essential drugs in sentinel sites.
8. Provide universal access and coverage for detecting, treating and controlling hypertension.
   - There are proven cost-effective lifestyle and medical interventions to prevent and manage hypertension. However, in Africa, uptake is still unacceptably low.[3]
   - Universal health coverage will be the main step forward to ensure that persons with hypertension have access to effective, affordable and accessible care.
     - Governments must have the political will to acknowledge the hypertension crisis, and the commitment to convince their parliaments to approve budgets needed for universal coverage.
     - Failure to implement universal coverage may result in increased healthcare expenditure on the complications of hypertension.
9. Support high-quality research to produce the evidence that will guide interventions.
   - Data from randomised, controlled trials on hypertension management are lacking in SSA.
   - Research is vital in formulating a sound healthcare policy to evaluate the performance of interventions in hypertension control and take managerial decisions in the overall NCD policy.[28]
   - Research into hypertension in Africa should be essential, especially where it can inform resource-allocation decisions.
     - African governments should encourage all multidisciplinary, multidirectional and collaborative approaches at national and international levels, and take a firm commitment to develop research guided through priority intervention, as suggested by the WHO.[26]
     - National cardiac and/or hypertension societies should take responsibility for identifying research priorities, building national and international research networks and partnerships, and advocating for investment in research to support best practices.
     - PASCAR, with its good continental research network, will continue taking the leadership for research training and funding while ensuring to develop and sustain research activities to guide cost-effective interventions for hypertension control.
10. Invest in population-level interventions for preventing hypertension, such as reducing salt intake and obesity levels, increasing fruit and vegetable intake and promoting physical activity.
    - The relationship between BP and the risk of developing stroke or heart disease is ongoing, starting at a systolic pressure > 115 mmHg.[1]
    - Hypertension is a preventable cause of morbidity and mortality.
    - High-quality evidence in non-acutely ill adults shows that reduced sodium intake reduces BP.[29]
    - These two previous facts highlight the importance of high risk and population-based strategies in BP management and control.
      - Therefore, advocate for a healthy public policy and large national programme for hypertension prevention and control.
      - Use national multi-sectoral policies and plans that specifically address physical activity and nutrition, including dietary salt, in preventing hypertension and NCDs.
      - Wider implementation of successful governmental actions including smoke-free policies, marketing of unhealthy foods and alcohol, sin taxes (e.g. sugar taxes), and regulation of sodium content in processed foods.

How to adapt the PASCAR 10 actions at country level

This roadmap can be implemented as is or adapted to overcome local barriers and develop solutions that are more relevant to

specific national settings. In the latter case, we recommend that national roadmaps be developed, using a multi-sectoral approach in collaboration with inter-governmental organisations, heart health advocacy foundations, cardiovascular scientific organisations, healthcare leaders, providers from primary and specialised care, private-sector stakeholders and people affected by CVD.

Effective advocacy towards policy-makers and politicians in national governments is mandatory for success. Screening among politicians might be an effective way to increase awareness and encourage governments to act.

The PASCAR task force recommended the following steps:

- Step 1: where applicable, national cardiac societies (otherwise national hypertension societies or cardiovascular specialists) should take the leadership to develop and convene a multisectoral coalition against hypertension. At this step, persuading the government and all other stakeholders to collaborate is essential.
- Step 2: this coalition will then assess the epidemiological profile of hypertension and review and synthesise existing official data and published and unpublished literature. This step also includes a map of all existing policies.
- Step 3: the coalition conducts policy dialogues with multiple local stakeholders. Local problems, specific barriers to hypertension control and potential solutions should be discussed and appropriate strategies selected according to context. At this step, it is important to understand existing policies and their current effect. Within the same nation, appropriate strategies may also need adaptation. Some stakeholders who will be invited to the policy dialogue include the ministry of health, various health sector staff (physicians and non-physicians), health workers, key opinion leaders such as politicians and religious people, and also alternative medicine specialists and traditional healers, who may have a significant influence on people with hypertension in some settings.
- Step 4: the coalition develops a clear national strategy and time-bound plan for detecting, treating and controlling hypertension.

The PASCAR coalition against hypertension takes responsibility for fostering the development of national roadmaps and supporting national cardiac and hypertension societies at all levels.

Conclusions

Although there is significant scientific evidence that costeffective lifestyle and medical interventions could control hypertension and prevent health-threatening complications, such as heart disease and stroke, the African region still bears a very high disease prevalence, coupled with poor rates of detection, treatment and control. This context is a barrier to the achievement of the universal global action plan and gives reasons for urgent action.

The PASCAR task force on hypertension roadmap was conceived by a variety of leaders and stakeholders in the field to provide the most appropriate strategy to have 25% control of hypertension by 2025. The roadmap identifies major barriers to disease control and priority areas of intervention, and 10 actions to improve the control of hypertension by 2025 are proposed. The most important steps to put forth in this continental roadmap include:

1. Advocate for government leadership and policy.
2. Allocate funding and resources.
3. Design simple and practical guidelines.
4. Promote large-scale screening.
5. Integrate hypertension detection, treatment and control in all existing programmes.
6. Promote task sharing and expand the scope of practice.
7. Promote the use of inexpensive, good-quality BP machines and generic medications.
8. Promote universal coverage for hypertension diagnosis and management.
9. Support high-quality research to produce the best evidence for interventions.
10. Invest in population preventive measures.

This is a unique moment in history for the African CVD community to have worked with global leaders in the field in defining a clear agenda to address the hypertension crisis. Support for this programme from the African Union and all stakeholders will help achieve the WHO global action plan of 2013–2020 for NCD reduction, specifically focusing on heart attack, stroke and other CVDs. The WHO and other UN organisations will support national efforts with upstream policy advice and sophisticated technical assistance, ranging from assisting governments to setting national targets in implementing relatively simple steps, which can make a huge difference.

Our sincere thanks go to all fraternal organisations, including the WHF, the International Forum for Hypertension Control and Cardiovascular Disease Prevention in Africa, the Africa Heart Network, and all national cardiac societies for supporting this initiative. We are grateful to the Clinical Research Education, Networking and Consultancy for co-drafting the manuscript and providing first versions of some figures and tables, and all

the reviewers for providing useful feedback. We also thank all members of the PASCAR task force on hypertension who worked on this project and provided feedback throughout the roadmap development, and all other partners who provided support.

Dr Poulter's institution has received grant support for research in hypertension from Pfizer and Servier and he has received speaker honoraria from AstraZeneca, Lri Therapharma, Napi and Servier. All other authors report no relationships that could be construed as a conflict of interest.

The project was fully funded by PASCAR. The Pan-African Society of Cardiology received unrestricted educational grants from Servier and AstraZeneca.

References

1. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al*. 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**(7):1281–357.
2. Zhou B, Bentham J, Di Cesare M, Bixby H, Danaei G, Cowan MJ, *et al*. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; **389**(10064): 37–55.
3. WHO | A global brief on hypertension [Internet]. [cited 2015 Dec 20]. Available from: http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/
4. Opie LH, Seedat YK. Hypertension in sub-Saharan African populations. *Circulation* 2005; **112**(23): 3562–3568.
5. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of Undiagnosed hypertension in sub-Saharan Africa: A systematic review and meta-analysis. *Hypertension* 2015; **65**(2): 291–298.
6. Adeloye D, Basquill C. Estimating the prevalence and awareness rates of hypertension in Africa: A systematic analysis. Schnabel RB (ed). *PLoS One* 2014; **9**(8): e104300.
7. Dzudie A, Kengne AP, Muna WFT, Ba H, Menanga A, Kouam Kouam C, *et al*. Prevalence, awareness, treatment and control of hypertension in a self-selected sub-Saharan African urban population: a cross-sectional study. *Br Med J Open* 2012; **2**(4): 1–10.
8. Ogah OS, Rayner BL. Recent advances in hypertension in sub-Saharan Africa. *Heart* 2013; **99**(19): 1390–1397.
9. WHO | United Nations high-level meeting on noncommunicable disease prevention and control [Internet]. [cited 2017 Mar 11]. Available from: http://www.who.int/nmh/events/un_ncd_summit2011/en/
10. Transforming our world: the 2030 Agenda for Sustainable Development: Sustainable Development Knowledge Platform [Internet]. [cited 2017 Apr 2]. Available from: https://sustainabledevelopment.un.org/post2015/transformingourworld.
11. Adler AJ, Prabhakaran D, Bovet P, Kazi DS, Mancia G, Mungal-Singh V, *et al*. Reducing cardiovascular mortality through prevention and management of raised blood pressure: A World Heart Federation roadmap. *Glob Heart* 2015; **10**(2): 111–122.
12. WHO-PEN_Final_for_web.030610.pdf - essential_ncd_interventions_lr_settings.pdf [Internet]. [cited 2017 Mar 11]. Available from: http://www.who.int/nmh/publications/essential_ncd_interventions_lr_settings.pdf.
13. Nyirenda MJ. Non-communicable diseases in sub-Saharan Africa: understanding the drivers of the epidemic to inform intervention strategies. *Int Health* 2016; **8**(3): 157–158.
14. Dzudie A, Ojji D, Anisiuba BC, Abdou BA, Cornick R, Damasceno A, *et al*. Development of the roadmap and guidelines for the prevention and management of high blood pressure in Africa: Proceedings of the PASCAR hypertension task force meeting: Nairobi, Kenya, 27 October 2014. *Cardiovasc J Afr* 2015; **26**(2): 82–85.
15. Dzudie A, Kane A, Kramoh E, Anzouan-Kacou J-B, Damourou JM, Allawaye L, *et al*. Development of the roadmap for reducing cardiovascular morbidity and mortality through the detection, treatment and control of hypertension in Africa: report of a working group of the PASCAR hypertension task force. *Cardiovasc J Afr* 2016; **27**(3): 200–202.
16. SurveyMonkey: logiciel gratuit de sondage en ligne et de questionnaire [Internet]. [cited 2017 Apr 2]. Available from: https://fr.surveymonkey.com/
17. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. - PubMed - NCBI [Internet]. [cited 2017 Mar 12]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/7901634.
18. Recommendations for prevention, diagnosis and management of… : Journal of Hypertension [Internet]. [cited 2017 Apr 2]. Available from: http://journals.lww.com/jhypertension/Citation/2003/11000/Recommendations_for_prevention,_diagnosis_and.3.aspx.
19. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension [Internet]. [cited 2017 Mar 19]. Available from: http://www.thelancet.com/commissions/hypertension
20. Mensah G, Roth G, Sampson U, Moran A, Feigin V, Forouzanfar M, *et al*. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990–2013: a systematic analysis of data from the Global Burden of Disease Study 2013: cardiovascular topic. *Cardiovasc J Afr* 2015; **26**(2): S6–10.
21. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2224–2260.
22. Nugent R. Chronic diseases in developing countries: Health and economic burdens. *Ann NY Acad Sci* 2008; **1136**(1): 70–79.
23. GHI_Brochure.pdf [Internet]. [cited 2017 Apr 10]. Available from: http://www.who.int/cardiovascular_diseases/global-hearts/GHI_Brochure.pdf?ua=1.
24. Inequities in the global health workforce: the greatest impediment to health in sub-Saharan Africa. - PubMed - NCBI [Internet].[cited 2017 Mar 12]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17617671.
25. Gaziano TA, Abrahams-Gessel S, Denman CA, Montano CM, Khanam M, Puoane T, *et al*. An assessment of community health workers' ability to screen for cardiovascular disease risk with a simple, non-invasive risk assessment instrument in Bangladesh, Guatemala, Mexico, and South Africa: an observational study. *Lancet Glob Health* 2015; **3**(9): e556–563.
26. WHO | Global Action Plan for the Prevention and Control of NCDs 2013–2020 [Internet]. [cited 2017 Mar 12]. Available from: http://www.who.int/nmh/events/ncd_action_plan/en/
27. Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Feb 11]. Available from: https://clinicaltrials.gov/ct2/show/NCT02742467.
28. Van de Vijver S, Akinyi H, Oti S, Olajide A, Agyemang C, Aboderin I, *et al*. Status report on hypertension in Africa – Consultative review for the 6th Session of the African Union Conference of Ministers of Health on NCD's. Pan Afr Med J [Internet]. 2013 Oct 5 [cited 2017 Jan 1];16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3932118/
29. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and metaanalyses. *Br Med J* 2013; **346**(apr03 3): f1326.

Diabetes News

News from the 2018 Cape Town World Congress of Internal Medicine

Why hypertension matters: the silent killer

Launching the 2018 World Congress of Internal Medicine (WCIM), the South African Hypertension Society (SAHS) hosted a media brief on the importance and urgency of detection and management of hypertension. 'Findings from global and South African cohorts show critically low awareness of hypertension…' This message from Dr Martin Mpe, president of the SAHS, underscores the fact that hypertension is the most important preventable cause of morbidity and mortality worldwide.[1]

The importance of blood pressure as a risk factor for cardiovascular disease is long recognised. Hypertension is causally linked to stroke, myocardial infarction, end-stage kidney disease, congestive heart failure, peripheral vascular disease and blindness. Inadequate control of blood pressure is responsible for 60% of strokes globally and 30% of ischaemic heart disease.[1] Hypertension is also related to dementia and sexual dysfunction.

Treatment adherence (medicine, diet, lifestyle) to control hypertension is crucial and Dr Mpe noted that '…poor adherence is of no benefit and is the same as doing nothing,' with only one-third of treated patients achieving target. It is, however, problematic that the target population that should benefit from advances in hypertension treatment are not even aware of their blood pressure levels.

There are no symptoms of hypertension, 'the silent killer', and this can hinder diagnosis. Sub-Saharan Africa has a burden of 73% undiagnosed hypertension.[1] In 2010, 40% of South African adults older than 25 years showed measured hypertension.[2] South African demographic and health survey figures from 2016 indicate a prevalence of hypertension of 46% in women and 44% in men older than 15 years.[3]

Awareness is the gateway to improved blood pressure control. The International Hypertension Society (IHS) introduced May Measurement Month in 2017, to raise awareness of the importance of measuring blood pressure. Prof Alta Schutte, president of the IHS, elaborated on the survey outcomes. Of 1.5 million people screened from 89 countries (including South Africa) during May 2018, 18.4% were found to have high blood pressure that was untreated, and 40.4% of those on treatment were not controlled to target (unpublished data). South African data from the 2017 survey shows that 56% of those on treatment are not adequately controlled.[4]

Our older population

While increasing age is a risk factor for hypertension, and although the size of the older population is increasing, relative global prevalence of hypertension continues to climb. Prof Neil Poulter, Oxford, UK, points out that lifestyle is key in the prevention and management of hypertension. As populations develop, there is a shift in lifestyle towards reduced physical activity, an increase in alcohol and tobacco consumption, unhealthy eating habits, using too much salt and being overweight, all of which are risk factors for hypertension.[5]

With 1.56 billion people predicted to have hypertension by 2025, the urgency to detect and manage this condition is paramount for non-communicable disease management. Prof Brian Rayner, Hypertension Institute, UCT, recommends that individuals be encouraged to know their own blood pressure numbers. Blood pressure monitoring is a simple procedure, using many validated devices available on the market. Servier Pharmaceuticals sponsored the May Hypertension Awareness campaign and an educational video for patients and practitioners on how to correctly measure blood pressure.

Source: DeNovo Medica
www.denovomedica.com

References

1. Chow CK, Teo KK, Rangarajan S, *et al*. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *J Am Med Assoc* 2013; **310**(9): 959–968.
2. Day C, Groenewald P, Laubscher R, *et al*. Monitoring of non-communicable diseases such as hypertension in South Africa: Challenges for the post-2015 global development agenda. *S Afr Med J* 2014; **104**(10): 680–687.
3. National Department of Health, Statistics South Africa, South African Medical Research Council. *South Africa demographic and health survey 2016: Key indicators*.https://www.statssa.gov.za/publications/Report%2003-00-09/Report%2003-00-092016.pdf.
4. Beaney T, Schutte A, Tomaszewski M, *et al.* May Measurement Month 2017: an analysis of blood pressure screening results worldwide. *Lancet Glob Health* 2018; **6**(7): e736–e743.
5. Poulter NR, Prabhakaran D, Caulfield M. Hypertension. *Lancet* 2015; **386**(9995): 801–812.

How to deal with the mass killer, hypertension

High blood pressure is the single biggest contributor to the global burden of disease, with hypertension leading to 10.7 million deaths every year.[1] Most worrying is a recent global study showing that on average, more than half of those affected don't know they have it.[2] Because cardiovascular disease affects a third of adults in the world, it is the largest epidemic ever known to mankind.[3]

With mortalities increasing year on year, awareness, and therefore treatment and control rates, have been shown to worsen as the economic status of populations drop.[2] Prof Neil Poulter, immediate past president of the International Society of Hypertension (ISH), says that between the highest-income countries and the lowest, there was an 8.2% drop in awareness, a 15% drop in treatment rates and a 6.3% drop in control. This prompted the ISH to mount an unprecedented global blood pressure (BP) awareness campaign during May last year.[4]

Speaking at the 34th World Congress of Internal Medicine (WCIM) that was held in Cape Town in October, Prof Poulter said an earlier study showed that just 46.5% of 57 840 hypertensive people canvassed knew they had hypertension, followed by a dramatic drop off between those treated (40.6%) and those controlled (13.2%). In the subsequent global ISH screening and awareness initiative, dubbed 'May Measurement Month' (MMM, 2017), volunteers screened over 1.2 million people in 80 countries. They uncovered over 150 000 people with untreated raised BP (17.3% of those untreated) and over 100 000 with treated but uncontrolled BP (46.3% of those treated). The ISH went one better this year, screening over 1.5 million people in 89 countries and detecting over 220 000 with untreated raised BP (18.4% of those untreated) and over 110 000 with treated but uncontrolled BP (just 40.4% of those treated).

He described the MMM campaigns as a major success and a 'heart-warming, fantastic volunteer effort.'

Take-home lessons

'So, we need to put screening in place and provide suitable drugs – most people are not getting enough drug combinations. You need two or more drugs to manage hypertension properly,' said Prof Poulter.

Drug guidelines are confusing, differing in the European Union, America and Britain, with different drug combinations recommended for different race groups. Prof Poulter favours the British combination-drug guidelines.

'Our problem is that world-wide we don't know what the best combinations are. We know that patients need at least two drugs, sometimes three, ideally in a single pill, for the best outcomes. A single (combination-drug) pill gives more effective and rapid BP control than monotherapy and two 'free' drugs. You get reduced side effects, enhanced adherence, improved cardiovascular protection and they're more cost-effective,' said Prof Poulter.

Prof Poulter has just completed a major trial of three different two-drug combinations for lowering BP in black Africans in six sub-Saharan countries (the CREOLE study), with definitive but yet-to-be-released results. He said he hopes to present them 'somewhere prestigious' early next year.

'We now know what works for black Africans. Our primary end-point was to lower ambulatory systolic BP after six months,' he revealed, while keeping tight-lipped about the much-anticipated findings.

Clearing up muddy treatment waters

In two slightly differing presentations to the Cape Town WCIM, Prof Poulter reviewed existing combination-drug trials and decried the American lower treatment threshold BP guideline of 130/80 mmHg. He said that although the SPRINT study, which influenced this lower threshold, had reported lower rates of fatal and non-fatal major cardiovascular events from any cause, at systolic BP targeted to < 120 mmHg, the Americans measured BP 'in a way nobody does in this room – they used a machine with the patient alone in a back room, which gives lower BPs than those measured in your clinics.' He recommends sticking with the higher 140/90 mmHg diagnostic threshold for hypertension.

Meanwhile, reports in the prestigious *Lancet* and *British Medical Journal* differ over the BP targets recommended. What guidelines in the world tend to agree on, he said, was that treating with two drugs as initial therapy was the way to go. Just two drugs in a single tablet has already improved compliance by 21%. If a patient was above a certain level of risk, they should also be on a statin, regardless of cholesterol levels, until at least 80 years of age, he added.

Prof Poulter's conclusions from the ACE inhibitors vs ARB controversy in managing hypertension are that individual trial data and meta-analyses are relatively consistent in showing the superiority of ACE inhibitors. ARBs are better tolerated but do not reduce mortality rate or cardiac events as well as ACE inhibitors and should be used if patients cough on ACE inhibitors. Prof Poulter concluded his presentation with a telling cartoon of an obese man, with a frothy pint of beer in one hand and a cigarette butt in his mouth, sticking his hand through a hole in a wall, on the other side of which, an unseeing doctor measures his BP and puts pills in an outstretched palm.

Session moderator, Prof Sajidah Khan, an interventional cardiologist at the Gateway Private Hospital in Umhlanga, said that in the very country that most funds prevention (North America), the sale of ultra-processed foods this year rose by 2.3% compared to a 71% increase in Africa and Eastern countries. Simultaneously, the revenue growth for the world's biggest tobacco retailer, Philip Morris, rose by 2.8%. It was therefore unsurprising that 80% of all cardiovascular disease occurs in lower- to middle-income countries. The damaging myths about statins paled by comparison with this.

Prof Brian Rayner, head of the Division of Nephrology and Hypertension at the Groote Schuur Hospital and University of Cape Town, said a three-pill regimen would address huge unmet needs in South Africa and the continent. He said up to 90% of hypertensive South African patients remain untreated and agreed with Prof Poulter that the American guidelines, 'have set us back and created confusion in the definition of hypertension – there's a big difference between a target and the definition,' he added.

References

1. Poulter NR, Prabhakaran D, Caulfield M, *et al.* Hypertension. *Lancet* 2015; **386**(9995): 801–812.
2. Chow CK, Teo KK, Rangarajan S, Islam S, *et al.* Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *J Am Med Assoc* 2013; **310**(9): 959–968.
3. Dena Ettehad, Connor A Emdin, Amit Kiran *et al.* Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; **387**(10022): 957–967.
4. Beaney T, Schutte AE, Tomaszewski M, *et al.* May Measurement Month 2017: an analysis of blood pressure screening results worldwide. *Lancet Glob Health* 2018; **6**(7): e736–743.

Evolving evidence about diet and health

Nutritional research initially focused almost entirely on conditions of nutritional deficiencies (e.g. scurvy, beriberi, pellagra). By the 1950s, with the increase in coronary heart disease in high-income countries, attention shifted to a range of so-called diet–heart hypotheses.

These included the putative and harmful effects of fats (especially saturated fats) and the protective effects of the so-called Mediterranean diet to explain why individuals in the USA, northern Europe and the UK were more prone to coronary heart disease, whereas those in European countries around the Mediterranean (or Japan) seemed to have lower risks.

Some of the initial studies were enormously influential while undergoing limited scrutiny as to the rigor of their methods. The lack of replication of these early claims should have prompted caution and re-examination of whether fats (especially saturated fats) were indeed harmful.

More recently, studies using standardised questionnaires, careful documentation of outcomes with common definitions, and contemporary statistical approaches to minimise confounding have generated a substantial body of evidence that challenges the conventional thinking that fats are harmful. Also, some populations (such as the US population) changed their diets from one relatively high in fats to one with increased carbohydrate intake. This change paralleled the increased incidence of obesity and diabetes.

The focus of nutritional research has recently shifted to the potential harms of carbohydrates. Indeed, higher carbohydrate intake can have more adverse effects on key atherogenic lipoproteins (e.g. increase the apolipoprotein B-to-apolipoprotein A1 ratio) than can any natural fats. Additionally, in short-term trials, extreme carbohydrate restriction led to greater short-term weight loss and lower glucose concentrations compared with diets with higher amounts of carbohydrate.

Robust data from observational studies support a harmful effect of refined, high-glycaemic-load carbohydrates on mortality. The realisation that cardiovascular disease is a global epidemic, with most cases occurring in developing countries, has also stimulated studies involving multiple countries at different economic levels.

Last year, the Prospective Urban Rural Epidemiology (PURE) study of 135 335 individuals from 18 countries in five continents showed that a diet high in carbohydrates (more than approximately 60% of energy) but not high in saturated fats, was associated with higher risk of death. However, in PURE, even the group with the highest level of fats (i.e. quintile 5; mean total fat intake 35% of energy, and saturated fat intake 13% of energy) was not as high as the average in studies from Finland (37 and 20%, respectively), Scotland (37 and 17%, respectively), or the USA (38 and 16%, respectively), done in the 1960s and 1970s.

Therefore, a marked reduction in fat intake in several countries might have occurred over the past few decades in several countries. It is not clear that further reductions in dietary fat intake will lead to reductions in incidence of disease.

In countries (or individuals) with high carbohydrate intakes, limiting intake could be beneficial. In a recent issue of *The Lancet Public Health*, Sara Seidelmann and colleagues examine the 25-year follow-up data from the Atherosclerosis Risk in Communities (ARIC) study and place their findings in the context of a meta-analysis of published studies about carbohydrate intake.

The authors concluded that the epidemiological association between carbohydrate intake and death is U-shaped, with the lowest risk occurring with a carbohydrate intake of 50–55% of energy, and with both lower and higher intakes being associated with higher risk of death (hazard ratio 1.20, 95% CI: 1.09–1.32 for low carbohydrate consumption; 1.23, 1.11–1.36 for high carbohydrate consumption). Such differences in risk associated with extreme differences in intake of a nutrient are plausible, but observational studies cannot completely exclude residual confounders when the apparent differences are so modest.

Based on first principles, a U-shaped association is logical between most essential nutrients versus health outcomes. Essential nutrients should be consumed above a minimal level to avoid deficiency and below a maximal level to avoid toxicity. This approach maintains physiological processes and health (i.e. a so-called sweet spot). Although carbohydrates are technically not an essential nutrient (unlike protein and fats); a certain amount is probably required to meet short-term energy demands during physical activity and to maintain fat and protein intakes within their respective sweet spots.

On the basis of these principles, moderate intake of carbohydrate (e.g. roughly 50% of energy) is likely to be more appropriate for the general population than are very low or very high intakes. This would translate to a generally balanced diet that includes fruit, vegetables, legumes, whole grains, nuts, fish, dairy and unprocessed meats, all in moderation.

The findings of the meta-analysis should be interpreted with caution, given that so-called group thinking can lead to biases in what is published from observational studies, and the use of analytical approaches to produce findings that fit in with current thinking. The ideal approach to meta-analysis would be a collaboration involving investigators of all the large studies ever done (including those that remain unpublished) that have collected data about carbohydrate intake and clinical events, and pool the individual data using transparent methods. This approach is likely to provide the best and most unbiased summary of the effects of carbohydrates on health, rather than reliance on the results of any single study.

Future observational studies should also consider new methods, which include triangulation, to assess whether there is a coherent pattern of information about the links between consumption of a nutrient, such as carbohydrates, with a panel of physiological or nutritional biomarkers and clinical outcomes. When appropriate, this approach should be complemented by large and long-term clinical trials investigating the effects of different dietary patterns (constructed from information about the effects of individual nutrients and foods), because the effect of individual nutrients is likely to be modest. When coherent information emerges from different approaches and is replicated, this will form a sound basis for robust public health recommendations.

The Lancet Public Health 2018; **3**(9): e408–409.

The management and staff of Clinics Cardive Publishing wish you and your family a wonderful holiday season and a healthy and peaceful 2019. May your holidays be filled with joy, peace and good cheer!

We take this opportunity to thank you for your loyal support during 2018 and look forward to being of service during 2019.

Please note our offices will close on 14 December and will be open from 08 January 2019.

pharma dynamics
EFFECTIVE AFFORDABLE HEALTHCARE
A Lupin Group Company

Slower onset for consistent flow[1]

Carzin XL, the extended release doxazosin offers:

- A **slower** onset of action vs IR formulations to allow fewer titration steps and to minimize side-effects[2].
- **Effective** treatment for urinary outflow obstruction and BPH symptoms[3].
- **Safe** BPH treatment for normotensive and hypertensive patients[3].

carzin XL
DOXAZOSIN 4 mg

MORE THAN
53%
COST SAVING vs THE ORIGINATOR [4]

For further product information contact **PHARMA DYNAMICS** P O Box 30958 Tokai Cape Town 7966 **Fax** +27 21 701 5898
Email info@pharmadynamics.co.za **CUSTOMER CARE LINE** 0860 PHARMA (742 762) / +27 21 707 7000 **www.pharmadynamics.co.za**

CARZIN XL. Each tablet contains 4 mg doxazosin. S3 A41/7.1/0557. NAM NS2 10/34/0376. For full prescribing information, refer to the professional information approved by SAHPRA, 12 June 2015. **1)** Pompeo ACL, *et al.* A randomised, double blind study comparing the efficacy and tolerability of controlled release Doxazosin and tamsulosin in the treatment of benign prostatic hyperplasia. Int J. Clin Pract Oct 2006;60(10):1172-1177. **2)** Kirby RS, *et al.* A Combined analysis of double-blind trials of the efficacy and tolerability of doxazosin-gastrointestinal therapeutic system, doxazosin standard and placebo in patients with benign prostatic hyperplasia. British Journal of Urology International 2001 Feb;87(3):192-200. **3)** Approved professional information. **4)** Database of Medicine Prices (13 April 2018). Department of Health website. *http://www.mpr.gov.za* - Accessed on 13 April 2018. **CXLE469/04/2018.**