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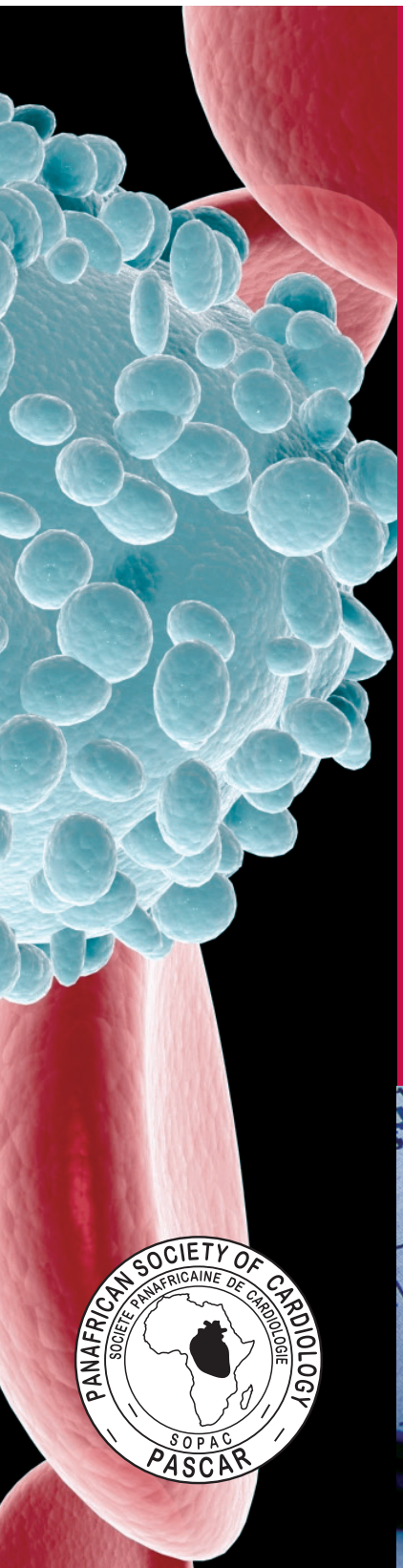

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Editorial

Can we reduce bleeding risk after interventional procedures?

Farrel Hellig

Clinical and interventional cardiology has made a huge positive impact on the lives of cardiac patients. Many patients have improved quality of life, increased longevity and fewer major clinical events such as myocardial infarction or stroke.

An important component of therapies for heart disease is the use of anticoagulants and/or antiplatelet medications. However, in some individuals, these therapies, prescribed with the purpose of improved patient outcome, have the very opposite effect as they promote bleeding, a major side effect of modern cardiovascular medicine.

While guidelines help us to make choices based on balancing the risks of thrombosis and bleeding, individual cases may require a unique tailored approach based on their personal clinical profile and their history. One of the greatest clinical challenges for the modern cardiologist is bleeding in a patient who needs anticoagulation or antiplatelet drugs. This is particularly true when the clinical scenario makes discontinuation of such therapy dangerous, while bleeding is itself life threatening. Bleeding increases the mortality rate[1-4] and therefore bleeding prevention or creating an environment where it is safer to discontinue drugs if bleeding occurs is a goal worth striving for.

In this edition of the journal are two publications that deal with the issue of bleeding mitigation in two different scenarios where such medications are used in standard practice. The first publication, Abelson *et al*.,[5] reflects on the nine-year, single-centre experience of left atrial appendage occlusion (LAAO), a technique designed to eliminate the need for anticoagulation in patients with atrial fibrillation (AF) who have bled or are at high bleeding risk. The second article by Vachiat and colleagues[6] focuses on a methodology in the cathlab, which allows for a reduced period of dual antiplatelet therapy (DAPT) in patients with symptomatic complex or diffuse coronary disease with high bleeding risk. This editorial examines the following: the value of these procedures in the studied population, the limitations of the publications, and the placement of these findings in an African context.

In the Abelson article, page 33, the study population had a mean age of 74 years. Patients were at a high risk of both stroke and bleeding ($CHADS_2$-VASc score 3.9/HAS-BLED score 2.99) and 71% had previously suffered a major bleed. These are the typical patients chosen for LAAO in prior clinical studies and registries and, therefore, LAAO was an appropriate therapeutic option for these patients.

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Patients received dual antiplatelet therapy for one month post procedure. This is a short duration when compared to regimens in other studies, and it is reassuring to note that the stroke rate was not different to studies where the duration was longer. These patients were treated with LAAO because of their inability to tolerate anticoagulation, so the shortest possible duration of post-procedural anticoagulation was ideal. Further study is required on the optimal post-procedural duration of therapy and what that therapy should be. Options include warfarin, direct oral anticoagulants (DOAC), DAPT, single antiplatelet therapy (aspirin or P2Y12 inhibitor) or zero therapy in very high bleeding risk cases.

In this study, patients continued on aspirin long term. Many such patients have another indication for long-term aspirin, such as coronary disease, but long-term use of aspirin in patients who do not need aspirin for other reasons is a matter that needs to be resolved. Aspirin itself carries a significant bleeding risk[7] and is particularly problematic with regard to gastrointestinal bleeding, which was the indication for LAAO in the majority of cases in the dataset. Patients who were on no aspirin at follow up did not demonstrate increased stroke risk – but these numbers are small and this requires further randomised investigation.

In the article by Vachiat *et al*.,[6] page 28, of which I am a co-author, patients with diffuse, calcified coronary artery disease were treated with DAPT post intervention, but a number of patients had discontinued DAPT by three months and the majority by six months. The patients were of the same average age (74 years) and had similar bleeding risk to those in the Abelson study. There is increasing emerging data on shorter-duration DAPT usage post drug-eluting stent (DES), with even one month of DAPT, followed thereafter by a single antiplatelet drug after modern DES implantation.[8]

However, the types of patients in the Vachiat article displayed a greater degree of lesion complexity. There were acute coronary syndrome cases included and stenting in elderly patients (average 74 years and 35% over 80 years) with diffuse disease and considerable calcification, long lesions [average drug-eluting balloon (DEB) length 37 mm] and small vessel lumens (mostly 2.5 mm). Such anatomy is associated with more stent under-expansion, longer and more overlapping stents, as well as smaller stent usage. Therefore, these cases carry a higher risk of late stent complications, usually mandating a longer-than-average duration of DAPT.

Shortening the duration of DAPT in these patients requires avoidance of stent implantation. Therefore, the strategy of rotational atherectomy to enhance vessel compliance, followed by balloon dilatation and then DEB to prevent restenosis is a logical approach. The procedural success rate was high (100%),

indicating that the approach is achievable. Bleeding was avoided despite the high risk, but it is important that if bleeding were to occur, there was the option to discontinue DAPT without incurring major risk.

Both studies included appropriate cases and had a high rate of procedural success. Outcomes of the procedures were good and in line with literature published in other geographical regions. It is important that local datasets confirm the ability to replicate published outcomes in our region and the authors are to be commended for these efforts. Both studies are limited by their observational nature and small numbers, but the publications are nonetheless of value.

Bleeding avoidance is a major focus of current cardiovascular research. Newer anticoagulant drugs with lower bleeding risk and a change in antiplatelet monotherapy to non-aspirin alternatives are the focus of current investigations. These, together with procedural enhancements, such as seen in these two publications, will hopefully successfully reduce bleeding risk going forward, while continuing to prevent stroke and myocardial infarction.

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Cardiovascular Topics

Delayed retinal vein recovery responses indicate both non-adaptation to stress as well as increased risk for stroke: the SABPA study

Leoné Malan, Mark Hamer, Roland von Känel, Konstantin Kotliar, Roelof D van Wyk, Gavin W Lambert, Walthard Vilser, Tjalf Ziemssen, Markus P Schlaich, Wayne Smith, Martin Magnusson, Annemarie Wentzel, Carlien E Myburgh, Hendrik S Steyn, Nico T Malan

Abstract

Objectives: Low or high sympatho–adrenal–medullary axis (SAM) and hypothalamic–pituitary–adrenal axis (HPA) dysregulation reflect chronic stress. Retinal vessel dynamics may relate to SAM, HPA activity and stroke risk. Our objectives were therefore to assess the relationships between retinal vessel, SAM and HPA responses, and to determine stroke risk.
Methods: A prospective bi-ethnic gender cohort (n = 275, 45 ± 9 years) was included. Urine/serum/saliva samples for SAM [norepinephrine:creatinine ratio (u-NE)] and HPA [adrenocorticotrophic hormone (ACTH), cortisol] were obtained at baseline, three-year follow up and upon flicker light-induced provocation. Diastolic ocular perfusion pressure was measured as a marker of hypo-perfusion. Retinal arterial narrowing and venous widening calibres were quantified from digital images in the mydriatic eye. A validated stress and stroke risk score was applied.

Results: An interaction term was fitted for venous dilation in u-NE tertiles ($p \leq 0.05$) and not in u-NE median/quartiles/quintiles. Independent of race or gender, tertile 1 (low u-NE) had a 112% increase in u-NE, decreases in cortisol, and no changes in ACTH over three years (positive feedback). Tertile 3 (high u-NE) contradictorily had decreases in u-NE and cortisol, and increases in ACTH (negative feedback). In tertile 1, reduced arterial dilation, and faster arterial vasoconstriction and narrowing were related to higher SAM activity and hypo-perfusion ($p \leq 0.05$), whereas delayed venous dilation, recovery and widening were related to cortisol hypo-secretion ($p \leq 0.05$). In tertile 1, delayed venous recovery responses predicted stress and stroke risk [odds ratio 4.8 (1.2–19.6); p = 0.03]. These associations were not found in u-NE tertiles 2 and 3.
Conclusions: In response to low norepinephrine, a reflex increase in SAM activity occurred, enhancing arterial vasoconstriction and hypo-perfusion. Concomitant HPA dysregu-

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lation attenuated retinal vein vasoactivity and tone, reflecting delayed vein recovery responses and non-adaptation to stress. These constrained vein recovery responses are indicative of increased chronic stress and stroke risk.

Keywords: retina, stress, norepinephrine, HPA, hypo-perfusion, stroke

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The retina shares embryonic origins with the brain, with similar anatomy and blood-barrier physiology. The retina is therefore of particular interest as a marker of cerebrovascular[1] and neurodegenerative diseases.[2] Local perfusion mechanisms are also similar as an increase in neuronal activity within the brain evokes local increases in blood flow or functional hyperaemia.[3] Functional hyperaemia ensures that active neurons receive sufficient oxygen and nutrients to maintain tissue functionality in the blood–retinal barrier (BRB).[4]

The inner BRB is formed by specialised retinal microvessels, surrounding pericytes and astrocyte end-feet to form a functional neurovascular unit (coupling).[4-6] Astrocyte end-feet envelope arterioles and capillaries, covering the vascular surface, and directly interact or communicate with vascular smooth muscle cells and pericytes[5] (Fig. 1). Retinal vessels, therefore, offer an easily accessible view of the vasculature that responds to flicker light-induced provocation (FLIP), and which might reflect emotional stress pathology and stroke risk.

It is well-known that chronic stress facilitates the release of neurotransmitters and hormones such as norepinephrine, adrenocorticotrophin (ACTH) and cortisol via key neuroendocrine signalling pathways, namely the sympathetic–adrenal–medulla axis (SAM) and hypothalamic–pituitary–adrenal axis (HPA).[5-12] Dysregulation of the SAM and HPA hormones are related to structural degeneration in the hippocampus and prefrontal cortex, while impaired functioning reflect cerebrovascular perfusion deficits.[13] Stress, facilitating higher sympathetic activity and metabolic demands, promotes active transport of norepinephrine in the central nervous system (CNS),[13,14] increasing local blood flow or functional hyperaemia[3] and risk for ischaemic stroke.[15,16]

Stress hormones released from astrocyte end-feet may, therefore, have a direct effect on retinal vessel dilation or constriction, as norepinephrine is an effective stimulator of adenylate cyclase, which compromises integrity of the BRB.[5] Similar cerebral neurovascular mechanisms in the brain–retina axis may further underscore the interrelationship between psychopathology and neurodegenerative disease.[17,18] Indeed, Alzheimer's disease and depression as neurodegenerative diseases have recently been associated with delayed retinal vessel dilation upon FLIP, reflecting increased sympathetic tone.[17]

We have previously reported that the stroke risk markers, retinal artery narrowing and vein widening,[18] were related to depressed heart-rate variability (HRV)[19] and stroke risk in a bi-ethnic cohort.[20] It is therefore feasible to link neurodegenerative disease and psychopathology assessments in the BRB, as the inner neural retinal layers and cell components express adrenergic receptors (AR) namely α_{1a}-AR,[10] α_{2a}-AR[21,22] as well as glucocorticoid receptors (GCR).[2] α_{1a}-AR increases norepinephrine release and vasoconstriction, whereas α_{2a}-AR inhibits norepinephrine release to protect ganglion cells in the optic nerve head (Fig. 1).

Norepinephrine or adrenergic receptor-driven changes in retinal vessel dynamics and tone may reflect neuronal hyperactivity or adrenergic drive. The GCR protect retinal neurons by suppressing inflammation and inhibiting microglial cells to block the production of cytotoxic molecules.[23] Corticosteroid hormones control vascular smooth muscle tone by their permissive effects in potentiating vasoactive responses to catecholamines through GCR.[24] Flicker provocation, as acute mental stressor, may therefore reflect norepinephrine (SAM) and HPA's function on sensory processing via receptor activation or inhibition.

We previously observed that the cardiac and retinal microvasculature reflected depressed HRV and hypo-perfusion.[18-20,25-27] Whether stress hormones will disturb retinal vessel responsiveness to increase the risk for stroke has yet to be determined. The aim of this study was therefore (1) to investigate temporal relationships between the retinal vasculature, SAM and HPA responses over three years and upon provocation, and (2) to determine stress and stroke risk.

Methods

The Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) prospective study was conducted from late summer until late autumn in 2008/9, and after three years, in 2011/12. A teachers' cohort (20–65 years), having similar socio-economic status, was included.[25] Baseline exclusion criteria were tympanum temperature ≥ 37.5°C, pregnancy and/or lactation, α- and/or or β-blocker use, psychotropic substance use, as well as vaccination and/or blood donation three months prior to participation. Only participants who participated in both phases (n = 359) were included for the current investigation. Additional exclusions were poor-quality retinal vessel images and missing data (n = 65), stroke (n = 1), HIV infection (n = 19), and a user of central nervous stimulants (n = 1). The final participant sample comprised 273 individuals.

Participants were fully informed about the objectives and procedures prior to recruitment and provided written, informed consent. The study conformed to the Helsinki Declaration (2004) and was approved by the ethics review board of the North-West University, Potchefstroom campus (approval number NWU-0003607S6).

During the working week, 24-hour ambulatory blood pressure and ECG monitors (Cardiotens CE120®, Meditech, Budapest, Hungary) were fitted to teachers at their school of employment at approximately 07:00. A 24-hour standardised diet plus 24-hour urine sampling commenced, after which participants resumed their normal daily activities. At 15:00, participants were transported to the North-West University for retinal vessel imaging and an overnight stay in a relaxed, well-controlled environment. For the remaining clinical measures each participant received his/her own room and was informed on the experimental set-up and sampling conditions to lessen

anticipation stress. Hereafter, registered clinical psychologists supervised the completion of the depression questionnaire[25] and participants were advised to go to bed at 22:00, fasting overnight.

The next morning, after the last 24-hour blood pressure (BP) recording at 07:00, the Cardiotens CE120® apparatuses were disconnected. BP and two lead ECG time-domain HRV analyses[19] were done using the CardioVisions 1.19 personal edition software (Meditech, Budapest, Hungary). Anthropometric and total energy expenditure measures were performed according to standardised procedures. Hereafter, participants were in a

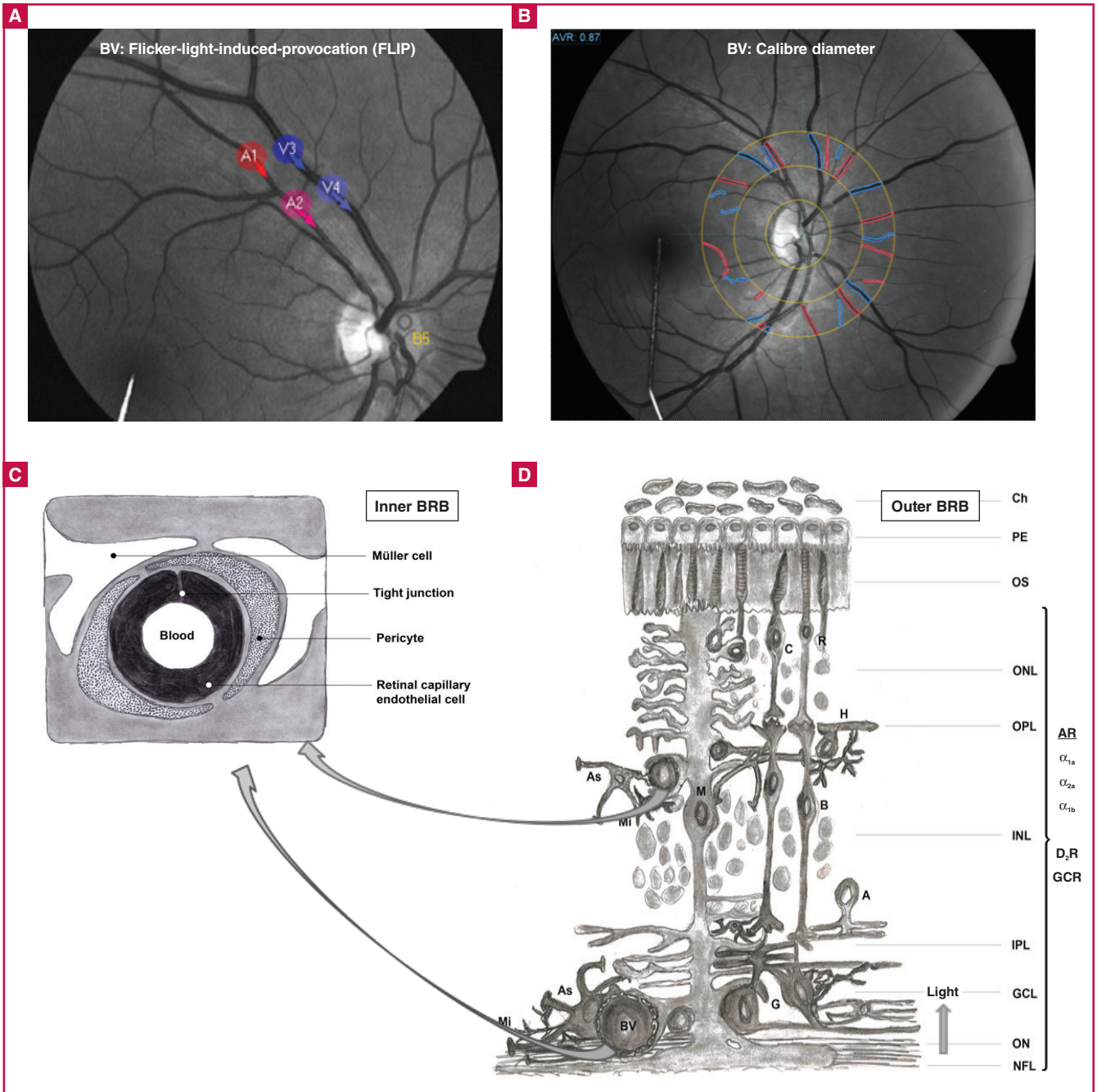

Fig. 1. Presenting retinal haemodynamic assessment sites and neurovascular coupling between glial cells and blood vessels (BV). A. The selected artery (A = red) and vein (V = blue) areas to determine BV responses upon flicker light-induced provocation. B. Retinal BV to determine arterial narrowing (red) and vein widening (blue). C, D. The blood vessel characteristics in the inner and outer blood–retinal barrier (BRB). The inner BRB (C) contains capillary endothelial cells and the outer BRB (D) contains pigment epithelial (PE) cells. D shows the inner and outer BRB retinal neural layers (bottom to top). NFL, optic nerve fibre layer; ON, optic nerve; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer with horizontal cells (H), bipolar cell dendrites (B), amacrine cells (A), astrocytes (As), microglia (Mi); Müller cells (M); ONL, outer nuclear layer with rods (R) and cones (C); OS, outer segment layers; PE, pigment epithelial cells; Ch, choroid; AR, adrenergic receptors in the OPL (α_{1a}-AR, α_{1b}-AR, α_{2a}-AR); D_2R, dopamine$_2$ receptors; GCR, glucocorticoid receptors (Malan *et al.*[4] Adapted by Louise Malan).

semi-recumbent position for at least 30 minutes before saliva and blood sampling. After all assessments, immediate available feedback was given in the privacy of their rooms.

Retinal vessel analyses considering arteriolar and venular calibres (hereafter referred to as arteries and veins) were done at follow up. One hour prior to measurements, no intake of food or caffeine-containing beverages, alcohol, smoking or exercise were allowed and this is well-described elsewhere.[25-27] Analyses were performed in a well-controlled light- and temperature-regulated laboratory using the Retinal Vessel Analyser (Imedos Systems GmbH, Jena, Germany) with a Zeiss FF450^{Plus} camera and the software Vessel-Map 2, Version 3.02.[28]

Participants were introduced to the procedure and screened for acute anterior angle chamber glaucoma risk with a small light source by a trained registered nurse. Mydriasis was induced in the right eye of the participant by instilling a drop containing tropicamide 1% and benzalkonium chloride 0.01% (m/v). Retinal haemodynamic responses were assessed upon provocation (FLIP) by measuring the diameter of retinal arteries and veins continuously. The absolute vessel diameter of measured arterial and venous segments was calculated individually as a median value before the first flickering. Three single curves were obtained during each flicker cycle in each subject and consisted of (1) 30 seconds of baseline before the flicker application, (2) 20 seconds of flicker application, and (3) 80 seconds thereafter were recalculated as a percentage of their baseline values and averaged to one.[17]

An innovative approach was applied to assess SAM and HPA activity by obtaining time-domain HRV and salivary α-amylase and cortisol responses upon provocation. Salivary sampling was done prior to and after provocation (changes from baseline were calculated in µM and in %). A salivette cotton swab was placed in the mouth and passive-drooling sampling was done for one to two minutes (Salimetrics®). Samples were immediately placed on ice and frozen at –80°C until analysis. The tweezers used to place the saliva cotton swab (Sarstedt Inc, Leicester, UK) in the mouth was kept in a 0.5% chlorhexidine gluconate solution and rinsed with distilled water before sampling.

Retinal artery and vein calibres were measured as monochrome images to indicate arterial narrowing and vein widening (indicative of stroke risk).[4,16] First-order vessel branches were manually selected in a measuring zone located between 0.5 and 1.0 optic disc diameters from the margin or the optic disc (Fig. 1B). Upon selection of the vessel, software automatically delineated the vessels' measuring area. Identification of vessels was done by two experienced scientists who had to agree on the vessel type before selection. Automated software calculations, based on the Knudtson revision of the Parr–Hubbard formulae, determined estimates from the six largest arteries and veins and were expressed as measuring units (MU). One MU is equivalent to 1 µm when the dimensions of the eye being examined correspond to those of the normal Gullstrand eye. Reproducibility was computed for a randomly selected cohort with a correlation coefficient of 0.84.

Microvasculature perfusion as a retinal/cerebral hypo-

Table 1. Dependent sample *t*-tests presenting clinical risk marker changes over a three-year period by norepinephrine:creatinine (u-NE nmol/l:mmol/l) tertile status

	u-NE tertile 1 median (min–max): 8.74 (1.05–14.77) (n = 93)		*u-NE tertile 2 median (min–max): 21.23 (15.05–28.62)* (n = 91)		*u-NE tertile 3 median (min–max): 40.62 (28.69–113.63)* (n = 91)	
Whites, *n* (%)	54 (58.1)		44 (48.4)		68 (74.7)	
Men, *n* (%)	58 (64)		50 (54)		29 (32)	
Age ± SD (years)	43.2 ± 8.9		45.3 ± 9.5		47.4 ± 8.9	
	Baseline/ follow up	*Difference (95% CI)*	*Baseline/ follow up*	*Difference (95% CI)*	*Baseline/ follow-up*	*Difference (95% CI)*
Potential vasculature risk factors						
Depression	6.7/6.2.	–0.8 (–1.9, 0.3)	7.4/7.1	–0.3 (–1.4, 0.7)	7.5/7.1	–0.6 (–1.5, 0.3)
WC, cm	92.7/98.0	7.2 (3.8, 6.8)**	94.1/96.2	2.1 (0.8, 3.3)**	93.1/95.8	2.7 (1.0, 4.4)**
Physical activity, kcal/24 h	3182.2/3622.2	440.1 (–135.0, 1015.1)	2805.8/3385.6	579.8 (278.7, 880.8)**	2866.8/3195.7	328.8 (92.9, 564.7)**
Cotinine, ng/ml	26.3/21.9	–4.4 (–10.5, 1.7)	24.6/34.6	10.0 (0.2, 19.9*	32.1/32.8	0.7 (–12.8, 14.2)
γ-GT, u/l	38.1/37.4	–0.7 (–8.5, 7.2)	49.0/41.6	–7.4 (–16.8, 1.9)	35.2/30.5	–0.4.7 (–10.0, 0.6)
CRP, mg/l	4.5/5.0	0.5 (–2.7, 3.7)	5.6/4.1	–1.6 (–2.9, –0.3)*	5.0/3.3	–1.7 (–2.6, –0.8)**
HDL-C, mmol/l	1.1/0.9	–0.1 (–0.2, –0.1)**	1.2/1.1	–0.2 (–0.2, –0.1)**	1.2/1.1	–0.1 (–0.2, –0.1)**
TG, mmol/l	1.3/1.3	0.01 (–0.1, 0.1)	1.4/1.3	–0.1 (–0.4, 0.2)	1.2/1.2	–0.1 (–0.2, 0.0)
HbA_{1c}, %	5.7/5.8	0.1 (–0.1, 0.2)	5.8/5.8	0.0 (–0.1, 0.1)	5.7/5.8	0.1 (–0.04, 0.3)
Stress hormone markers						
NE (ng/ml)	23.9/45.4	21.5 (14.7, 28.3)**	41.6/58.2	16.6 (6.4, 26.9)**	66.7/65.3	–1.4 (–13.5, –1.7)
Creatinine, mmol/l	16.8/17.9	1.1 (1.8, 3.9)	11.4/16.6	5.1 (2.5, 7.7)**	8.4/12.4	4.0 (2.1, 5.9)**
u-NE, nmol/l:mmol/l	8.6/18.2	9.6 (6.5, 12.6)**	21.3/24.1	2.7 (–0.8, 6.1)	49.7/40.5	–9.2 (–15.6, –2.8)**
Cortisol, nmol/l	400.1/245.1	–154.4 (–187.9, –120.9)*	374.4/243.7	–130.7 (–164.1, –97.3)**	357.6/213.2	–145.9 (–178.1, –113.7)**
ACTH, pg/ml	19.0/18.0	–0.97 (–3.3, 1.3)	18.6/18.8	0.27 (–2.6, 3.1)	15.6/18.4	3.2 (1.3, 5.2)**
Time-domain heart-rate variability						
SDNN (ms)	239.4/134.9	–104.5 (–293.7, 84.8)	127.7/120.1	–7.8 (–15.5, –0.1)*	132.0/127.8	–4.2 (–12.9, 4.4)
Blood pressure						
24-h SBP, mmHg	128/128	0.2 (–3, 2)	128/130	2.0 (0.0, 4.0)*	127/126	–1.5 (–4, 1)
24-h DBP, mmHg	79/79	0.0 (–2, 1)	80/80	0.3 (–1, 2)	80/77	–2 (–4, –1)**

Depression, Patient Health Questionnaire-9 (DSM-IV criteria); WC, waist circumference; γ-GT, gamma-glutamyl transferase; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HbA_{1c}, glycated haemoglobin; ACTH, adrenocorticotrophic hormone; SDNN, standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes, which equal the square-root of variance.
Values are presented as arithmetic mean at baseline/follow up as well as the difference over three years (95% CI).
p-values obtained from dependent sample *t*-tests; *$p \leq 0.05$; **$p \leq 0.001$.

perfusion risk marker[18] was measured by instilling a local anaesthetic drop (Novasine Wander 0.4% Novartis) in the right eye to measure intra-ocular pressure (IOP) (Tono-Pen Avia Applanation Tonometer; Reichert 7-0908, ISO 9001, New York, USA). Diastolic ocular perfusion pressure (DOPP) was calculated prior to FLIP: [diastolic blood pressure (DBP)–IOP mmHg]. Hypertensive/diabetic retinopathy was diagnosed by a registered ophthalmologist.

For SAM sampling, overnight eight-hour urine sampling was performed at baseline with 24-hour sampling at follow up. The sampling periods of eight and 24 hours compare favourably for detection of norepinephrine in urine.[29] At the three-year follow up, participants began and ended sampling with an empty bladder on day one and commenced with a 24-hour standardised dinner. Urine was collected for the next 24 hours in a three-litre container, washed with 9 ml of 20% HCl (UriSet24, Sarstedt®, Nümbrecht, Germany). Urine samples were stored at –80°C until analysis, which occurred within one year from collection.

The 3-Cat Urine ELISA Fast Track kits (SKU: BA E-6600, LDN, Nordhorn, Germany) were used where a standard range of 0.5–1 000 ng/ml was reported. Mean levels of norepinephrine 42 ng/ml (standard error ± 4.4) at baseline with 49 ng/ml (standard error ± 4.6) at follow up were apparent in the SABPA cohort,[25] with intra- and inter-assay variability of 2.7 and 8.6%, respectively. Urine creatinine was measured using the enzymatic method (COBAS Integra 400 Plus, Roche, Basel, Switzerland) where a standard range of 6–14 mmol/l was reported. Salivary cortisol and α-amylase concentrations were determined using commercial luminescence immunoassay kits (LIA) (IBL, Hamburg Germany) and inter-assay (< 5%) and intra-assay (< 4%) variability was reported.

For HPA sampling, fasting blood samples were obtained before 09:00 in both phases after the subjects had been awake for 90 minutes and in a semi-recumbent position.[25] Samples were handled according to standardised procedures and stored at –80°C until analysis. Serum cortisol and ACTH were analysed with an electrochemiluminescence immunoassay (e411, Roche, Basel, Switzerland). Normal ranges for ACTH are between 10 and 60 pg/ml.

For confounder biochemical analyses, serum high-density lipoprotein cholesterol (HDL-C), an ischaemic stroke risk marker,[30-33] was analysed with an enzyme-rated method (Unicel DXC 800 – Beckman and Coulter, Germany). HDL-C ≥ 1.17 mmol/l is acceptable for normal HDL-C functioning, whereas ≤ 1.04 mmol/l reflects an increased risk for cardiovascular disease.[31] Serum high-sensitivity C-reactive protein (CRP), serum gamma glutamyl transferase (γ-GT) and whole-blood EDTA glycated haemoglobin (HbA_{1c}) were analysed with turbidimetric inhibition immunoassays (Cobas Integra 400 Plus, Roche, Basel, Switzerland). Serum cotinine was analysed with a homogeneous immunoassay (Modular Roche automised systems, Basel, Switzerland). Intra- and inter-assay coefficients for all analyses were less than 10%.

Statistical analysis

Statistica version 13.3 (TIBCO Software Inc, Palo Alto, USA, 2018) was used for data analyses. Three-way ANCOVAs independent of *a priori* covariates were computed to determine main effect interactions (race × gender × u-NE median/tertiles/quartiles/quintiles) for stroke[4,18,26] and neuronal hyperactivity risk markers.[25-27] Retinal risk covariates were selected *a priori*

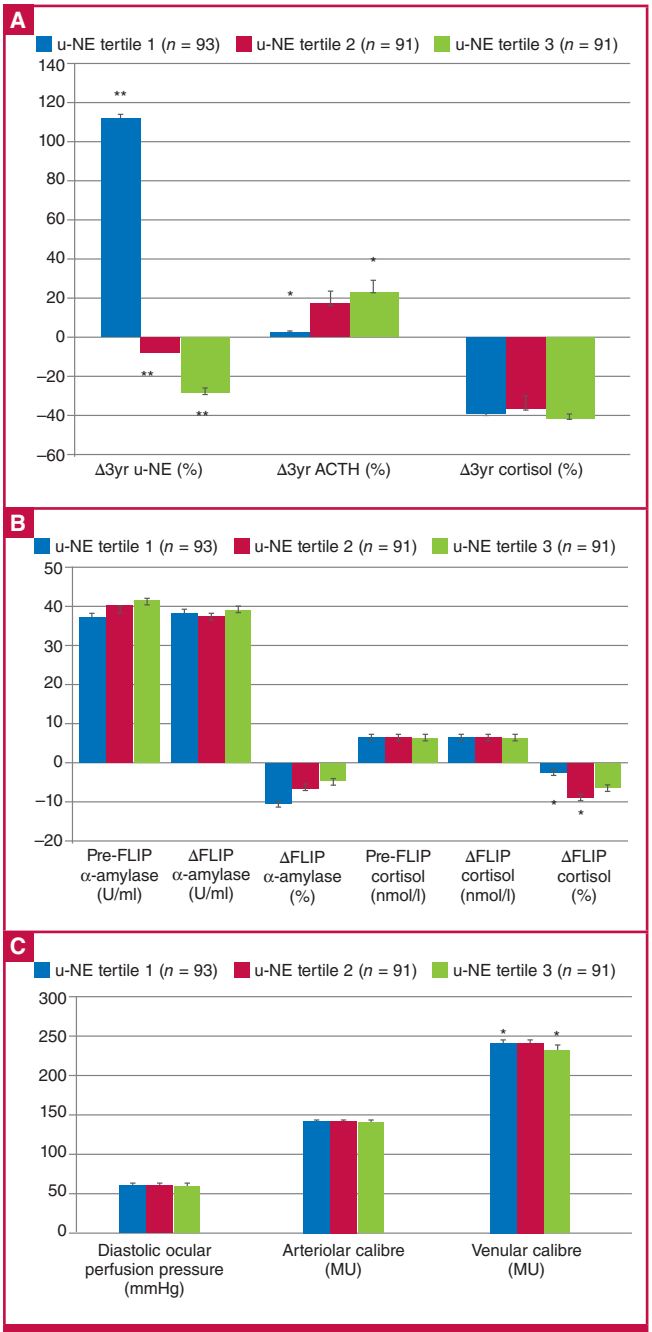

Fig. 2. Comparing stress hormones and retinal vessel risk markers. Data presented as median values across increasing u-NE tertiles (nmol/l:mmol/l) [u-NE tertile 1, median (min–max): 8.74 (1.05–14.77); u-NE tertile 2, median (min–max): 21.23 (15.05–28.62); u-NE tertile 3, median (min–max): 40.62 (28.69–113.63)]. A. Stress hormone three-year changes, with salivary stress hormone changes (B) prior to and upon flicker light-induced provocation (FLIP). C. Retinal vessel risk markers. Significance is shown using *p*-values of non-parametric Kruskal–Wallis tests. u-NE, norepinephrine:creatinine ratio; Δ3yr, three-year changes; ACTH, adrenocorticotrophic hormone. $^{*}p \leq 0.05$; $^{**}p \leq 0.001$.

Table 2. Comparing unadjusted stress hormones, HDL-C and retinal vessel calibres across norepinephrine:creatinine (u-NE nmol/l:mmol/l) tertile groups

	Tertile 1	*Tertile 2*	*Tertile 3*	p-*values*		
	u-NE median (min–max): 8.74 (1.05–14.77) (n = *93*)	*u-NE median (min–max): 21.23 (15.05–28.62)* (n = *9*)	*u-NE median (min–max): 40.62 (28.69–113.63)* (n = *91*)	*u-NE tertiles 1 vs 3*	*u-NE tertiles 1 vs 2*	*u-NE tertiles 2 vs 3*
3-yr stress hormones changes						
Δ3yr u-NE (%)	111.6 (4.1, 207.4)	–7.08 (–46.0, 53.4)	–27.8 (–54.0, 21.1)	0.01 (0.01)	0.01 (0.01)	0.01 (0.04)
Δ3yr ACTH (%)	2.5 (–30.1, 37.2)	16.1 (–20.6, 58.4)	26.2 (–15.8, 83.9)	0.02 (0.01)	0.25 (0.09)	0.91 (0.32)
Δ3yr cortisol (%)	–37.9 (–53.6, –17.7)	–34.0 (–49.8, –13.0)	–41.7 (–54.5, –19.3)	1.00 (0.59)	1.00 (0.32)	0.50 (0.19)
Δ3yr HDL-C (%)	–11.4 (–24.6, 0.81)	–13.3 (–27.6, 1.67)	–11.8 (–20.0, 4.88)	1.00 (0.63)	1.00 (0.79)	1.00 (0.48)
Saliva stress hormones prior to and upon FLIP						
Pre-FLIP α-amylase (U/ml)	36.8 (20.4, 73.9)	39.7 (17.5, 72.0)	41.4 (26.0, 62.2)	1.00 (0.89)	1.00 (0.87)	1.00 (0.83)
ΔFLIP α-amylase (U/ml)	38.3 (22.0, 64.3)	37.6 (19.3, 66.9)	38.8 (22.7, 68.4)	1.00 (0.89)	1.00 (0.89)	1.00 (0.76)
ΔFLIP α-amylase (%)	–9.79 (–35.3, 44.8)	–5.6 (–48.4, 64.5)	–4.30 (–36.7, 39.2)	1.00 (0.96)	1.00 (0.89)	1.00 (1.00)
Pre-FLIP cortisol (nmol/l)	5.5 (3.94, 8.05)	5.1 (3.55, 8.59)	5.1 (3.34, 7.04)	0.64 (0.21)	1.00 (0.50)	1.00 (0.59)
ΔFLIP cortisol (nmol/l)	5.3 (3.79, 8.11)	4.87 (3.38, 7.39)	4.7 (3.20, 6.65)	0.37 (0.12)	0.69 (0.24)	1.00 (0.74)
ΔFLIP cortisol (%)	–0.2 (–9.12, 7.28)	–8.2 (–14.9, 1.46)	–5.2 (–11.4, 3.48)	1.00 (0.33)	0.05 (0.02)	0.39 (0.10)
Structure: retinal arteries and veins						
Retinal artery (MU)	151.2 (143.1, 158.9)	152.1 (141.0, 160.0)	151.4 (141.7, 157.4)	1.00 (0.97)	1.00 (0.65)	1.00 (0.63)
Retinal vein (MU)	245.3 (231.9, 257.8)	243.1 (227.2, 261.0)	239.5 (226.7, 249.8)	0.17 (0.05)	1.00 (0.87)	0.29 (0.11)
Functionality: arteries						
Mean maximal arterial dilation, (% baseline)	3.7 (2.3, 5.2)	3.9 (1.9, 5.6)	3.6 (1.9, 5.3)	1.00 (0.85)	1.00 (0.70)	1.00 (0.57)
Time of maximal arterial constriction (from the start of flicker) (s)	44.5 (37.0, 56.5)	50.0 (43.0, 62.0)	48.0 (38.0, 68.0)	0.55 (0.24)	0.05 (0.01)	0.82 (0.35)
Functionality: veins						
Mean maximal venous dilation (% baseline)	3.9 (3.0, 5.0)	4.4 (3.1, 5.9)	3.8 (2.8, 4.7)	0.80 (0.37)	0.89 (0.30)	0.01 (0.03)
Post-FLIP vein recovery (% of baseline)	100.6 (100.3, 101.0)	100.5 (100.2, 100.9)	100.4 (100.1, 100.7)	0.10 (0.03)	1.00 (0.52)	0.44 (0.16)
Diastolic ocular perfusion pressure (mmHg)	69.0 (64.0, 75.0)	69.0 (59.0, 77.0)	69.0 (63.0, 75.0)	1.00 (0.07)	1.00 (0.46)	1.00 (0.61)

Data are presented as median values (inter-quartile ranges) whereas significance is shown using *p*-values of non-parametric Kruskal–Wallis tests followed by multiple comparison tests (uncorrected *p*-values of Mann–Whitney *U-test*).
Δ3yr, three-year changes; FLIP, flicker light-induced provocation; ΔFLIP, changes during FLIP; ACTH, adrenocorticotrophic hormone; HDL-C, high-density lipoprotein cholesterol.

and included age, waist circumference (WC), cotinine smoking status, γ-GT, HbA_{1c}, HDL-C, hypertensive/diabetic retinopathy and DOPP.[4,18] An interaction term was fitted for retinal vein dilation [$F_{1, 254}$ = 4.34 (p = 0.014)] in u-NE tertiles, and not in median/quartiles or quintiles. Hence the cohort was stratified into baseline norepinephrine:creatinine (u-NE in nmol/l:mmol/l) ratio tertile groups supporting assessment for SAM activity/adrenergic drive and potential monoamine depletion.[33-36] The

Table 3. Forward stepwise linear regression analyses depicting associations between retinal vessel calibres, stress hormones and risk markers in norepinephrine:creatinine (u-NE nmol/l:mmol/l) tertile 1

	u-NE tertile 1 median (min–max): 8.74 (1.05–4.77) (n = 92)	
Δ3yr stress hormones (%)	*Arteries (MU)*	*Veins (MU)*
Adjusted R^2	0.32	0.38
	β (95% CI)	β (95% CI)
Δ3yr u-NE (%)	–	–
Δ3yr cortisol (%)	–	–
Baseline HDL-C (mmol/l)	–0.20 (–0.38, –0.02), p = 0.040	–
Stress hormone levels prior to FLIP		
Adjusted R^2	0.26	0.33
	β (95% CI)	β (95% CI)
Saliva α-amylase (U/ml)	–0.28 (–0.50, –0.06), p = 0.010	-
Saliva cortisol (nmol/l)	–	–0.33 (–0.53, –0.13), p = 0.002
Diastolic ocular perfusion pressure (mmHg)	–0.24 (–0.46, –0.02), p = 0.024	–

Δ3yr; three-year stress hormone changes (%); Prior to FLIP, saliva stress hormone levels prior to FLIP. Δ, changes; FLIP, flicker light-induced provocation; HDL-C, high-density lipoprotein cholesterol.
Additional covariates included age, waist circumference, cotinine smoking status, log-normalised gamma-glutamyl transferase, glycated haemoglobin, hypertensive/diabetic retinopathy, diastolic ocular perfusion pressure and the respective retinal artery/vein diameter.

Table 4. Ocular media and fundus assessment at three-year follow up across norepinephrine:creatinine (u-NE nmol/l:mmol/l) tertiles

	Count, prevalence (%)		
	u-NE tertile 1 (n = 93)	*u-NE tertile 2 (n = 91)*	*u-NE tertile 3 (n = 91)*
Referred to opthalmologist	6 (6.7)	7 (7.8)	11 (12.5)
Hypertensive/diabetic retinopathy	41 (44.6)	47 (51.7)	54 (59.3)*
Retinopathy included, *n* (%)			
Intra-ocular pressure < 11 mmHg	12 (13.3)	8 (8.9)	9 (10.2)
Optic head (cup:disc ratio > 0.50)	17 (18.9)	12 (13.5)	21 (24.1)
Optic nerve head damage†	8 (8.9)	9 (10.2)	6 (6.7)
Acute anterior glaucoma risk	1 (1.1)	6 (6.7)	8 (9.1)
Retinal atrophy	2 (2.2)	0 (0.00)	0 (0.0)
Drusen	0 (0.0)	1 (1.1)	0 (0.0)
Ciliary blood vessels	1 (1.1)	0.(0.0)	0 (0.0)
Exudates	0 (0.0)	1 (1.1)	0 (0.0)
Haemorrhaging	4 (4.44)	1 (1.1)	1 (1.1)
Arteriovenous nicking	31 (33.7)	38 (41.8)	39 (42.9)
Neovascularisation	1 (1.1)	0 (0.0)	0 (0.0)
Cotton wool ischaemia	0 (0.0)	0 (0.0)	0 (0.0)
Focal narrowing	1 (1.1)	2 (2.2)	1 (1.1)
Macula scarring	1 (1.1)	0 (0.0)	0 (0.0)

Chi-squared statistics were used to determine prevalence in u-NE tertile 1 vs u-NE tertile 3 [u-NE tertile 1, median (min–max): 8.74 (1.05–14.77); u-NE tertile 2, median (min–max): 21.23 (15.05–28.62); u-NE tertile 3, median (min–max): 40.62 (28.69–113.63)].
†Optic nerve head damage, cup-to-disc ratio ≥ 0.3 plus intra-ocular pressure ≥ 21 mmHg. *$p \leq 0.05$.

Table 5. Forward stepwise regression analyses depicting associations between retinal vessel and stress hormone responses prior to and post flicker light-induced provocation (FLIP) in norepinephrine:creatinine (u-NE nmol/l:mmol/l) tertile 1

	u-NE tertile 1 median (min–max): 8.74 (1.05–14.77) (n = 93)			
	Artery max dilation (%)	*Artery time max constriction (s)*	*Vein max dilation (%)*	*Vein post-FLIP recovery to baseline (%)*
Δ3yr stress hormones (%)				
Adjusted R^2	0.16 β (95% CI)	0.15 β (95% CI)	0.20 β (95% CI)	< 0.10 β (95% CI)
u-NE (%)	–0.20 (–0.4, –0.0), $p = 0.055$	–	–	–
Serum cortisol (%)	–	–	–	–
Stress hormone levels prior to FLIP				
Adjusted R^2	< 0.10 β (95% CI)	0.14 β (95% CI)	< 0.10 β (95% CI)	< 0.10 β (95% CI)
Saliva α-amylase (U/ml)		–0.25 (–0.5, 0.0), $p = 0.029$	–	–
ΔFLIP stress hormones (%)				
Adjusted R^2	< 0.10 β (95% CI)	0.15 β (95% CI)	0.22 β (95% CI)	0.15 β (95% CI)
Saliva α-amylase (%)	–	NS	–	–
Saliva cortisol (%)	–	NS	–0.34 (–0.6, –0.1), $p = 0.003$	–0.25, (–0.5, 0.0), $p = 0.028$
Baseline HDL-C (mmol/l)	–	–	0.26 (0.0, 0.1), $p = 0.022$	–0.33 (–0.6, –0.1), $p = 0.004$

Δ3yr; three-year stress hormone changes (%); Prior to FLIP, saliva stress hormone levels prior to flicker light-induced provocation/FLIP; ΔFLIP, stress hormone changes (%) obtained directly after FLIP. Δ, changes; NS; non-significant, HDL-C; high-density lipoprotein cholesterol.
Additional covariates included age, waist circumference, cotinine smoking status, log-normalised gamma-glutamyl transferase and glycated haemoglobin; hypertensive/diabetic retinopathy and diastolic ocular perfusion pressure.

Table 6. Logistic regression analysis to predict the probability of chronic stress-related stroke risk in a cohort with low urinary norepinephrine:creatinine (u-NE nmol/l:mmol/l) ($n = 90$)

	Chronic stress-related stroke risk			
Nagelkerke R^2 0.62	*Odds ratio*	*5th percentile*	*95th percentile*	*p-value*
DOPP (mmHg)	1.07	0.99	1.17	0.104
FLIP HRV (ms)	1.52	0.42	1.05	0.078
FLIP cortisol (%)	1.08	0.74	1.58	0.705
FLIP delayed venous recovery (% of baseline)	4.82	1.18	19.59	0.028

Covariates included high-density lipoprotein cholesterol and hypertensive/diabetic retinopathy. DOPP, diastolic ocular perfusion pressure; FLIP HRV, time-domain heart-rate variability standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes, which equal the square-root of variance.

respective median (min–max) u-NE concentrations were: u-NE tertile 1 median (min–max): 8.74 nmol/l:mmol/l (1.05–14.77); u-NE tertile 2 median (min–max): 21.23 nmol/l:mmol/l (15.05–28.62); u-NE tertile 3 median (min–max): 40.62 nmol/l:mmol/l (28.69–113.63). Normality was tested and skewed data were $\log_{10}$ normalised.

The clinical characteristic proportions of the cohort were determined at baseline using chi-squared (χ^2) statistics. Stress risk-marker changes were computed with dependent sample *t*-tests. Kruskal–Wallis tests determined significance, followed by multiple comparisons tests and non-parametric Mann–Whitney *U*-tests when comparing retinal and stress hormone median values.

Multiple linear regression analyses determined associations between the retinal vasculature and the stress hormones in each of the u-NE tertiles. Retinal vessel responses upon provocation (FLIP) included four dependent variable models: artery maximal dilation (%), artery time to constrict (s), vein maximal dilation (%) and vein post-FLIP recovery to baseline value (%). The

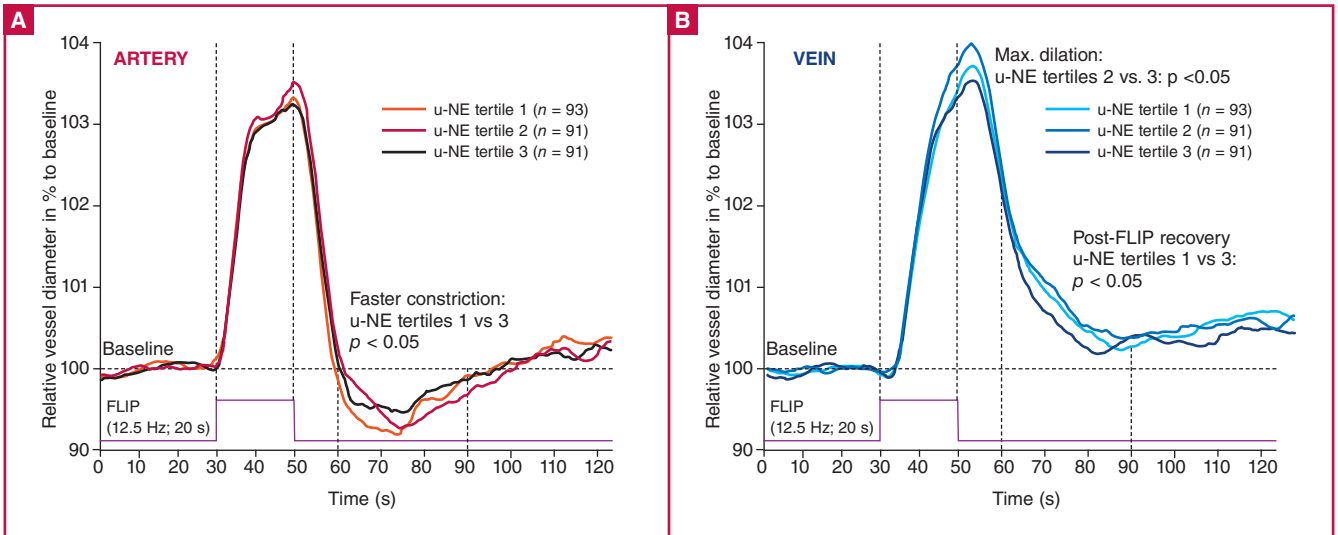

Fig. 3. Comparing median retinal artery (A) and vein (B) responses during monochromatic flicker light-induced provocation (FLIP) in increasing norepinephrine:creatinine (u-NE nmol/l:mmol/l) tertiles. Exact *p*-values were determined with Mann–Whitney *U*-tests. Grey vertical stripes indicate the time interval 10–40 seconds after flicker cessation where arterial constriction and an emphasised decrease of venous diameter are expected. Delayed vein recovery responses (% of baseline) were determined by calculating the average vessel diameter between 50 and 80 seconds after the end of flicker. u-NE tertile 1, median (min–max): 8.74 (1.05–14.77); u-NE tertile 2, median (min–max): 21.23 (15.05–28.62); and u-NE tertile 3, median (min–max): 40.62 (28.69–113.63).

retinal vessel calibre models included two dependent variable models: retinal arteries and veins. Independent variables for these six models included *a priori* covariates, the respective retinal artery/vein diameter and stress hormone responsiveness (1) difference over three years (Δ3yrs) (%), (2) prior to FLIP, and (3) upon provocation (Δ FLIP%). Multiple linear regression analyses were repeated by controlling for HRV, physical activity and the use of cortisone derivatives, α- and/or β-blockers at follow up.

We recently developed a method of determining risk for chronic stress and stroke (filed 31 July 2020, international patent application no. PCT/IB2020/05726). We applied this score to determine whether retinal vascular responses would predict chronic stress and stroke risk. Logistic regression analyses were computed and included the covariates: stress hormone changes over three years or upon provocation, HRV, diastolic ocular perfusion pressure, HDL-C and hypertensive/diabetic retinopathy. The statistical significance level was set at $p \leq 0.05$ (two-tailed). The F to enter in regression models was fixed at 2.5.

Table 7. Forward stepwise regression analyses depicting associations between retinal vessel and stress hormone responses prior to and post flicker light-induced provocation (FLIP) in norepinephrine:creatinine (u-NE nmol/l:mmol/l) tertiles 2 and 3

	u-NE tertile 2 median (min–max): 21.23 (15.05–28.62) (n = 87)			
	Artery max dilation (%)	*Artery time max constriction (s)*	*Vein max dilation (%)*	*Vein post-FLIP recovery (% of baseline)*
Δ3yr stress hormones (%)				
Adjusted R^2	0.25 β (95% CI)	< 0.10	0.20 β (95% CI)	< 0.10 β (95% CI)
u-NE (%)	–	–	–	–
Serum cortisol (%)	0.21 (0.03, 0.39)*	–	–	–
Stress hormone levels prior to FLIP				
Adjusted R^2	0.25 β (95% CI)	< 0.10 β (95% CI)	< 0.10 β (95% CI)	< 0.10 β (95% CI)
Saliva cortisol (nmol/l)	–0.26 (–0.46, –0.06)*	–	–	–
ΔFLIP stress hormones (%)				
Adjusted R^2	0.29 β (95% CI)	< 0.10 β (95% CI)	0.25 β (95% CI)	0.15 β (95% CI)
Saliva α-amylase (%)	–	–	–	–
Saliva cortisol (%)	–	–	–	–0.36 (–0.60, –0.13)*
	u-NE tertile 3 median (min–max): 40.62 (28.69–113.63) (n = 89)			
	Artery max dilation (%)	*Artery time max constriction (s)*	*Vein max dilation (%)*	*Vein post-FLIP recovery (% of baseline)*
Δ3yr stress hormones (%)				
Adjusted R^2	0.22 β (95% CI)	0.12	0.20 β (95% CI)	< 0.10 β (95% CI)
u-NE (%)	–	–	–	–
Serum cortisol (%)		–0.22 (–0.42, –0.02)*	–	–
Stress hormone levels prior to FLIP				
Adjusted R^2	< 0.10 β (95% CI)	0.11 β (95% CI)	< 0.10 β (95% CI)	< 0.10 β (95% CI)
Saliva cortisol (nmol/l)	–	– NS	–	–
ΔFLIP stress hormones (%)				
Adjusted R^2	0.15 β (95% CI)	0.17 β (95% CI)	0.15 β (95% CI)	< 0.10 β (95% CI)
Saliva α-amylase (%)	–	–	–	–
Saliva cortisol (%)	–	–	–	–

Δ3yr; three-year stress hormone changes (%); Prior to FLIP, saliva stress hormone levels prior to FLIP; ΔFLIP, stress hormone changes (%) obtained directly after FLIP. Δ, changes.
Additional covariates included age and log-normalised waist circumference, cotinine, gamma-glutamyl transferase and glycated haemoglobin; hypertensive/diabetic retinopathy, diastolic ocular perfusion pressure and the respective retinal arterial/vein diameter.

Results

Tertile characteristics (Table 1) showed an increasing trend across u-NE tertiles for central obesity and decreasing trends in cortisol and HDL, particularly in u-NE tertile 1. Again in u-NE tertile 1, consistent inflammation (CRP) and raised BP were observed, whereas a decrease occurred in u-NE tertile 3.

Stress hormones: Fig. 2A and Table 2 (median ± 95% CI) show u-NE increases in u-NE tertile 1 (111.6%) but decreases in u-NE tertiles 2 and 3 over three years ($p \leq 0.01$). ACTH levels did not change in u-NE tertiles 1 and 2, however the increase in u-NE tertile 3 was higher compared to tertile 1 ($p \leq 0.001$). In u-NE tertile 1 (Fig. 2B), saliva post-FLIP cortisol (%) was lower compared to u-NE tertile 2 ($p \leq 0.05$). Vein widening (Fig. 2C) was apparent in u-NE tertile 1 (245.3 MU) compared to u-NE tertile 3 (239.5 MU) ($p \leq 0.05$). In Table 2 , medians were compared and a five-second faster arterial constriction (Fig. 3A) was evident in u-NE tertile 1 compared to u-NE tertile 2 ($p \leq 0.05$). In Fig. 3B, veins dilated significantly more in u-NE tertile 2 when compared to u-NE tertile 3 ($p \leq 0.05$). The venous post-FLIP recovery response was delayed ($p \leq 0.05$) in u-NE tertile 1 compared to u-NE tertile 3. In Table 4, hypertensive/diabetic retinopathy was higher in u-NE tertile 3 compared to tertile 1.

Stress hormones and retinal vasculature associations: multiple stepwise linear regression associations between retinal vessel calibres (Table 3) and retinal FLIP responses (Table 5), and stress hormones of u-NE tertile 1 are presented. Reduced arterial dilation, faster constriction, narrowing and hypo-perfusion were associated with increased SAM activity. Delayed venous dilation, recovery and widening were associated with cortisol hypo-secretion and low HDL-C ($p \leq 0.05$).

In u-NE tertile 1 (Table 6), delayed vein recovery responses predicted stress and stroke risk, having large clinical significance [odds ratio 4.8 (1.2–19.6); $p = 0.03$]. Associations between the retinal vasculature and cortisol secretion in u-NE tertiles 2 and 3 showed effective cortisol functioning but no relationship existed with norepinephrine (Table 7). Controlling for HRV, physical activity and the use of cortisone derivatives, α- and/or ß-blockers at follow up did not change the outcome of our findings.

Discussion

We aimed to (1) assess the relationships between the retinal vasculature, SAM and HPA activity over three years and upon provocation, and (2) determine chronic stress and stroke risk. Findings showed that in the presence of low norepinephrine, a reflex increase in SAM activity occurred, enhancing arterial vasoconstriction and hypo-perfusion. Concomitant HPA dysregulation attenuated retinal vein vasoactivity and tone, reflecting delayed vein recovery responses and non-adaptation to stress. These constrained vein recovery responses demonstrated increased chronic stress and stroke risk, having large clinical significance.The main findings are presented below (Fig. 4).

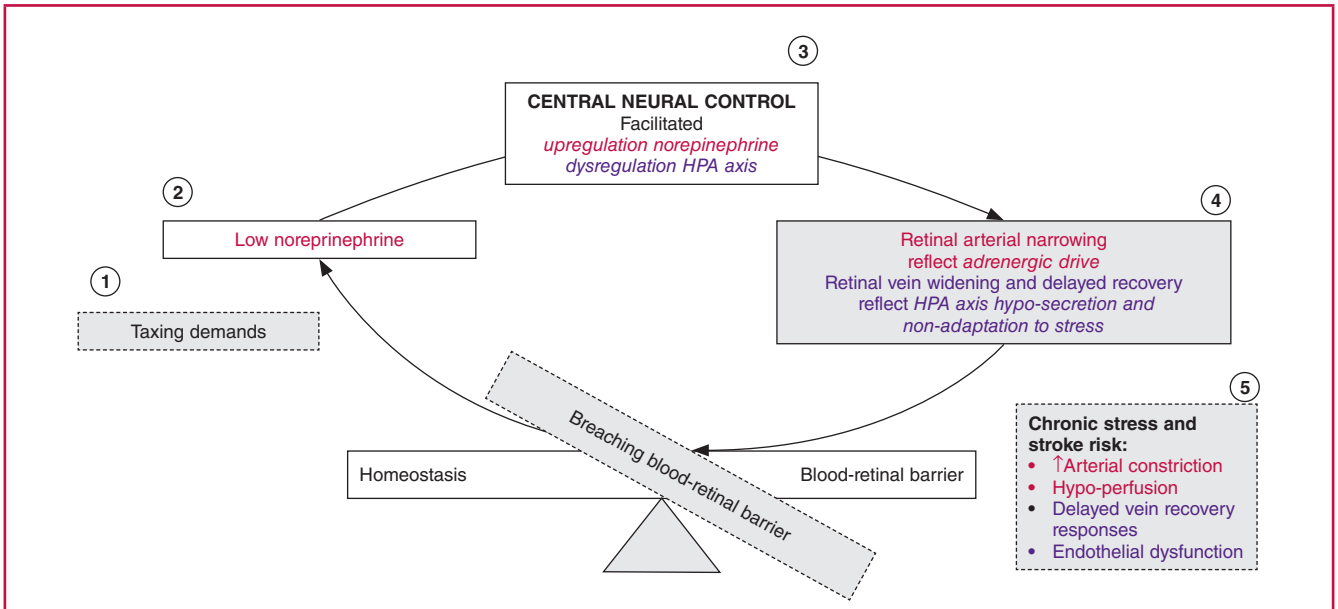

Fig. 4. Graphical representation of the main findings indicating the relationship between chronic stress-related stroke risk and retinal vein recovery responses.

Norepinephrine and the retinal vasculature

In 2008, Krishnan and Nestler[36] discussed the monoamine hypothesis of depression, which posits that depression is caused by decreased monoamine function in the brain. Findings in the low-u-NE group (tertile 1) support this low monoamine premise, as initial low norepinephrine or monoamine concentrations facilitated central neural control. An upregulation of norepinephrine occurred over three years, resulting in neuronal hyperactivity or adrenergic drive. In support, Ferrier *et al.*[6] suggested that the presence of chronic stress increases human sympathetic firing, which is dependent on norepinephrine release within the brain and the activation of central neural control mechanisms to maintain homeostasis.[34,36] Catecholamine surges following systemic insults, such as stress, is further directly involved in the regulation of cytokine expression and exemplifies the consistently high CRP level of 5 mg/l in the u-NE tertile 1, a worsening clinical condition.[33-36]

The noradrenergic cell groups A6 (locus cœruleus) project axons to the hypothalamic paraventricular nucleus (PVN) to activate the SAM and promote norepinephrine release during acute and chronic stress.[11,36] However, the specific neurovascular coupling mechanism in the human retina when neuronal hyperactivity and chronic stress are apparent are not quite so clear. Retinal neurons such as the amacrine and horizontal cells synthesise catecholamines,[10] as well as high-affinity α_{1a} and α_{2a}-AR, which are expressed in Müller and ganglion cells, and the inner plexiforme, inner nuclear and photoreceptor layers of the retina.[10,22,37-39] Upon activation of α_{2a}-AR, norepinephrine release is inhibited to protect ganglion cells against disturbed ocular perfusion pressure[40] and arterial occlusion by reducing intracellular cyclic adenosine monophosphate (cAMP) production.[3,5] Müller cells and other astrocytes have intimate contact with both synapses and blood vessels via α_{2a}-AR activity, which enables regulation of blood flow.[41,42]

A cycle of events may occur where chronic stress as the initial trigger reflects low norepinephrine and potential monoamine depletion (in u-NE tertile 1), and where central homeostatic reflexes are activated to facilitate upregulation of an endogenous catecholamine, norepinephrine. This happens via activation of the hypothalamic PVN with sensitisation of α_{1a}-AR (vasoconstriction) and desensitisation of vasodilatory α_{2a}-AR in the retina. This may indicate that chronic stress induces central neural control mechanisms, potentially over-riding autoregulation in the retina. Furthermore, norepinephrine may also bind with dopamine 2 receptors (D_2R) as potential signal transducers for norepinephrine in the outer and inner retinal nuclear layers.[43] Retinal dopamine is synthesised and released from dopaminergic amacrine cells[43] and binds to high-affinity D_2R to activate norepinephrine release.[43,44] In support of this notion, Jäkel and Dimou[45] reported that hetero-receptor cellular communication occurs between the different glial cell types under pathological conditions.

Chronic stress may be such a pathological condition,[4] as central neural control with upregulation of norepinephrine in u-NE tertile 1 may have decreased α_{2a}-affinity/specificity. This may allow D_2R receptors to relay higher norepinephrine vasoconstrictive signalling, thereby inducing reduced arterial dilation, faster constriction, narrowing and hypo-perfusion in u-NE tertile 1. Another study demonstrated desensitisation of α_{1a}-AR upon provocation to protect the BRB,[10] potentially explaining the lack of saliva α-amylase responses in our low-u-NE cohort. This lack of variation in saliva α-amylase upon provocation concurs with another study's findings where chronic stress or burn-out was associated with attenuated α-amylase responses.[46] An adrenergic drive marker, depressed HRV, was also suggested as an objective stress marker.[35] However, we could not confirm HRV as a risk marker for either chronic cardiomyocyte injury[25-27] or chronic stress and stroke risk in the current cohort.

The observed adrenergic drive or neuronal hyperactivity in u-NE tertile 1 increased arterial vascular resistance and tone, and may impair myogenic control. Considering the chronic pre-diabetic status and adrenergic drive in u-NE tertile 1

individuals, a profile of endothelial dysfunction[47] emerges, which could enable the α_{1b}-adrenoceptor subtype to mediate adrenergic vasoconstriction in retinal arteries.[48] The overall reflex increases in u-NE, and pre-FLIP α-amylase levels support the notion of adrenergic-induced vasoconstriction. These changes have presumably been mediated via the following catecholamine receptors: α_{1a}-AR, α_{1b}-AR, desensitised α_{2a}-AR and D_2R.[10,22,37,39,43,44] Such a profile compromises the integrity of the BRB[33] and increases susceptibility for ischaemic stroke risk.[15,16,34]

Cortisol and the retinal vasculature

Compared with SAM responses, the HPA has a particularly high threshold for activation[12,49] and facilitates the ability to cope with, adapt to, and recover from stress.[2] A homeostatic negative feedback response occurred in u-NE tertile 3, where increases in ACTH and decreases in cortisol levels were observed, and which were not related to retinal vascular dysregulation. In u-NE tertile 1, however, no increases in ACTH level occurred despite decreases in cortisol level. This potentially reflects a positive feedback response of HPA hypo-activity, which is indicative of chronic uncontrollable stress.[12,49] In rodent models a low norepinephrine level[10] in the central amygdala and hypothalamus (PVN) inhibited HPA responses to neural stress stimuli such as photic stimulation.[50] This might explain attenuation of the negative feedback exerted by glucocorticoids in u-NE tertile 1, probably by reducing hippocampal glucocorticoid receptors and facilitating consistently raised ACTH levels.

HPA regulation, particularly by cortisol, protects neurons by suppressing inflammation and inhibiting microglial TNF-α release and GCR signalling to permit the formation of proliferating Müller glia-derived progenitor cells.[12,51] Cortisol hypo-secretion in adrenergic-driven u-NE tertile 1 might, therefore, reduce immune function suppression and explain the observed low-grade inflammation and retinal vein widening. Retinal veins consist of a single layer of endothelial cells and few smooth muscle cells.[52] Retinal vein vascular tone and diameter changes in u-NE tertile 1 may therefore affect vein drainage resistance and upstream pressure in retinal capillaries. Indeed, HPA dysregulation reflected lower vein vasoactivity and tone, which delayed recovery responses upon provocation and implies non-adaptation to stress.

In support, the observed prolonged stress responses in hippocampal (ventral subiculum) lesions of rats were accompanied by enhanced depletion of corticotrophic hormone immunoreactivity over time[2] and, in humans, were related to neurodegenerative disease risk (depression and the late onset of Alzheimer's disease).[53] In a previous study, retinal vein widening reflected self-reported chronic depressive symptoms and a compromised NO-synthase system in a black cohort.[18] Presently, HPA dysregulation in u-NE tertile 1, independent of race and gender, might decrease nitric oxide (NO) bioavailability by inhibiting NO-synthase directly[54] and explain compromised vein dynamics in the retina.[54] In the current low u-NE group, retinal vein responses were not related to self-reported chronic depression, but only to stress hormone dysregulation. This discrepancy and the lack of association between cardiovascular disease risk markers and self-reported chronic depression concurs with previous observations,[4,27] as well as with the most recent findings by Levis *et al.*[55] Applying a validated chronic stress and stroke risk marker may prove to be superior to self-reported chronic depression.

Stress and ischaemic stroke susceptibility

Small vessels in the brain react to hydrostatic pressure and will regulate vascular tone to maintain a constant blood flow, or autoregulation.[34] Central control with dysregulated HPA and downregulated HDL-C enhanced endothelial dysfunction in u-NE tertile 1, increasing susceptibility for ischaemic stroke.[15] The greater FLIP venous dilation in u-NE tertile 1, slower recovery to baseline and widening have now been associated with both cortisol hypo-secretion and low HDL-C levels. This may impede constant blood flow and autoregulation, and facilitate ischaemic stroke susceptibility.[15] Central control may indeed override autoregulation when chronic stress is apparent.

Neuronal hyperactivity may drive and dominate these responses as low HDL-C level in turn influences cerebrovascular function and breaching of the BRB.[10,13-15] Intra-retinal lipid transport depends on HDL-C, the major apolipoprotein constituent of apolipoprotein E (ApoE).[56-58] The 22% decrease (1.1–0.9 mmol/l) observed in u-NE tertile 1 may be indicative of a high risk (< 1.04) for depression,[56] retinal pathology,[58] cognitive decline[59] and ischaemic stroke.[60] Low HDL-C levels reflected chronic stress[51] and clinical depression,[61] endorsing the prevalence of chronic stress in u-NE tertile 1. It is important to note that certain depression treatments may downregulate norepinephrine, such as tricyclic antidepressants (e.g. serotonin re-uptake inhibitors). Subsequent upregulation of norepinephrine can occur, which will disturb neurovascular coupling[62] and potentiate stroke risk.

Neural mechanism for chronic stress and stroke risk

In response to low norepinephrine levels, a reflex increase in sympathetic activity/adrenergic drive occurred as a compensatory mechanism to low monoamine levels. Higher adrenergic drive may potentiate catecholamine receptor sensitisation (potentially α_{1a}-AR, α_{1b}-AR, D_2R) and/or chronic α_{2a}-AR desensitisation.[10,22,37-39,43,44] Indeed, higher adrenergic drive increased vasoconstriction and hypo-perfusion or ischaemia in retinal arteries. Consistent high blood pressure and vasoconstrictive signalling may exert deleterious effects on the retinal ganglion cells.[40] Concomitant HPA dysregulation, resembling uncontrollable stress, was related to delayed venous dilation, recovery and widening. Most prominently, the delayed venous recovery upon provocation may indicate a prolonged retrograde propagation of the vascular response, reflecting lower vein vaso-activity and tone. Consistent low-grade inflammation will further increase the risk for endothelial dysfunction, a breach in BRB,[34] as well as ischaemic stroke.[4] Delayed vein recovery responses upon provocation suggest non-adaptation to stress, which constrained recovery and autoregulation. Indeed, delayed retinal venous recovery predicted chronic stress and stroke risk (OR 4.8), having large clinical significance.

Limitations

Our study is limited as the sample size was relatively small and it should be repeated in larger longitudinal studies. However, within a well-controlled setting, we were able to apply (1) an

innovative approach by determining HRV and salivary stress hormone levels upon provocation to substantiate SAM and HPA activity, and (2) a clinical stress and stroke risk score. Our findings contribute to the sparse information on neural mechanisms and chronic stress-induced stroke risk in the human brain–retina axis.

Conclusion

In response to low norepinephrine levels, a reflex increase in sympathetic activity occurred, resulting in increased norepinephrine levels and hypo-perfusion, potentiating risk for retinal ganglion cell health. Concomitant HPA dysregulation changed retinal vein dynamics as delayed recovery responses reflected non-adaptation to stress. Indeed, constrained or delayed venous recovery responses predicted chronic stress and stroke risk.

The ethics on publishing scientific articles were followed. We gratefully acknowledge the voluntary collaboration of the participants. The SABPA study would not have been possible without the valuable contributions from co-investigators and technical staff.

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WV is chief executive officer of the Imedos Systems GmbH (Jena, Germany) and a freelance researcher. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A comparison of AAIR versus DDDR pacing for patients with sinus node dysfunction: a long-term follow-up study

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Abstract

Objectives: The aim of the study was to compare the clinical outcomes [atrial fibrillation (AF), atrio-ventricular (AV) block, device sepsis and lead revision] of patients with sinus node dysfunction (SND) between atrial-pacing atrial-sensing inhibited-response rate-adaptive (AAIR) versus dual-chamber rate-adaptive (DDDR) pacing. The choice of AAIR pacing versus DDDR pacing was determined by AV nodal functional testing at implant.

Methods: We conducted a retrospective review of consecutive patients who underwent AAIR and DDDR pacing over a 10-year period.

Results: One hundred and sixteen patients required pacing for symptomatic SND. Fifty-four (46.6%) patients received AAIR pacemakers and 62 (53.4%) received DDDR pacemakers based on AV nodal functional testing at implant. Patients who had AV Wenkebach with atrial pacing at 120 beats per minute received DDDR pacing. Overall the mean age of patients with SND was 65 years and 66.4% were females, 30% were diabetics and 71% were hypertensives. Pre-syncope/syncope (84%) and dizziness (69%) were the most common symptoms. Sinus pauses and sinus bradycardia were the most common ECG manifestations. Over a median follow up of five (IQR: 2–11) years, four patients (7.4%) developed AF in the AAIR group compared to three (4.8%) in the DDDR group (p = 0.70). AV block occurred in one patient in the AAIR group, who required an upgrade to a DDDR pacemaker. There was no difference in device sepsis or need for lead revision between the two groups.

Conclusion: We found that AV nodal functional testing with atrial pacing at the time of pacemaker implantation was a useful tool to help guide the implanter between AAIR or DDDR pacing. Patients who underwent AAIR pacing had a low risk of AF, AV block or lead revision. In resource-limited settings, AAIR pacing guided by AV nodal functional testing should be considered as an alternative to DDDR pacing.

Keywords: cardiac pacing, sinus node dysfunction, single-lead atrial pacing, dual-chamber pacing, atrial fibrillation, atrio-ventricular block

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Symptomatic sinus node dysfunction (SND), also known as sick sinus syndrome, is usually due to age-related degeneration of the sinus node. SND can manifest on the ECG as a variety of ECG abnormalities, including sinus bradycardia, sinus arrest, sino-atrial block, chronotropic incompetence and the tachy–brady syndrome.[1] The most common symptoms of SND include syncope, dizzy spells, fatigue and exercise intolerance due to chronotropic incompetence.[2]

A diagnosis of symptomatic sinus node dysfunction requires correlation of symptoms with ECG findings. Secondary or reversible causes of SND may require specific treatment. The only treatment for primary symptomatic SND, usually due to age-related degeneration, is the insertion of a permanent pacemaker. SND is the second most common cause for cardiac pacing, accounting for approximately 30% of all pacemaker implantations.[3]

The indications and modes for pacemaker implantation for SND have been published. Both the European Society of Cardiology (ESC) guidelines[4] and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines[5] recommend dual-chamber rate-adaptive (DDDR) pacing over atrial-pacing atrial-sensing inhibited-response rate-adaptive (AAIR) pacing. This recommendation is based on the subsequent risk of atrio-ventricular (AV) block, a higher risk of paroxysmal atrial fibrillation (AF) and the higher risk of complications with AAIR pacing in patients who require subsequent ventricular pacing.[6] However, the numbers of patients who develop these complications are low, and with the higher cost of DDDR pacing, the initial increased risks of the additional ventricular lead, together with the harmful effects of inappropriate ventricular pacing, AAIR pacing has remained a reasonable option for patients with SND, especially in resource-limited settings.[7] This is particular relevant for developing countries in Africa where pacemaker implanters implant mainly single-chamber pacemakers because of cost and expertise.[8]

The future development of AV block has been recognised as a potential problem with AAIR pacing. The incidence of AV block in patients with SND has been reported to range from < 1% to 4.5% per year.[9–13] In an observational study of AAIR and DDDR pacing with long-term follow up, the annual incidence of AV block in the AAIR group was low (1.1%). Atrial pacing with an AV Wenckebach rate lower than 120 beats per minute (bpm) was found to be a predictor of high-grade AV block.[7] The DANPACE study, the largest randomised study of AAIR versus

DDDR pacing, reported a higher incidence of paroxysmal AF with AAIR pacing compared to DDDR pacing, with a high risk of complications with subsequent pacemaker lead revisions.[6]

This study aimed to compare the outcomes (development of AF, AV block, lead revision and device sepsis) of AAIR versus DDDR pacing in patients with symptomatic SND using AV nodal functional testing at the time of implant (patients received DDDR pacing if there was evidence of AV Wenkebach or AV block with atrial pacing at 120 bpm).

The rationale for using AV nodal functional testing was based on a previous observational study that compared AAIR versus DDDR pacing with very long-term follow up. The authors reported that AV nodal functional testing using a Wenkebach block point lower than 120 bpm was found to be a predictor of later high-grade AV block.[7] Patients also received a DDDR pacemaker if there was evidence of bundle branch block (BBB) or AV block (except 1st degree AV block and fascicular blocks) at baseline. While the risk of development of AV block in patients with BBB remains unclear, the decision to implant a pacemaker is consistent with the DANPACE trial. A previous study reported an increase in cardiovascular death rate in patients with BBB, which may be related to the future development of AV block.[14,15]

Methods

A retrospective study was conducted on consecutive patients implanted with an AAIR or DDDR pacemaker for symptomatic SND at Groote Schuur Hospital (GSH) between 2007 and 2017. GSH is a large, government-funded teaching hospital in Cape Town, South Africa. GSH is a tertiary referral centre, based on a networking hub with secondary hospitals in the region, and therefore the recruited patients are representative of the general population.

Ethics approval was obtained from the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (UCT), HREC REF: 493/2017.

Clinical records were obtained from cardiologists' and cardiac technologists' implant records and patients' hospital files. All patients with a diagnosis of SND who received a pacemaker were included. Demographic and clinical variables were recorded on a clinical report form.

Socio-demographic variables including age, gender, presenting symptoms, co-morbidities, medications, ECG and echocardiographic findings were retrieved. Other parameters obtained were the mode of pacing and outcomes after pacing, including occurrence of complications such as the development of AF, AV block, lead revision and device sepsis.

Statistical analysis

The collected data were checked for quality and coding was done prior to entry. Two different people entered the data twice and checked to ensure no double or wrong entries. Continuous and discrete data are presented as mean ± SD and as counts (percentage), respectively. All mean ages reported were calculated at primary implantation. The Statistical Package for the Social Sciences 24.0 (SPSS, Inc, Chicago, IL, USA) for Windows was used. The chi-squared test was used to test for group differences at $p < 0.05$ significance level.

Results

A total of 211 patients received a permanent pacemaker between January 2007 and July 2017 at GSH. One hundred and sixteen patients (54.9%) received a pacemaker for symptomatic SND, 54 (46.6%) received an AAIR pacemaker and 62 (53.4%) a DDDR pacemaker based on BBB, AV block at baseline and AV nodal functional testing (Table 1).

A comparison of the baseline demographics, clinical presentation and co-morbidities of the patients who received AAIR and DDDR pacemakers is shown in Table 1. Overall, the majority (66.4%) of patients was female and symptomatic, with pre-syncope or syncope being the most common clinical presentation (84.4%). Patients in the DDDR group were also more likely to have experienced palpitations at presentation (22.6%, $p = 0.05$). There were no major differences in co-morbidities (hypertension, diabetes mellitus, renal disease, cerebrovascular disease, ischaemic heart disease) between the two groups.

The ECG subgroups of sinus node dysfunction are shown in Table 2. Patients who received DDDR pacing had a higher likelihood of having BBB (6.5%) and evidence of AV block (24.2%) at baseline. There were no significant differences in ECG categories of SND (sinus bradycardia, sinus pauses/arrest, sino-atrial exit block, tachy–brady syndrome) between the AAIR and

Table 1. Baseline demographics and clinical presentation of patients who received AAIR versus DDDR pacing for sinus node dysfunction

Characteristic/parameter	*AAIR (n = 54)*	*DDDR (n = 62)*	p-*value*
Females, *n* (%)	38 (70.4)	39 (62.9)	0.396
Age at first implantation, mean ± SD (years)	65.8 ± 15.2	65.0 ± 15.4	0.766
Pre-syncope/syncope, *n* (%)			
Yes	45 (83.3)	53 (85.5)	0.750
No	9 (16.7)	9 (14.5)	
Tiredness, *n* (%)			
Yes	23 (42.6)	27 (43.5)	0.917
No	31 (57.4)	35 (56.5)	
Dizziness, *n* (%)			
Yes	44 (81.5)	54 (87.1)	0.405
No	10 (18.5)	8 (12.9)	
Palpitations, *n* (%)			
Yes	5 (9.3)	14 (22.6)	0.053
No	49 (90.7)	48 (77.4)	
Heart failure, *n* (%)			
Yes	2 (3.7)	4 (6.5)	0.684
No	52 (96.3)	58 (93.5)	
Hypertension, *n* (%)			
Yes	41 (75.9)	41 (66.1)	0.248
No	13 (24.1)	21 (33.9)	
Diabetes mellitus, *n* (%)			
Yes	18 (33.3)	17 (27.4)	0.489
No	36 (66.7)	45 (72.6)	
Renal disease, *n* (%)			
Yes	2 (3.7)	4 (6.5)	0.684
No	52 (96.3)	58 (93.5)	
Cerebrovascular events, *n* (%)			
Yes	5 (9.3)	4 (6.5)	0.732
No	49 (90.7)	58 (93.5)	
Ischaemic heart disease, *n* (%)			
Yes	24 (44.4)	27 (43.5)	0.923
No	30 (55.6)	35 (56.5)	

AAIR: atrial-pacing atrial-sensing inhibited-response rate-adaptive; DDDR: dual-pacing dual-sensing dual-response rate-adaptive.

Table 2. Electrocardiographic diagnoses of patients who received AAIR versus DDDR pacing for sinus node dysfunction

ECG description	*AAIR* (n = *54*)	*DDDR* (n = *62*)	p-*value*
SND ECG diagnosis, *n* (%)			
SND only	44 (81.5)	32 (51.6)	
SND + BBB	1 (1.9)	4 (6.5)	
SND + AV block	0 (0.0)	15 (24.2)	< 0.001
SND + atrial tachyarrhythmia	9 (16.7)	11 (17.7)	
SND ECG categories, *n* (%)			
Sinus pauses/arrest	25 (46.3)	29 (46.8)	
Sinus bradycardia	20 (37.0)	20 (32.3)	0.700
Sino-atrial exit block	3 (5.6)	2 (3.2)	
Tachy–brady syndrome	6 (11.1)	11 (17.7)	

AAIR: atrial-pacing atrial-sensing inhibited-response rate-adaptive; DDDR: dual-pacing dual-sensing dual-response rate-adaptive; SND: sinus node disease; BBB: bundle branch block.

DDDR groups. Sinus pauses/arrest (47% overall in both groups) and sinus bradycardia (34% overall in both groups) were the most common ECG manifestations. Sino-atrial exit block and tachy–brady syndrome were less common.

A comparison of the development of AF, AV block, mortality, device sepsis and need for lead revision between AAIR and DDDR pacing is shown in Table 3. Over a median follow up of 5.0 (IQR: 2–11) years, four patients developed AF in the AAIR group (7.4%) compared to three (4.8%) who developed AF in the DDDR group (p = 0.70). One patient (1.9%) in the AAIR group developed AF and AV block and required an upgrade to DDDR pacing. Deaths occurred in 18 (33.3%) patients in the AAIR group and 14 (22.6%) in the DDDR group. Two (3.7%) and two (3.2%) patients were lost to follow up in the AAIR and DDDR groups, respectively. There were no significant differences between the AAIR and DDDR groups with regard to mortality, device sepsis or the need for subsequent lead revision. Six patients needed lead revisions due to lead malposition or dislodgement (four right atrial and two right ventricular leads).

Discussion

The only effective treatment for symptomatic SND is the insertion of a permanent pacemaker. The choice of permanent pacemaker is either an AAIR pacemaker with an atrial lead or a DDDR pacemaker with atrial and ventricular leads. While most guidelines recommend DDDR pacing as the first choice of pacing, AAIR pacing remains an acceptable second choice, especially in resource-limited settings where the cost of DDDR pacing is prohibitive. The major disadvantage of AAIR pacing is the future development of AV block, which requires the addition of a ventricular lead.

Table 3. Comparison of mortality and the development of AF, AV block, device sepsis or lead revision between the AAIR and DDDR pacing groups

	Pacing mode		
Complication/procedures	*AAIR* (n = *54, 46.6%*)	*DDDR* (n = *62, 53.4%*)	p-*value*
Mortality, *n* (%)	18 (33.3)	14 (22.6)	0.196
AF, *n* (%)			
Yes	4 (7.4)	3 (4.8)	0.703
No	50 (92.6)	59 (95.2)	
AVB, *n* (%)			
Yes	1 (1.9)	1 (1.6)	1.000
No	53 (98.1)	61 (98.4)	
Sepsis, *n* (%)			
Yes	1 (1.9)	1 (1.6)	1.000
No	53 (98.1)	61 (98.4)	
Lead revision, *n* (%)			
Yes	4 (7.4)	2 (3.2)	0.415
No	50 (92.6)	60 (96.8)	

AAIR: atrial-pacing atrial-sensing inhibited-response rate-adaptive; DDDR: dual-pacing dual-sensing dual-response rate-adaptive; AF, atrial fibrillation; AVB: atrio-ventricular block.

In this study, we report only one case (1.9%) of AV block who required upgrade to DDDR pacing over a median follow up of five years. The risk of development of AV block in patients with SND is reported to be between < 1% and 4.5% per year.[9–13] A possible reason for the low risk of AV block in our cohort is that routine functional AV block testing was used in all patients to decide on the choice of pacemaker. We used a standard pacing protocol of atrial pacing at the time of implant to determine the AV Wenkebach rate. All patients received a DDDR pacemaker if AV Wenkebach or higher-degree AV block was present with atrial pacing at 120 bpm.

An AV Wenkebach rate lower than 120 bpm was found to be a predictor of high-grade AV block in a previous retrospective study comparing AAIR with DDDR pacing and the authors reported an annual incidence of AV block to be 1.1%.[7] In the DANPACE trial, the risk of AV block or slow AF occurred in 54 out of 707 patients (7.6%) with an incidence of 1.5% per year. A lower Wenkebach rate of 100 bpm was used to determine the need for DDDR pacing in the DANPACE study, which could explain why the AAIR group had a higher risk of AV block compared to our study. We propose that AV functional testing be used to help guide implanters on the choice of pacemaker, especially in resource-limited environments where the cost of DDDR pacing is prohibitive.

To evaluate the cost saving of selective AAIR pacing versus routine DDDR pacing, we compared the total cost of AAIR and DDDR pacing in this study with a hypothetical scenario where all patients received DDDR pacing. Using data from South Africa from the PASCAR 2011–2016 survey,[8] the total procedural costs of AAIR (US$1 030 per pacemaker) and DDDR (US$1 380 per pacemaker) pacing for 116 patients (including one upgrade from AAIR to DDDR pacing) was estimated to have cost US$142 560. The procedural costs if all patients received DDDR pacing was estimated to have been US$160 080. The cost saving therefore amounted to US$17 520. This equates to a saving of 17 AAIR pacemakers or 12 DDDR pacemakers in this study.

The DANPACE randomised trial reported a higher rate of paroxysmal AF, but not chronic AF, in patients who received AAIR pacing compared to DDDR pacing (heart rate 1.27 with AAIR pacing, p = 0.02)[6] However, extended follow up of the DANPACE trial reported no differences in AF hospitalisation between AAIR and DDDR pacing, with an annual incidence of 1.4%.[15] We report a lower rate and no difference in the subsequent development of paroxysmal or persistent AF in both pacing groups (7.4% in the AAIR group compared to 4.8% in the DDDR group, p = 0.70). These findings are similar to a prior study by Masumoto who also reported no difference in the development of AF between AAIR and DDDR pacing (6.4% in the AAIR group compared to 9.4% in the DDDR group at 10 years of follow up).[7] The above data suggest that the choice

of pacemaker for SND should not be guided by the risk of subsequent AF alone.

This study showed no difference in the rate of device infection between the two groups (1.9% in the AAIR versus 1.6% in the DDDR group, $p = 1.00$). These findings are similar to those observed in the DANPACE trial, which showed no difference in device infection between AAIR and DDDR pacing (0.4% in both groups, $p = 0.98$).[6] This study also showed no difference in the need for lead/s revision (7.4% in AAIR versus 3.2% in DDDR group, $p = 0.42$). Similar findings were observed in the DANPACE trial where no differences in the need for lead revision were found between the two groups (5.2% in the AAIR versus 4.2% in the DDDR groups, $p = 0.42$).[6] The DANPACE trial reported that subsequent lead revision was associated with a high complication rate. This study had only six lead revisions and no complications were noted in any of these six patients.

Study limitations

This was a retrospective study from a single institution with a relatively small number of patients. The conclusions are therefore hypothesis generating. However, the results reflect real-world practice in a contemporary South African population. Larger randomised trials using AV nodal functional testing as required need to be adopted. The interpretation of ECGs showing AF was made by cardiac technologists who routinely perform pacemaker device interrogations in the device clinic. It is possible that the technologists may not have recognised AF and may have under-reported episodes of AF. This study has all the limitations of a retrospective study, including missing information. It is possible that patients in the AAIR group who developed AV block may have been lost to follow up or died. However, the numbers of deaths between the two groups were similar.

Conclusion

In this typical elderly population who presented with symptomatic SND, we found functional AV nodal testing with atrial pacing at the time of pacemaker implantation to be a useful tool to help guide the implanter about the choice of AAIR or DDDR pacing. Patients who underwent AAIR pacing had a low subsequent risk of AF, AV block or lead revision. In resource-limited settings, AAIR pacing should be considered as an alternative to DDDR pacing. Patients with AAIR pacemakers should be counselled regarding future symptoms of AV block, and device follow up may be required on a six-monthly basis to rule out the need for ventricular pacing. Randomised trials are required to further define the role of AV nodal functional testing.

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Study of congenital heart defects among neonates in Jos, Nigeria: prevalence and spectrum

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Abstract

Background: There are few reports of the prevalence of CHD in the neonatal period in sub-Saharan Africa. The only available study in Nigeria was carried out before the widespread availability of echocardiography in the country. We sought to determine the prevalence and spectrum of congenital heart defects (CHD) among neonates in Jos, Nigeria.

Methods: This cross-sectional study enrolled neonates less than one week of age from the two largest hospitals and their immunisation centres. Relevant information was obtained and an echocardiogram was performed on each neonate.

Results: There were 3 857 neonates recruited over a two-year period; male-to-female ratio was 1.1:1. A total of 111 babies had CHD, with a prevalence of 28.8 per 1 000. Sixty-four neonates had mild CHD, with a prevalence of 16.6 per 1 000, while moderate and severe CHD were found in 27 (7.0 per 1 000) and 20 (5.2 per 1 000), respectively.

Conclusion: CHD is prevalent in Nigerian neonates and there is therefore a need for advocacy to improve access to its diagnosis at birth for appropriate management.

Keywords: congenital heart defects, neonates, prevalence, echocardiography, Nigeria

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Congenital heart defects (CHD) are common birth lesions, defined as gross structural abnormalities of the heart or intrathoracic great vessels that are of actual or potential functional significance.[1] One-third of deaths from birth defects are due to CHD, with 48% of these occurring in the first year of life. CHD therefore contribute significantly to infant mortality.[2-4]

The epidemiology of CHD is best studied using birth prevalence and this has shown an increasing trend from 4.5 per 1 000 live births in the 1970s to 9.4 per 1 000 live births in the 21st century.[5] Epidemiological studies have also been conducted in children after the neonatal period and a higher prevalence of CHD is reported in younger children.[6] Since up to 25% of deaths from CHD occur within the first month of life,[7] it is critical to detect these defects as early as possible, not only to facilitate early intervention but also for a more accurate estimation of the disease burden where birth prevalence data are not available.

The majority of reports on CHD in Nigerian children have been on those being followed up in paediatric cardiology clinics or referred for echocardiography.[8,9] This limits the estimation of the current prevalence of CHD in the country, where the only study on the birth prevalence of CHD was reported over 50 years ago and before the era of echocardiography.[10] We therefore set out to determine the prevalence and spectrum of CHD in neonates in Jos, Nigeria, so as to provide more accurate estimates of the burden of CHD in the country. This will provide a better platform for advocacy on the need to improve access to cardiac interventions for children with CHD in the country.

Methods

The study was conducted in two tertiary heath institutions: the Jos University Teaching Hospital (JUTH) and the Plateau State Specialist Hospital (PSSH) in Jos, north-central Nigeria. They are the two largest hospitals in the city, which has a population of about 816 000 people.[11] The two hospitals together handle an average of 30 to 40 deliveries weekly.

Neonates are usually discharged 24 hours after uncomplicated vaginal delivery unless they are sick and admitted for in-patient care. Sick neonates born elsewhere may also be admitted for in-patient care in these hospitals, both of which have functional immunisation units that are equally accessible to neonates born elsewhere. The delivery, postnatal and immunisation units of the two hospitals served as recruitment points for the neonates in this study.

This was a cross-sectional study to determine the prevalence and spectrum of CHD among neonates in the immediate postnatal period (first week of life) over a period of two years from February 2017 to January 2019. The study population included neonates delivered or attended to within the first week of life in JUTH and PSSH and their affiliated immunisation centres. All babies aged one week or younger, delivered or provided with treatment or immunisation services in JUTH and PSSH were eligible for the study as long as their mothers or caregivers provided written informed consent.

A total-population approach to sampling was employed in this study where all babies who met the inclusion criteria in the two health institutions were recruited and sampled within the study period upon consent. The neonates were recruited on weekdays before their discharge from the hospital or before routine vaccinations at the immunisation centres.

Approval for the study was obtained from the Institutional and Health Research Ethics Committee of JUTH, while permission was obtained from PSSH and the affiliated immunisation centre before the study commenced. Written informed consent was also obtained from each neonate's mother or primary caregiver.

Five residents in paediatrics at JUTH served as research assistants and were trained by the lead investigator for two days on the study protocol, administration of questionnaires, the required clinical examination, and documentation of findings, including echocardiogram findings.

A semi-structured proforma developed specifically for this study was used to obtain clinical and demographic information about the neonates and their parents, from mothers/caregivers. Physical examination findings of the neonates were also documented in the proforma, which was pre-tested on 34 babies to identify and address ambiguities, determine ease of administration, appropriateness of the questions, and to estimate the average duration of data collection.

Demographic and clinical information about every neonate was documented by the trained research assistants. Demographic data such as maternal parity, age and educational status of parents, the neonate's gender, postnatal age, as well as gestational age at the time of delivery, were recorded. The neonates' birth weights (taken immediately after birth) were obtained from their delivery records. Their crown-to-sole lengths and occipitofrontal circumferences (OFC) were measured in centimetres using an infantometer and non-stretchable tape, respectively, according to standard methods.[12] Three measurements of each were taken and the average (to the nearest 0.1 cm) was determined and recorded.

A transthoracic Doppler echocardiogram was performed by the lead researcher, who has been trained in and routinely performs paediatric echocardiography, on all the enrolled neonates using a Vivid e® portable echo machine (GE, China, May 2016). A diagnosis of CHD was made in any newborn with single or multiple structural heart defects. The diagnosis of the various types of CHD was made based on the ICD-10 diagnostic codes.[13]

The CHD were classified as cyanotic or acyanotic defects, based on the presence or absence of cyanosis, and also as mild, moderate or severe lesions.[5,10-13] Mild lesions included small atrial septal defects (ASD) 3–5 mm in diameter, and small ventricular septal defects (VSD) < 3 mm in diameter. Other mild lesions included pulmonary stenosis (PS) with peak gradient < 30 mmHg, and bicuspid aortic valve without aortic stenosis or incompetence. Although patent ductus arteriosus (PDA) < 1.5 mm in diameter after the first week of life was also considered a mild lesion, since the study was carried out in the first week of life, PDA < 1.5 mm in diameter was not categorised as CHD in this study. (Small ASD was differentiated from a patent foramen ovale by the absence of a flap in the latter.[13])

Moderate lesions were: large ASD > 5 mm in diameter, moderate-sized PDA and VSD measuring 1.5–3 mm and 3–6 mm, respectively, complex forms of VSD associated with other CHD, non-critical coarctation of the aorta, moderate pulmonary stenosis with peak gradient of 30–60 mmHg, and mild-to-moderate aortic stenosis with ≤ 50 mmHg peak gradient.

Severe lesions included all cyanotic CHD, as determined by the presence of central cyanosis, which was defined as oxygen saturation < 95% in the absence of other causes,[14] and acyanotic CHD such as large VSD > 6 mm, large PDA > 3 mm, atrioventricular septal defects (AVSD), severe pulmonary stenosis with peak gradient > 60 mmHg, severe aortic stenosis > 50 mmHg peak gradient, and any critical CHD such as severe duct-dependent lesions requiring urgent surgical intervention for survival. These included hypoplastic left heart syndrome (HLHS), critical coarctation of the aorta (CoA), critical aortic stenosis, tricuspid atresia without shunt defects, total anomalous pulmonary venous connection (TAPVC) and severe tetralogy of Fallot (TOF).[15]

Septal defects were further classified based on the location of the defect in the septum: ostium primum, ostium secundum and sinus venosus defects for ASDs and peri-membranous, inlet, outlet and muscular defects for VSDs.[16]

Newborns found to have CHD were referred to the Paediatric Cardiology unit in JUTH for in-patient care or out-patient follow up, depending on the infant's clinical condition. Pre-term neonates with PDA were managed according to the hospital's protocol.

Statistical analysis

Data were processed and analysed using STATA® statistical software version 14.0 (Texas, USA). Means and standard deviations were used as summary indices for numerical data such as age, weight, length and OFC, while non-numerical data such as gender, and type and severity of CHD were presented as frequencies or percentages, or as charts. The unpaired student's *t*-test was used to test the difference between means of continuous variables such age, weight and gestational ages of neonates with and without CHD.

Analysis of variance (ANOVA) was used to compare means of more than two groups, while the chi-squared test was used to compare non-numerical characteristics such as gender, place of delivery and type of care received by neonates with and without CHD. Multivariate analysis was also performed to determine the association of CHD with maternal age, and neonateal gestational age and weight. A 95% confidence interval was used in this study as the interval estimate and a *p*-value of ≤ 0.05 was considered statistically significant.

Results

A total of 3 857 babies were recruited into the study. There were 2 016 males and they comprised 52.3% of the total. The neonates were born at a mean gestational age of 36.9 ± 9.2 weeks. The

Table 1. Demographic and clinical parameters of neonates and their mothers

Parameter	*Mean ± SD (95% CI)*	*Range*
Gestational age at delivery (weeks)	36.9 ± 9.2	23–44
Preterm	583 (15.1)	
Term	2988 (77.4)	
Post term	72 (2.0)	
Unknown	214 (5.5)	
Neonatal age (days)	2.2 ± 1.9	1–7
Gender		
Male	2016 (52.3)	
Female	1841 (47.7)	
Neonatal birth weight (kg)	3.08 ± 0.6	0.69–5.1
Low birth weight	352 (9.1)	
Normal birth weight	3,189 (82.7)	
Macrosomia	102 (2.6)	
Not documented	214 (5.6)	
Neonatal length (cm)	48.9 ± 2.9	32–62
< 45	271 (7.0)	
45–55	3550 (92.1)	
> 55	36 (0.9)	
Occipitofrontal circumference (cm)	34.5 ± 1.7	28–40
< 33	339 (8.8)	
33–37	3452 (89)	
> 37	66 (1.7)	
Parity	2.8 ± 1.9	1–14
Maternal age (years)	28.6 ± 8.4	15–52
< 18	11 (0.3)	
18–35	3264 (84.6)	
> 35	514 (13.3)	
Unknown	68 (1.8)	

birth weight was documented in 3 643 (94.5%) neonates and ranged from 0.69 to 5.1 kg with a mean of 3.08 ± 0.6 kg. The mean lengths and OFC were 48.9 ± 2.9 cm and 34.5 ± 1.7 kg, respectively. The mothers had a mean age of 28.6 ± 8.4 years and a median parity of 2.0 ± 1.9 (Table 1).

Almost two-thirds of the neonates (2 340/3 857 or 60.7%) were delivered in JUTH and PSSH. The remainder (1 517 or 39.3%) were delivered elsewhere but seen in these hospitals and were either admitted or came for their first immunisation within the first week of life in either of the two study centres. Over 80% (1 262/1 517) of the latter were born in smaller hospitals while the remaining 255 (16.8%) were born at home. Approximately

Table 2. Distribution based on place of delivery and type of care received

	Number (3 857)	*Percentage*
Place of delivery		
JUTH/PSSH	2 340	60.7
Other hospitals	1 262	32.7
Home	255	6.6
In-patient care		
Yes	388	10.1
JUTH/PSSH	244	62.9
Other hospitals	120	30.9
Home	24	6.2
No	3 469	89.9
JUTH/PSSH	2 096	60.4
Other hospitals	1 142	32.9
Home	231	6.7

JUTH, Jos University Teaching Hospital; PSSH, Plateau State Specialist Hospital.

Table 3. Factors associated with the severity of lesions

	CHD			
Characteristics	*Mild** n *(%)*	*Moderate*** n *(%)*	*Severe**** n *(%)*	p-*value*
Gender				
Male	32 (51.6)	16 (25.8)	14 (22.6)	
Female	32 (65.3)	11 (22.4)	6 (12.3)	0.27
Place of delivery				
JUTH/PSSH	42 (65.6)	14 (21.9)	8 (12.5)	
Other hospitals	20 (47.6)	12 (28.6)	10 (23.8)	
Home	2 (40.0)	1 (20.0)	2 (40.0)	0.25
In-patient care				
Yes	12 (34.3)	11 (31.4)	12 (34.3)	
No	52 (68.4)	16 (21.1)	8 (10.5)	0.001§
Maternal age in years (mean ± SD)	30.5 ± 5.7	29.2 ± 5.1	33.1 ± 5.4	0.06
Neonatal weight in kg (mean ± SD)	2.8 ± 0.6	2.7 ± 0.7	3.1 ± 0.5	0.09
Gestational age in weeks (mean ± SD)	36.3 ± 9.7	35.2 ± 10.4	34.6 ± 11.9	0.77

*17.9 per 1 000 live births; **6.0 per 1 000 live births; ***3.4 per 1 000 live births; §statistically significant.

10% (388) of the overall 3 857 neonates were admitted for in-patient care (Table 2).

CHD was detected in 111 of the 3 857 neonates with a prevalence of 28.8 per 1 000. Sixty-two (55.9%) males had CHD (male-to-female ratio 1.3:1) (Table 3). Sixty-four of the 2 340 neonates delivered in JUTH and PSSH had CHD, with a hospital birth prevalence of 27.4 per 1 000 live births. Conversely, CHD was present in 42 of the 1 262 neonates delivered in other hospitals, with a prevalence of 33.3 per 1 000, while five of the 255 neonates delivered at home had CHD, prevalence 19.6 per 1 000 (Fig. 1).

Nine (8.1%) of the 111 neonates with CHD had cyanotic defects, which is a prevalence of 2.3 per 1 000; six (66.7%) of these had critical CHD, with a prevalence of 1.6 per 1 000 population. Only one of the six neonates with critical CHD was delivered in either of the study institutions with a hospital birth prevalence of 0.3 per 1 000 live births. The most common critical CHD in this study was HLHS observed in four (66.7%) of the six affected neonates (Table 4).

Acyanotic CHD contributed 91.9% of all the CHD detected, being observed in 102 of the 111 neonates with CHD, which is a prevalence of 26.4 per 1 000. The most common acyanotic CHD

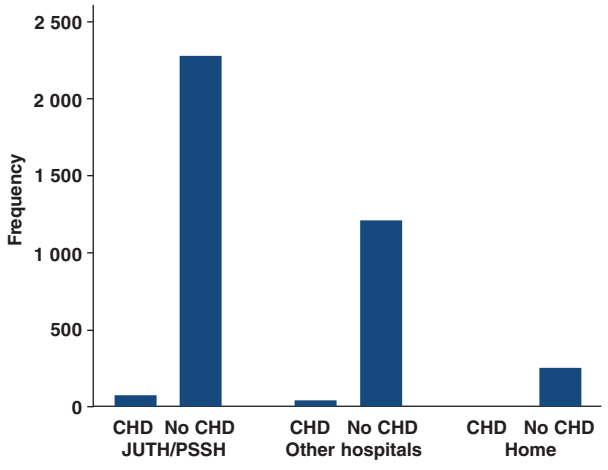

Fig. 1. Distribution of CHD by place of delivery

Table 4. Prevalence and spectrum of CHD

	Total (3 857)	*Male (2 016)*	*Female (1 841)*
Spectrum of CHD	n *per 1 000*	n *per 1 000*	n *per 1 000*
Acyanotic CHD	102 (26.4)	55 (27.3)	47 (25.5)
Atrial septal defect	24 (6.5)	10 (5.0)	14 (7.6)
Ventricular septal defect	34 (9.2)	16 (7.9)	18 (9.8)
Combined atrial and ventricular septal defect	13 (3.4)	10 (5.0)	3 (1.5)
Atrioventricular septal defect	5 (1.3)	3 (1.5)	2 (1.1)
Isolated pulmonary stenosis	9 (2.3)	7 (3.5)	2 (1.1)
Isolated patent ductus arteriosus	5 (1.3)	2 (1.0)	3 (1.5)
Coarctation of the aorta	4 (1.1)	2 (1.0)	2 (1.1)
Bicuspid aorta valve	4 (1.1)	3 (1.5)	1 (0.5)
Aortopulmonary window	1 (0.3)	1 (0.5)	0 (0.0)
Double-outlet right ventricle	1 (0.3)	0 (0.0)	1 (0.5)
Partial anomalous pulmonary venous return	1 (0.3)	1 (0.5)	0 (0.0)
Cortriatriatum dexterum	1 (0.3)	0 (0.0)	1 (0.5)
Cyanotic CHD (severe)	9 (2.3)	7 (3.5)	2 (1.1)
Tetralogy of Fallot	1 (0.3)	0 (0.0)	1 (0.5)
Truncus arteriosus	1 (0.3)	1 (0.5)	0 (0.0)
Ebstein's anomaly	1 (0.3)	1 (0.5)	0 (0.0)
Critical CHD			
Hypoplastic left heart syndrome	4 (1.1)	3 (1.5)	1 (0.5)
Total anomalous pulmonary venous return	1 (0.3)	1 (0.5)	0 (0.0)
Transposition of great arteries	1 (0.3)	1 (0.5)	0 (0.0)

were isolated VSDs detected in 32 (31.4%) neonates, followed by isolated ASDs in 22 (21.6%). The ductus arteriosus was still patent in 1 643 (42.6%) of the neonates at enrolment. The highest frequency of ductal patency was in neonates recruited on the first day of life (1 220/1 643, 74.3%), and decreased markedly by the second and third days of life to 12.3% (202/1 643) and 6.5% (107/1 643), respectively. By the sixth day of life, only 11 neonates still had ductal patency. However, only seven neonates had a ductal diameter that exceeded 1.5 mm, therefore satisfying the criteria for classification as CHD; a prevalence of four per 1 000. Five (71.4%) of the seven neonates had isolated PDAs while the remaining two (28.6%) co-existed with other CHD; one ASD and one VSD (Table 4).

Isolated ASDs were present in 22 of the 24 (91.7%) neonates with ASD; one ASD co-existed with a PDA and the other with moderate pulmonary stenosis. Most (95.5%) of the isolated ASDs were ostium secundum defects; one (4.5%) was an ostium primum ASD. Thirty-two of the 34 (94.1%) neonates with VSD had isolated lesions; the other two co-existed, one with a PDA and the other with a mild pulmonary stenosis. The majority of the isolated VSDs were peri-membranous defects, which were detected in 17/32 (53.1%). Muscular VSDs were present in 14/32 (43.8%), while a sub-aortic VSD was detected in one (3.1%) of the neonates with isolated VSD (Fig. 2).

Sixty four of the 111 neonates with CHD had mild defects (16.6 per 1 000 population) while 27 had moderate CHD (7.0 per 1 000 population). Severe CHD was detected in 20 neonates with a prevalence of 5.2 per 1 000. Moderate and severe CHD were more common in males; 16/64 (25.8%) male versus female 11/49 (22.4%) and 14/64 (22.6%) male versus female 6/49 (12.3%), respectively, but these were not significantly different ($p = 0.75$ and $p = 0.08$, respectively). More female neonates (32/49 or 65.3%) had mild CHD compared with males: 32/64 or 51.6%, but the difference was also not significantly different; $p = 0.11$ (Fig. 3).

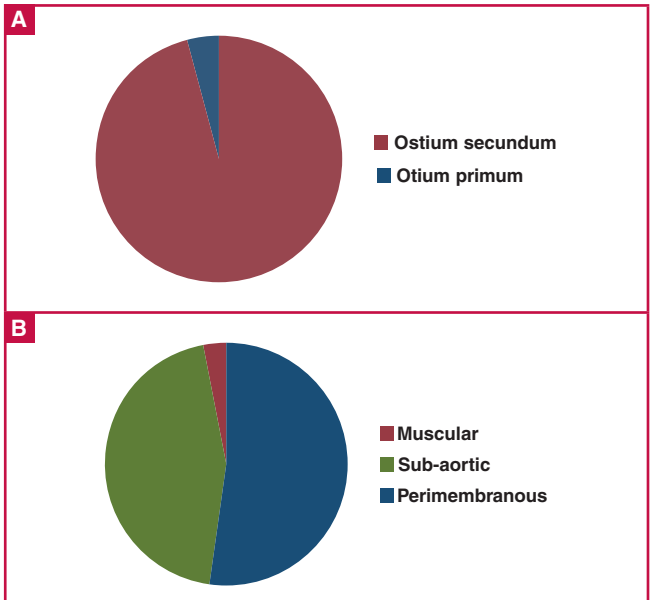

Fig. 2. A. Types of ASD detected. B. Types of VSD detected.

Mild CHD was present in 42 of the 2 340 neonates delivered in the study hospitals (17.9 per 1 000 live births) while moderate and severe lesions were present in 14 (6.0 per 1 000 live births) and eight (3.4 per 1 000 live births) patients, respectively.

Admitted neonates with CHD had more severe lesions compared with those who were not admitted ($p = 0.001$). There was no significant association between the severity of CHD and gender, place of delivery, maternal age, gestational age at delivery or birth weight (Table 3).

Mothers of neonates with CHD were older (30.6 ± 5.6 vs 28.4 ± 6.8 years, $p < 0.001$) and had higher parity (3.5 ± 2.0 vs 2.8 ± 1.9, $p < 0.001$). Neonates with CHD had lower birth weight (2.8 ± 0.6 vs 3.1 ± 0.6 kg, $p < 0.001$), were four times more likely to receive in-patient care [OR 4.4 (95% CI 2.8–6.8), $p < 0.001$] or had dysmorphic features ($p < 0.001$). There was no difference in mean gestational age between neonates born with CHD and

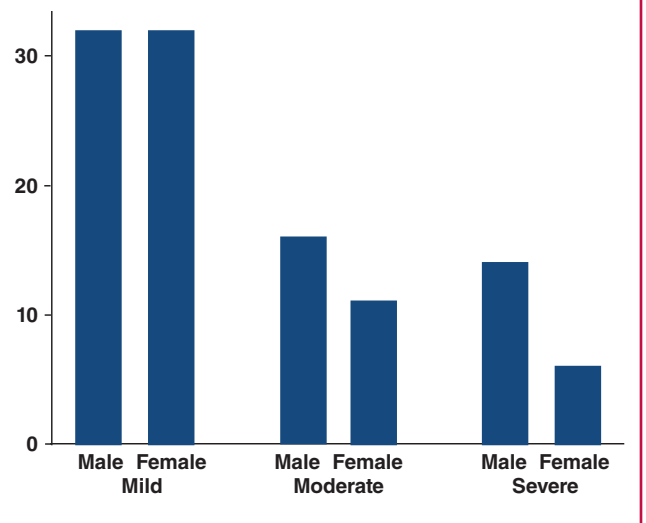

Fig. 3. The distribution of CHD based on severity

Table 5. Factors associated with CHD

Characteristics	*CHD (111)*	*No CHD (3 746)*	p-*value*
Gender			
Male	62	1 954	
Female	49	1 792	0.44
Place of delivery			
JUTH/PSSH	64	2 276	
Other hospitals	42	1 262	
Home	5	250	0.40
In-patient care			
Yes	35	353	
No	76	3 393	< 0.001§
Dysmorphism			
Yes	15	2	
No	96	3 744	< 0.001§
Maternal age in years (mean ± SD)	30.6 ± 5.6	28.4 ± 6.8	< 0.001§
Neonatal weight in kg (mean ± SD)	2.8 ± 0.6	3.1 ± 0.6	< 0.001§
Gestational age in weeks (mean ± SD)	35.7 ± 10.2	36.9 ± 9.1	0.19

§Statistically significant.

those with normal hearts (35.7 ± 10.2 vs 36.9 ± 9.1 years, $p = 0.19$) (Table 5). On multivariate regression analysis, the mother's age ($p = 0.006$), lower birth weight ($p = 0.003$), in-patient care ($p < 0.001$) and the presence of dysmorphism ($p < 0.001$) remained statistically significant predictors of CHD.

The five most common lesions detected were all acyanotic. Isolated VSDs and ASDs occurred more commonly and accounted for 9.2 and 6.5 per 1 000, respectively. The other three common lesions detected were combined ASD and VSD lesions, mild PS and AVSD, detected in 3.4, 2.3 and 1.3 per 1 000. A comparison of the relative distributions of the five most common subtypes in other regions is shown in Table 6.

Discussion

The prevalence of CHD in the first week of life in our study was found to be 28.8 per 1 000, with a hospital birth prevalence of 27.4 per 1 000 live births. Infants with mild CHD had a prevalence of 17.9 per 1 000, moderate CHD 6.0 per 1 000 and severe CHD 3.4 per 1 000. In addition, acyanotic CHD accounted for 91.9% of all the CHD identified, with VSD being the commonest acyanotic CHD found in 31.2%. Neonates with CHD were born to older women, had a lower mean birth weight and were more likely to be admitted for a medical illness.

Table 6. Comparison of the relative distributions of common CHD subtypes with other studies

	Study			
Variables	*Liu* et al.	*Hussain* et al.	*Sun* et al.	*Ige* et al.
Location	Global	Pakistan	China	Nigeria
Subtypes (per 1 000)				
Ventricular septal defect	3	3.1	0.8	9.2
Atrial septal defect	1.4	2.3	0.9	6.5
Patent ductus arteriosus	1.0	1.5	0.4	–
Tetralogy of Fallot	0.3	0.7	0.05	–
Pulmonary stenosis	0.5	0.6	0.01	2.3
Atrioventricular septal defect	–	–	–	1.3
Combined atrial and ventricular septal defects	–	–	–	3.4

The prevalence of CHD detected in this study is higher than the 15 per 1 000 reported from Pakistan,[17] even though the latter enrolled only sick babies admitted within the first 12 hours of life, who might have been expected to have a higher prevalence. In China, a prevalence of 22.9 per 1 000 was detected among three-month-old infants seen in a tertiary hospital.[18] The older age of the subjects in the Chinese study could explain their slightly lower prevalence compared to the present study.

Our finding is however at variance with that of a recent meta-analysis by Liu *et al*.,[19] who showed that the prevalence of CHD in Africa was significantly lower than that in other continents. The authors attributed this to poor access to appropriate healthcare resources in Africa, leading to low CHD detection rates. However, only four of the 260 studies (study populations from birth to six years) reviewed were from the continent of Africa, highlighting the paucity of data from the continent, which might have been responsible for the apparently low prevalence. This emphasises the need for more research on the prevalence of CHD among infants and young children in Africa. The present study helps to bridge this gap by contributing to the pool of data on CHD prevalence from this region.

The birth prevalence of 27.4/1 000 live births obtained in our study is much higher than the 8.0 per 1 000 reported by Dolk *et al*. across Europe and the 13.7 per 1 000 documented by Gillum *et al*. in the United States.[20,21] Both studies were registry-based studies documenting cases diagnosed after referral for evaluation for CHD, with the potential to underestimate mild lesions that are largely asymptomatic. A study in Saudi Arabia also documented a lower birth prevalence of 14.6 per 1 000 live births compared with the present study.[22] The latter enrolled only pregnant women attending antenatal clinics, who were followed up until delivery when their babies had echocardiography, unlike in our study where all neonates delivered at the two study hospitals were enrolled, irrespective of where they had received antenatal care. In addition to the different methodologies used, differences in the presence of causal mechanisms that predispose to CHD may account for the wide variations in the prevalence seen in different parts of the world.[23]

The birth prevalence obtained in this study is also much higher than the 3.5 per 1 000 (for live and still births) reported by the only available hospital-based prevalence done by Gupta and Antia in 1967.[10] While our study used echocardiography as the diagnostic tool, Gupta and Antia used clinical auscultation and autopsy of still-born babies to estimate the prevalence.[10] Echocardiography helps to detect even asymptomatic lesions, which would not be easily detected using clinical auscultation. Therefore, the absence of echocardiography obviously limited Gupta and Antia's detection of many mild and moderate lesions and possibly also some severe lesions that were asymptomatic in the immediate neonatal period.

Similar to previous reports, acyanotic CHDs were found to be more common than cyanotic lesions in our study, with VSD being the most frequent lesion, followed by ASD.[5,18] Although the relative distributions of septal defects in this study were much higher than the global prevalence reported by Liu *et al*.,[19] most of the lesions were mild. The high prevalence of VSDs, especially small lesions, have been shown to be responsible for the increase in the occurrence of mild CHD and therefore overall CHD rates found in the present study.[23]

In recent studies, septal defects have been linked to maternal exposure to particulate matter.[24,25] This provides one more reason to address the pressing matter of particulate air pollution and it would be important in future studies to identify factors that predispose to the development of CHD in our environment so that recommendations can be made concerning possible measures that could reduce their incidence.

Other CHD subtypes reported in this study also differed when compared to other countries and the global prevalence, and this could be as a result of the presence of relative causal mechanisms of the different lesions and the mode of entry of subjects into a study, as some lesions such as PS and CoA may be asymptomatic at birth and may be missed during the neonatal period.[23] HLHS accounted for two-thirds of our cases of critical CHD, which contrasts with reports from developed countries where the prevalence of this defect has decreased significantly, primarily due to prenatal echocardiography and the termination of affected pregnancies.[23,26]

The present study provides a more accurate representation of the prevalence of CHD in the country, compared to previous studies, because it was conducted in neonates with a higher likelihood of discovering critical CHD, which often results in early neonatal mortality.[27] In a recent nationwide registry report, 14% of the 1 296 CHD cases were below one month of age, and five cases of critical CHD were detected.[28] The registry subjects were children referred for cardiac evaluation and do not represent the true prevalence of critical CHD and other lesions detected.

Limitations are that this study was undertaken in only the north-central part of the country and our data may not reflect the burden of disease in other regions. Multicentre screening studies involving other parts of the country are needed to provide better estimates of the nationwide burden of CHD and the differences in prevalence and spectrum between regions.

Conclusion

There is a high prevalence of CHD among neonates in Jos, north-central Nigeria. Although most of the lesions detected were mild, attention should be given to newborn screening for CHD to mitigate morbidity and mortality from moderate and severe lesions, especially in sick neonates and those born to older women. Early identification of CHD is essential in providing accurate data for advocacy in order to make affordable paediatric cardiology and cardiac surgery services accessible to children born with CHD in Nigeria.

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No 'fat but healthy' paradox in cardiovascular risk: large Spanish analysis

A large Spanish study found that physical activity does not entirely undo the negative effects of excess body weight when cardiovascular health was determined according to three major risk factors for heart attack and stroke: diabetes, high cholesterol and high blood pressure.

'One cannot be "fat but healthy",' said study author Dr Alejandro Lucia of the European University, Madrid, Spain. 'This was the first nationwide analysis to show that being regularly active is not likely to eliminate the detrimental health effects of excess body fat. Our findings refute the notion that a physically active lifestyle can completely negate the deleterious effects of overweight and obesity.'

There is some evidence that fitness might mitigate the negative effects of excess body weight on heart health. It has been suggested that in adults and children, being 'fat but fit' might be associated with similar cardiovascular health to being 'thin but unfit'. Lucia said: 'This has led to controversial proposals for health policies to prioritise physical activity and fitness above weight loss. Our study sought to clarify the links between activity, body weight and heart health.'

The study used data from 527 662 working adults insured by a large occupational risk-prevention company in Spain. The average age of participants was 42 years and 32% were women.

Participants were categorised as normal weight [body mass index (BMI) 20.0–24.9 kg/m^2], overweight (BMI 25.0–29.9 kg/m^2), or obese (BMI 30.0 kg/m^2 or above). Additionally, they were grouped by activity level: (1) regularly active, defined as doing the minimum recommended for adults by the World Health Organisation (WHO); (2) insufficiently active, defined as some moderate to vigorous physical activity every week but less than the WHO minimum; (3) inactive (no exercise). Cardiovascular health was determined according to three major risk factors for heart attack and stroke, namely diabetes, high cholesterol and high blood pressure.

Approximately 42% of participants were normal weight, 41% were overweight and 18% were obese. The majority were inactive (63.5%), while 12.3% were insufficiently active, and 24.2% were regularly active. Some 30% had high cholesterol levels, 15% had high blood pressure and 3% had diabetes.

The researchers investigated the associations between each BMI and activity group and the three risk factors. At all BMI levels, any activity (whether it met the WHO minimum or not) was linked with a lower likelihood of diabetes, high blood pressure or high cholesterol compared to no exercise at all.

Lucia said: 'This tells us that everyone, irrespective of their body weight, should be physically active to safeguard their health.' At all weights, the odds of diabetes and hypertension decreased as physical activity rose. 'More activity is better, so walking 30 minutes per day is better than walking 15 minutes a day,' he said.

However, overweight and obese participants were at greater cardiovascular risk than their peers with normal weight, irrespective of activity levels. As an example, compared to inactive normal-weight individuals, active obese people were approximately twice as likely to have high cholesterol levels, four times more likely to have diabetes, and five times more likely to have high blood pressure.

Lucia said: 'Exercise does not seem to compensate for the negative effects of excess weight. This finding was also observed overall in both men and women when they were analysed separately.'

He concluded: 'Fighting obesity and inactivity is equally important; it should be a joint battle. Weight loss should remain a primary target for health policies, together with promoting active lifestyles.'

Source: Medical Brief 2020

Hybrid rotablation and drug-eluting balloon strategy

Ahmed Vachiat, Mpiko Ntsekhe, Farrel Hellig

Abstract

Aim: The aim was to assess the safety and efficacy of rotational atherectomy followed by drug-eluting balloon (DEB) in patients with a high risk of bleeding.

Methods: A retrospective review was carried out of hospital records of consecutive patients who underwent the hybrid procedure.

Results: The average age of the 23 patients was 74 years. Risk factors for bleeding included renal failure (35%), oral anticoagulation use (26%) and peptic ulcer disease (35%). All patients had procedural success. No bleeding was reported over the 24-month follow-up period. Dual antiplatelet therapy was stopped successfully in six patients (26%) at three months. Two patients had confirmed target-lesion failure (restenosis). Two patients died over the study period but the cause of death was not known to be cardiovascular disease related.

Conclusion: For patients at high risk of bleeding who require rotablation, the use of a drug-eluting balloon may be a safe, effective alternative.

Keywords: rotablation, drug-eluting balloon, calcification

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The revascularisation strategy for dealing with calcified lesions includes adequate lesion preparation to avoid complications and improve clinical outcomes. The techniques to prepare lesions include balloon angioplasty, using semi-compliant and non-compliant balloons, cutting balloons, rotational atherectomy and, recently, intravascular lithotripsy.[1] Post lesion preparation, the current recommendations and practice are to use drug-eluting stents (DES) requiring dual antiplatelet therapy (DAPT), which includes P_2Y_{12} inhibitors (clopidogrel, ticagrelor or prasugrel) for six to 12 months, and aspirin lifelong.

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Hybrid rotablation and drug-eluting balloon strategy is a new concept for calcified lesions and has a number of potential benefits.[2] Most patients referred with calcified lesions are elderly and have numerous co-morbidities and risk factors for bleeding, including atrial fibrillation, oral anticoagulants, renal failure and peptic ulcer disease.[2] The use of drug-eluting balloons (DEBs) offers a strategy for reducing bleeding risk, as the post-procedure addition of P_2Y_{12} inhibitors to aspirin for secondary prevention is required for only one month, following which they can be discontinued.[3]

Patients with calcified lesions often have diffuse disease and long lesions, potentially requiring long, small stents. These are prone to under-expansion, malapposition, delayed endothelialisation and chronic inflammation, stent fracture, neo-atheroma and polymer reactions,[4] all of which place patients at increased risk for early, late and very late stent thrombosis. Therefore, by eliminating the need for any stent implantation, DEBs may significantly reduce the risk of these stent-related adverse events.[4]

DEBs are designed to act as delivery vehicles to the target lesion of chemotherapeutic agents (paclitaxel, sirolimus), which have been coated on the balloon. The currently available DEBs have different excipient/coating techniques (Table 1).

The main DEBs available for use in our practice were the SeQuent® Please (B Braun) and IN.PACT Falcon (Medtronic). The SeQuent® Please DEB uses iopromide (a contrast medium) to act as the excipient to retain the drug on the balloon and to facilitate delivery of the drug to the vessel wall due to its lipophilicity. The dose of paclitaxel used is 3 µg/mm^3. The half-life of the drug is almost two months.[5] The IN.PACT Falcon DEB uses urea as an excipient with the antiproliferative agent paclitaxel (3.5 µg/mm^2). Although sirolimus-coated DEBs have recently been developed and used with promising clinical outcomes in *de novo* lesions,[6] we did not use any DEBs containing sirolimus in our cohort of patients.

Rotablation or rotational atherectomy has been practiced worldwide and standard protocols have been developed to improve the clinical outcomes of patients with calcified lesions. The new concept of a hybrid approach that combines the use of rotablation with a DEB adds to the pool of novel and beneficial interventional therapies for patients with calcified lesions.[7]

Although a strategy of hybrid rotational atherectomy and

Table 1. Drug-eluting balloons

Chemotherapeutic agent	*DEB type*	*Excipient/coating technique*
Pactixacel	SeQuen® Please	Lopromide matrix coating
	Pantera Lux	BTHC matrix coating
	IN.PACT Falcon	FreePac matrix coating
	DIOR	Shellac matrix coating
	Elutax	No excipient
	Lutonix	Polysorbate and sorbitol carriers
	Danubio	BTHC excipient
Sirolimus	Magic touch	

DEB, drug-eluting balloons; BTHC, butyryl-tri-hexyl citrate.

DEB is considered a viable alternative in patients with multiple co-morbidities and high risk for bleeding, data on effectiveness and safety are limited. There are no randomised, control trials comparing this strategy to conventional approaches, and the published observational experience consists predominantly of small, retrospective, single-centre cohorts.[2,8,9]

Given the paucity of available published data, we aimed to add to the information on effectiveness and safety of a hybrid approach to calcified lesions in a real-world setting by sharing our recent experience from a different geography and population. Important outcomes of interest included: (1) procedural success [defined as thrombolysis in myocardial infarction (TIMI) III flow with < 30% recoil]; (2) proportion of people not on DAPT beyond three months; (3) bleeding complications; (4) target-vessel restenosis.

Methods

The study was conducted using anonymised patient data from a high procedure-volume group cardiology practice in Johannesburg, South Africa between June 2015 and December 2018. The percutaneous procedures of interest were performed by one of two experienced interventional cardiologists.

This was a retrospective review of the patient records, files, angiograms and other available relevant material. Parameters included demographic, clinical (hypertension, diabetes and dyslipidaemia) and laboratory data, medication and angiographic data (Tables 2, 3). Consecutive adult patients who underwent a hybrid percutaneous intervention, defined as the combination of rotablation and DEB therapy for calcified lesions, in a minimum of one lesion were included in the analysis. Patients who did not have a complete set of procedural and follow-up date available for review were excluded.

Patients were given clopidogrel either prior to or post intervention. Ticagrelor and prasugrel were not used. Elective patients were only given intravenous heparin during the procedure to keep an activated clotting time level between 250 and 350 s. Enoxaparin 1 mg/kg bd subcutaneously was given for acute coronary syndrome patients unless the patients were on warfarin.

Rotablation was performed if the lesions were heavily calcified or uncrossable with a balloon. It was performed using the Rotablator (Boston Scientific, MN). The burr sizes ranged from 1.25 to 2.0 mm. The speed of the burr ranged between 170 000 and 180 000 rpm. Post rotablation, pre-dilatation of the lesion was performed with a semi-compliant balloon, non-compliant or cutting balloon for lesion optimisation and then followed with a DEB, which was inflated for 60 to 90 seconds at nominal pressures. The DEB was generally sized 1:1 per the vessel diameter and at least 2 mm longer on both sides of the lesion. The strategy in case of flow-limiting dissections (TIMI < 3) or significant recoil (> 30%) was to then use a DES. No bare-metal stents were used.

Table 2. Baseline characteristics of patients

Characteristics	*Number or mean*	*Percentage*
Number of patients	23	100
Age	73.7	
Male	18	78.3
Risk factors for CAD		
Diabetes	7	30.4
Hypertension	7	30.4
Dyslipidaemia	16	70
Smoking	3	13
Family history of CAD	3	13
Risk factors for bleeding		
Bleeding	3	13
Renal failure	8	35
Anticoagulation	6	26.1
Atrial fibrillation	3	13
Anaemia	12	52.2
Age > 80 years	8	34.8
EF < 50%	5	21.7
GFR < 15 ml/kg/min	2	8.7
GFR 16–29 ml/kg/min	1	4.3
GFR 30–59 ml/kg/min	6	26.1
GFR > 60 ml/kg/min	10	43.5

CAD, coronary artery disease; EF, ejection fraction; GFR, glomerular filtration rate.

Table 3. Procedure-related characteristics

Characteristics	*Number or mean*	*Percentage*
Access		
Femoral	20	87.0
Radial	3	13.0
Coronary artery rotablation and DEB		
Right coronary artery	6	26.1
Left anterior descending artery	10	43.5
Left circumflex artery	6	26.1
Ramus artery	3	13.0
Burr size (mm)		
1.25	14	60.9
1.5	6	26.1
1.75	8	34.8
DEB		
SeQuent® Please	15	65.2
IN.PACT	8	34.8
DEB diameter (mm)		
2.25	2	8.7
2.5	14	60.9
2.75	4	17.4
3.0	3	13.0
3.5	4	17.4
DEB length (mm)		
15	5	21.7
17	4	17.4
20	4	17.4
26	2	8.7
30	12	52.2
Cutting balloons	3	13.0
Stents in other vessels	15	65.2
DAPT < 3 months	6	26.1
MACE		
In-stent restenosis	2	8.7
Death	2	8.7

DEB, drug-eluting balloon; DAPT, dual antiplatelet therapy; MACE, major adverse cardiovascular events.

Results

There were 23 patients who had the rotablation and DEB strategy. The indication for the hybrid procedure was non-ST-segment myocardial infarction in 13 patients and unstable angina

in 10 patients. The average age was 74 years and 78.3% were males. The majority of patients were dyslipidaemic (78.3%) and hypertensive (74%); 30.4% were diabetic and 13% were smokers. Seven patients (30.4%) had a prior coronary artery bypass graft. The mean left ventricular ejection fraction was 52% and three (13%) patients had severe aortic stenosis (two patients had prior transcatheter aortic valve implantations and one had a prior balloon aortic valvuloplasty).

Risk factors for bleeding included chronic renal failure (35%), the use of oral anticoagulation (26%), atrial fibrillation (13%) and peptic ulcer disease (35%). The mean haemoglobin level was low, at 12.7 g/dl, and the mean creatinine level was raised, at 158 µmol/l, with an estimated glomerular filtration rate (eGFR) of 58 ml/kg/min. Mean total cholesterol was 4.4 mmol/l and the low-density lipoprotein cholesterol was 2.4 mmol/l.

The majority of the procedures were performed via the femoral route (87%) and 13% were performed radially. Cutting balloon was used in 13% of calcified plaques. The 1.25-mm burr was used in 61% of cases, followed by the 1.75-mm burr (35%) and the 1.5-mm burr (27%). The average length of DEB used was 37 mm. The DEB included SeQuent® Please (65%) and IN.PACT Falcon (35%). After the procedure, six patients received DAPT for a minimum of one month, 10 for six months, four for 12 months and one for longer than 12 months, and for two there were no follow up data. There were 15 patients who had stents inserted in other lesions.

Procedural success was reported in all 23 patients. Twenty of the 23 patients had follow-up information available at 24 months. Six patients (26%) were not on DAPT beyond three months and no patients had minor or major bleeding. Three patients underwent repeat coronary angiography for angina and two patients had evidence of target-vessel restenosis. Two patients died but the cause of death was not known.

Discussion

The strategy of DEB following rotablation is a relatively new concept. There were no published reports until the first study, which showed the safety and efficacy of percutaneous coronary intervention (PCI) using rotablation, followed by DEB in 2017.[2] The volume of published experience since then has been limited, therefore our small cohort study from South Africa adds to the global experience.

Our patients were elderly (mean age 74 years) and had significant risk factors for bleeding, including chronic renal failure (35%), the use of oral anticoaglation (26%) and peptic ulcer disease (35%). More than three-quarters of the patients had traditional risk factors such as hypertension and dyslipidaemia, and one-third were diabetic. The patients were also high risk in that a third had a prior coronary artery bypass graft. There were no minor or major bleeding episodes. Although the femoral approach was used in 87% of cases, the use of ultrasound guidance for femoral puncture proved to be a safe alternative to radial access.

The main findings from our retrospective patient review were that the procedure is feasible, that DAPT could be stopped by three months in a significant proportion (> 25%) of patients, that bleeding rates in this high-risk cohort over a 24-month period were extremely low, and that restenosis rates were acceptable.

DEBs have been used in current daily practice for in-stent restenosis (ISR), small-calibre vessels, bifurcation lesions, ostial lesions and undilatable lesions.[10-13] The BELLO study (Balloon Elution and Late Loss Optimization) was a randomised, multicentre study of small coronary vessels (< 2.8 mm), which showed that apaclitaxel DEB was associated with less angiographic late loss and similar rates of restenosis and revascularisation as a paclitaxel-eluting stent,[12] but more evidence is needed to compare DEB and newer-generation DES.

However, in a meta-analysis of over 5 000 patients looking at the most appropriate coronary PCI strategy, including sirolimus- and paclitaxel-eluting stents, DEBs, bare-metal stents and balloon angioplasty, sirolimus-eluting stents yielded the most favourable angiographic and clinical outcome for the treatment of small coronary arteries.[14] In our study, the 2.5-mm DEB and the 1.25-mm burr were used in 60.9% of patients in small-calibre vessels.

Restenosis rates of 30 to 40% after rotablation alone or following angioplasty alone were unacceptably high, which decreased to 23 to 43% following bare-metal stents.[15-17] There is a much more acceptable restenosis rate currently of one to 5% in the DES era. However the increased bleeding risk of being on DAPT suggests one should consider DEB.

Paclitaxel DEBs have been shown to be superior to balloon angioplasty for ISR in terms of major adverse cardiovascular events (MACE) and target-lesion revascularisation (TLR) for up to 36 months in a multicentre, randomised study, which showed that the multiple TLR was more frequent in the plain old balloon angioplasty (POBA) group, compared to the DEB group (13.2 vs 1.4%, $p = 0.021$). The MACE rate was significantly reduced in the DEB group compared to the POBA group (20.8 vs 52.6%, $p = 0.001$).[18]

The disadvantages of stent complications such as malapposition and under-expansion, delayed endothelialisation and chronic inflammation are eliminated with no permanent implant[4] and have led to new developments in the field of interventional cardiology. In our study, two patients (8.7%) had target-vessel restenosis. This restenosis rate was much lower than the POBA rates of 23 to 43% but higher than the DES restenosis rate of one to 5%.

Bioresorbable vascular scaffolds (BVS) have been developed with the attractive concept of resorbable material, avoiding the late complications of permanent metal scaffolds.[19] The BVS have been shown to be efficacious but due to definite stent thrombosis of 2.6% at 12 months, have not been shown to be superior to DES.[20] Recently, novel drug-eluting metal absorbable scaffolds consisting of absorbable magnesium scaffold backbones as an alternative to polymeric scaffolds have showed a favourable safety profile.[21] The polymer-free umirolimus stent has been shown to be superior to bare-metal stents in primary safety and primary endpoints in patients after one month of DAPT.[22] Further trials have also shown evidence to stop DAPT after one month in patients with high bleeding risk with zotarolimus stents.[23]

The attractive concept of stentless PCI has gained interest in the interventional cardiology community. Stentless PCI has been reported recently from Japan, which suggests that rotational atherectomy and DEB might be an alternative for patients who may be unsuitable for DES implantation.[9] Case reports of successful outcomes of patients with calcified diffuse lesions, patients with severe thrombocytopaenia and those with

chronic kidney disease, as well as patients with ostial lesions also recommend that one should consider this hybrid strategy.[9,24,25]

The study by Rissanen *et al*. enrolled 65 patients, who were followed for a period of 17 months; 82% of patients had at least one risk factor for bleeding. Risk factors in this study included anticoagulation (40%), anaemia (45%), active malignancy (1.5%), prior stroke (22%), severe renal dysfunction with an eGFR < 30 ml/kg/min (3%), age > 80 years (31%) and prior bleeding requiring intervention (25%). MACE occurred in 20% of patients at 24 months. The incidence of significant bleeding was 9% at 12 months.

This study, which was published in 2017, was the first to show that PCI using DEB after rotablation was safe and effective. Compared to our study, we had a similar elderly population with 34.8% aged > 80 years, fewer patients on anticoagulation (26.1%) and more with severe renal dysfunction (13%). More studies are needed to show the prevalence of rotablation and different novel ways to approach revascularisation in these patients with calcification and high risk of bleeding.

There were limitations to this study. This was a retrospective audit of files, which would limit one's acquisition of data and follow up. Patients were not routinely followed up with repeat coronary angiography, which could have affected the incidence of restenosis and new TLR.

Conclusion

The hybrid approach of rotablation and DEB is a novel approach in patients with coronary calcification and a bleeding risk. These patients are more commonly elderly male patients with renal failure. Bleeding risk can be reduced in these high-risk patients as DAPT could be stopped by three months in a significant proportion (> 25%) of patients. This study has also shown that bleeding rates in this high-risk cohort over a 24-month period was extremely low and that restenosis rates were acceptable. In our cohort, we have confirmed prior observations that the procedure of DEB following lesion preparation with rotational atherectomy is safe and effective for patients with a high risk of bleeding.

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Polypill plus aspirin reduces incidence of cardiovascular events by 31%: TIPS-3

Researchers have found that combined treatment with a polypill plus aspirin led to a 31% lower incidence of cardiovascular events than did placebo among participants without cardiovascular disease (CVD) who were at intermediate cardiovascular risk, according to the TIPS-3 study in the *New England Journal of Medicine* (NJEM).

No excess of major bleeding events was observed and the NEJM writes in an editorial that 'the findings of TIPS-3 support the inclusion of multi-drug therapy for cardiovascular disease prevention in the World Health Organisation "best buys" for non-communicable disease prevention and control as the lone health-system approach that is potentially highly cost-effective.'

The NEJM writes:
The polypill concept garnered substantial attention in 2003 after the publication of a modelling analysis that proposed that the use of fixed-dose combination therapy in persons with established atherosclerotic cardiovascular disease and in all other adults 55 years of age or older could reduce disease burden by 80% or more.

Notably, these models overestimated the effects of aspirin and folic acid and assumed full long-term adherence to the regimen. Subsequent randomised trials testing the effects of different polypills in small populations over short periods of time showed reductions in cholesterol level and blood pressure and increases in the percentages of participants adhering to the regimen in both primary-prevention and secondary-prevention settings. However, for primary prevention, concerns remained regarding the appropriateness of polypill components, including aspirin; the disadvantages of being unable to adjust the doses of individual drugs, potentially outweighing any benefits of a polypill approach; and the issue of medicalisation of healthy populations. Without data on clinical outcomes, debates about the polypill remained unresolved.

In 2019, the PolyIran cluster-randomised trial reported the first long-term outcomes of any polypill study in a largely primary-prevention population. Among 6 838 adults 50 to 75 years of age in Iran who were followed for a mean of five years, the polypill group had a 34% lower risk of major cardiovascular events than the group that received augmented usual care. This trial has now been closely followed by the publication in this issue of the Journal of TIPS-3 (the International Polycap Study 3). Among 2 850 intermediate-risk participants in nine countries who were followed for a mean of 4.6 years, those who had been randomly assigned to receive the polypill plus aspirin had a 31% lower risk of major cardiovascular events than those who had been randomly assigned to receive double placebo.

Some important unresolved questions remain. An excess of major bleeding events was not observed in the comparison of polypill plus aspirin with double placebo in TIPS-3 (or in the comparison of the aspirin-containing polypill with usual care in the PolyIran trial), but these analyses were probably underpowered for detecting significant harm. Furthermore, the bio-equivalence and long-term stability of polypill formulations should be shown. Finally, reasons for non-adherence to the polypill regimen due to preferences among physicians, patients, or both require further understanding.

Ischaemic heart disease and atherosclerotic stroke are among the leading causes of health loss globally. Yet, health systems either have not been sufficiently responsive or are unprepared to deliver equitable, high-quality primary care in cardiovascular disease prevention and control. The findings of TIPS-3 support the inclusion of multi-drug therapy for cardiovascular disease prevention in the World Health Organisation 'best buys' for non-communicable disease prevention and control as the lone health-system approach that is potentially highly cost-effective.

Other population-based strategies still need to be implemented urgently to achieve global goals. However, patients with atherosclerotic cardiovascular disease and persons who are at risk for atherosclerotic cardiovascular disease can also derive health benefits from pharmacotherapy, and therefore polypill therapy represents the most scalable intervention to date, given the totality of data.

Source: Medical Brief 2020

Nine-year, single-centre experience of left atrial appendage occlusion: patient characteristics, procedural outcomes and long-term follow up

Mark Abelson, Andre Phillips, Shirley Middlemost

Abstract

This is a review of 114 patients with atrial fibrillation who had left atrial appendage occlusion with an Amplatzer cardiac plug over a nine-year period done by a single operator. This shows that the procedure can be safely performed with a very low rate of major complications (< 1%) and a zero procedural mortality rate. Long-term follow up over an average of 38.5 months showed a 65% reduction in actual versus predicted stroke rate. This is similar to that seen with oral anti-coagulants and other published trials and registries involving left atrial appendage occlusion.

Keywords: atrial fibrillation, left atrial appendage occlusion, Amplatzer cardiac plug, Amulet

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Left atrial appendage occlusion (LAAO) is a treatment option for stroke prevention in patients with permanent or paroxysmal atrial fibrillation (AF) who have a $CHADS_2$-VASc score > 2 and have either contra-indications for oral anticoagulant therapy (OACT) or decline such therapy. Current European Society of Cardiology (ESC) guidelines have LAAO as a class 2b recommendation.[1] This study is a registry of LAAO done at MediClinic Vergelegen, Somerset West, South Africa, by a single operator from November 2010 to 31 March 2020.

Methods

All patients were prospectively entered into a database after informed consent was obtained. Patient follow up to 31 March 2020 was done either at a recent out-patient examination or telephonically. Those patients who were lost to follow up by 31 March 2020 were excluded.

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The first patient was enrolled in mid-November 2010. All patients, except two who had a Watchman device (Boston Scientific) implanted, had an Amplatzer (Abbott Vascular) device implanted. The first 40 patients received the Amplatzer cardiac plug (ACP I) and thereafter the Amulet device (ACP II).

All procedures were done under general anaesthetic with trans-oesophageal echocardiogram (TOE) guidance by one of only two TOE operators. Almost all patients had no pre-procedural TOE to look for left atrial appendage (LAA) thrombus and anatomical suitability for device-based occlusion. If patients were on OACT, this was stopped a few days earlier.

Following trans-septal puncture using TOE guidance, a heparin bolus was given intravenously (IV) to raise the activated clotting time to more than 250 seconds. All patients were loaded with a minimum of a litre of intravenous fluid prior to device sizing to raise LAA pressure to greater than 15 mmHg. Device sizing was initially determined by a combination of TOE and LAA angiogram measurements, and more recently a pre-procedural cardiac computed tomography (CT) was added to these measurements to help improve initial choice of device size.

The device was deployed in the usual manner via a 12- or 14-F angled delivery sheath depending on the device size required. The right femoral vein access site was closed routinely with a Perclose 6-F suture device. Some patients required an additional superficial skin suture due to persistent wound oozing. Heparin was reversed with IV protamine in order to reduce any bleeding risks.

As soon as the patients were awake and able to swallow, aspirin 300 mg and clopidogrel 600 mg oral loading doses were given. Patients were observed in cardiac high care overnight and were discharged home the next day following trans-thoracic echocardiogram (TTE) confirming the LAA device was *in situ* and there was no pericardial effusion. All patients were discharged on aspirin 75–100 mg and clopidogrel 75 mg daily unless contra-indicated.

All patients were seen at 30 days' follow up for TTE to confirm the device was *in situ*. Clopidogrel was stopped at one month and aspirin alone was continued indefinitely if there were no contra-indications. Thereafter, patients were either seen routinely on a six- or 12-month basis by the operator or referred back to the referring physician. No patients had a routine post-procedural TOE at follow up.

Results

A total of 131 patients were admitted to the cardiac catheterisation theatre for LAAO device implantation and 122 (93%) had a successful device implantation over the 112 months. In nine patients, the procedure was abandoned due to the presence of an LAA thrombus, inability to pass the TOE probe, the LAA

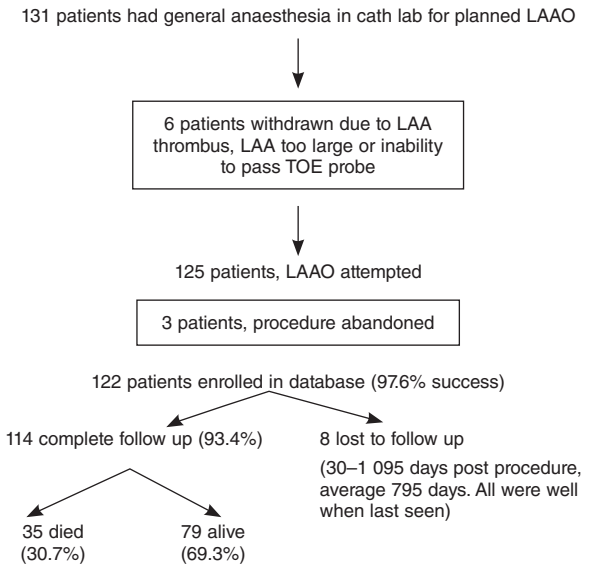

Fig. 1. Patients enrolled.

was too large for the largest available device, or the anatomy was deemed unsuitable to safely release the device. In only three cases was a device actually opened and not deployed, giving an implant success rate of 97.6% (122/125).

Eight patients were lost to follow up between 30 days and three years post procedure. The remaining 114 patients were followed up to the end of March 2020 or had died, giving complete data on 93.4% of patients who had had a device implanted (Fig. 1).

The average age of patients was 74.2 years (range 51–87; SD 8.1; median 75) and the average length of follow up was 38.5 months (range 1.2–111.5 months; SD 26.8; median 35.7); 75% were male. The average $CHADS_2$-VASc score was 3.9 (SD 1.2; median 4) and HAS-BLED score was 2.99 (SD 0.95; median 3) (Table 1).

In 71% (81) of patients, OACT was contra-indicated due to a previous life-threatening bleed, while 9% (10) had a high bleeding risk (HAS-BLED score > 3). In 20% (23) of patients, LAAO was indicated due to a combination of frailty not measured on HAS-BLED, repeated falls or lifestyle choice. Previous stroke or transient ischaemic attack (TIA) had occurred in 23% (26) of patients (Table 1).

There was one major complication (< 1%). An Amulet device embolised to the descending aorta shortly after its release and was successfully removed percutaneously via the right femoral artery. However, the patient did sustain radiation burns due to the complexity of retrieving the device. There were no deaths, pericardial effusions requiring aspiration or strokes.

There were nine minor complications, including one pericardial effusion seen at seven days, which was treated conservatively as the patient was haemodynamically stable with no evidence clinically or on TTE of cardiac tamponade. Seven patients had a minor bleed from the femoral vein puncture site that required a superficial skin suture to be placed post procedure. One patient had a TIA during a difficult procedure due to very awkward anatomy of the LAA. The procedure was eventually abandoned as the anatomy was deemed unsuitable for LAA closure (Table 2).

There were no significant leaks (> 5 mm) past the device. If a significant leak was seen on either TOE or left atrium angiogram immediately after device deployment, the device was either redeployed in a different position or the device size was changed. There were 14 (11%) device size changes.

One hundred and twenty patients (96%) were discharged on dual antiplatelet therapy (DAPT) for one month, and thereafter reduced to low-dose aspirin only. Five patients were discharged on aspirin only. The average length of hospital stay was 1.1 days (one to six days).

A total of 35 (30.7%) patients died during the follow-up study period (average of 2.5 years post procedure), ranging from 96 days post procedure (primary amyloidosis not previously diagnosed) to 2 700 days (seven years five months at the age of 86 years). There were six strokes (5.3% of total or 1.7% per year). The average CHADS-VASc score was 4, and four patients died due to the stroke or consequences thereof. The majority of patients died from cardiovascular causes (heart failure, myocardial infarction, sudden cardiac death), cancer, renal failure and complications arising from a fall. Three patients had a TIA.

There were 10 major bleeding events (8% or 2.8% per year). Two occurred while on DAPT soon after the procedure, resulting in the withdrawal of clopidogrel, while eight occurred while on aspirin only, resulting in cessation of all antiplatelet therapy. In

Table 1. Patient characteristics (n = 131)

Characteristics	*Values*
Age (years) (range, SD, mean)	74.2 (51–87, 8.1, 75)
Male:female (%)	75:25
$CHADS_2$-VASc score (SD, median)	3.9 (1.2, 4)
HAS-BLED score (SD, median)	2.99 (0.95, 3)
Previous stroke/TIA (%)	23
Previous major bleed (%)	71
High bleeding risk (HAS-BLED > 3) (%)	9
Frail, falls, lifestyle choice (%)	20

TIA: transient ischaemic attack.

Table 2. Adverse outcomes up to seven days post procedure (n = 125 patients)

Adverse outcomes	*Number (%)*
Major	
Death	0
Cardiac tamponade	0
Stroke	0
Device embolisation	1 (0.8)
Vascular injury	0
Bleed	0
Minor	
Transient ischaemic attack	1 (0.8)
Bleed – groin puncture site	7 (5.6)
Pericardial effusion (not treated)	1 (0.8)

Table 3. Long-term outcomes (n = 114 patients)

Long-term outcomes	*Total number*	*Total % (% per year)*
Death	35	30.7
Stroke	6	5.3 (1.7)
Major bleed	10	8 (2.8)
Single antiplatelet agent at last follow up	94	82.5
No antiplatelet agent at last follow up	17	14.9

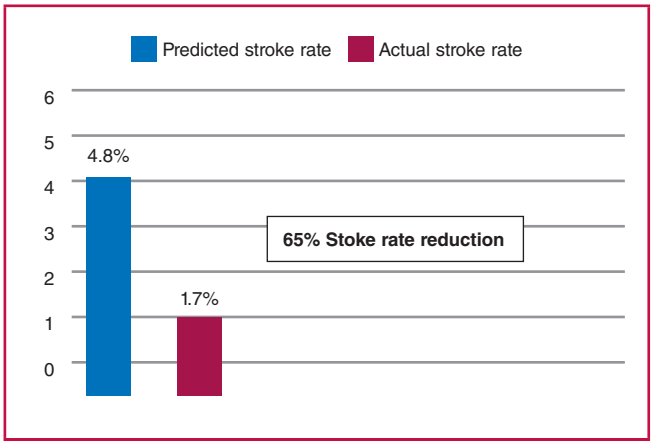

Fig. 2. Observed versus predicted stroke rate per year ($CHADS_2$-VASc score 3.9).

total, 17 patients (14.9%) were on no antiplatelet therapy at long-term follow up. None of these patients had an embolic event. At the last follow up, 97.4% of the patients were on single (82.5%) or no antiplatelet therapy (14.9%) (Table 3).

Discussion

This single-centre registry of LAAO using almost exclusively the Amulet device is in line with previously published registries of LAAO but has a longer period of follow up than most registries and trials.[2-8]

The indications for LAAO, age of the patients, and $CHADS_2$-VASc and HAS-BLED scores are very similar to other registries. Currently, almost all patients receiving LAAO have a relative or absolute contra-indication for OACT, with very few patients either refusing OACT or not having it because of a lifestyle choice due to high-risk activities. The current 2016 ESC guidelines list LAAO as a class 2b indication procedure.[1]

There were six strokes (stroke incidence 5.3%; 1.7% per year) documented during follow up, with four fatalities (Fig. 2). These occurred between six months and four years after LAAO implantation (average 2.6 years). All these patients were on low-dose aspirin only at the time of the stroke. The predicted stroke rate per year according to a $CHADS_2$-VASc score of 3.9 is 4.8%. This represents a 65% stroke risk reduction. This is in keeping with other published registries and trials on LAAO showing equivalence with warfarin[2-8] and the newer direct OACT.[16,17] There were three TIAs and no other documented thrombo-embolic (TE) events. (TE incidence was 7.9%; 2.5% per year). The predicted TE risk was 6.7%, equating to a 63% risk reduction.

There was no routine use of TOE at six to 12 weeks post device implant as there is currently no clear evidence linking the presence of device-related thrombus (DRT) and systemic embolic events.[14,15] Furthermore, starting patients on OACT to manage DRT carries significant risk in this particular group of patients in whom OACT was contra-indicated in over 80% of patients.

Only two of the six stroke patients were managed at our hospital. Both had a TOE post stroke. No DRT was seen in either patient. One patient who presented with a small stroke at three months post LAAO implantation was subsequently found to have a severe ipsilateral internal carotid artery stenosis, which was successfully stented. A year later, he suffered a further small stroke and TOE showed the Amulet device had shifted slightly and was partially protruding from the LAA orifice. Although no DRT was seen, the patient was started on lifelong OACT and remained well three years later.

A further patient who had a TIA a year post LAAO was found to have a significant patent foramen ovale (PFO) on TOE. There was no device-related thrombus, and the device was well seated and fully endothelialised. The PFO was subsequently closed percutaneously.

The overall mortality rate was 30.7%, however, this is not unexpected for this population of patients with AF who were elderly (average age 74 years; SD 8.1), had multiple co-morbidities ($CHADS_2$-VASc 3.9), and were followed up for a prolonged period of time (3.2 years; SD 2.17). The expected mortality rate in patients with AF is two to four times higher than the average population and worsens as the $CHADS_2$-VASc score increases.[9-13] The majority of patients died from cardiovascular causes or malignancy, which is in keeping with reported literature.

Limitations of this study include a single-centre, single-operator registry with a limited number of patients enrolled. Eight patients were lost to follow up and were not included in this registry. Not all patients were followed up by the operator and it is possible some embolic events were not reported.

Conclusion

This single-centre registry showing follow up over a prolonged period of time confirms the efficacy of LAAO as an acceptable alternative to OACT.

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Erratum

Relationship between physical activity and carotid intima–media thickness among teachers in South Africa: the SABPA study by Tamrin Veldsman, Mariette Swanepoel, Andries Monyeki, Sanette Brits, Leoné Malan, published in the *Cardiovascular Journal of Africa* 2020; **31**(6): 304–318.

DOI: 10.5830/CVJA-2020-024

In the Abstract, in Methods:

Ultrasound CIMT imaging was done using the SonoSite Micromaxx. Physical activity was done over seven consecutive days.

In the Abstract, in Results:

The prevalence of obesity according to BMI and sedentary behaviour was above 30%; hypertension was 38.9% and low-grade inflammation (CRP) was 41.1%.

Ethiopia Country Report

PASCAR and WHF Cardiovascular Diseases Scorecard project

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Abstract

Data collected for the World Heart Federation's Scorecard project regarding the current state of cardiovascular disease prevention, control and management, along with related non-communicable diseases in Ethiopia are presented. Furthermore, the strengths, threats, weaknesses and priorities identified from these data are highlighted in concurrence with related sections in the accompanying infographic. Information was collected using open-source data sets from the World Bank, the World Health Organization, the Institute for Health Metrics and Evaluation, the International Diabetes Federation and relevant government publications.

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On behalf of the World Heart Federation (WHF), the Pan-African Society of Cardiology (PASCAR) co-ordinated data collection and reporting for the country-level Cardiovascular Diseases Scorecard to be used in Africa.[1-3] Ethiopia, with assistance from the Society of Cardiac Professionals in Ethiopia (Ethiopian professional society) and non-communicable diseases (NCD) advisors/experts at the Ministry of Health of Ethiopia, was included as one of the countries to collate and verify the data. In this report, we summarise Ethiopia's strengths, threats, weaknesses and priorities identified from the collected data, along with needs to be considered in conjunction with the associated sections in the accompanying infographic. Data sets that were used included open-source data from the World Bank, the World Health Organization (WHO), the Institute for Health Metrics and Evaluation, the International Diabetes Federation (IDF) and government publications.

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Part A: Demographics

According to the World Bank (2018), Ethiopia is a low-income country (LIC) with 79% of its people living in rural areas.[4] In 2015, almost 30.8% of the population was living below the US$1.9-a-day ratio. Life expectancy at birth in 2018 was 64 and 68 years for men and women, respectively. The general government health expenditure was 1.4% of the gross domestic product (GDP), with the total health expenditure as a percentage of the GDP remaining stable and decreasing slightly to 4.2% in 2016/17.[5] The total expenditure on health in 2016/17 was US$3 102 527 667, while that on NCD was US$344.67 million.[5] The total expenditure on NCD as a percentage of health expenditure is 11.11%, of which 50.4% is government expenditure.[5] The country's GDP per capita was US$857.5 in 2019.[6]

Part B: National cardiovascular disease epidemic

The national burden of cardiovascular disease (CVD) and NCD risk factors

In 2017, the number of people affected by CVD in Ethiopia was 2 838 767.[7] One-third (33.7%) of these cases was rheumatic heart disease (RHD), followed by ischaemic heart diseases (IHD) (22.5%) and stroke (11.4%).[7] The estimated age-standardised mortality rate for Ethiopia in 2017 was 519/100 000 [95% uncertainty intervals (UI): 479–551] of the population, of which CVD was 182/100 000 (95% UI: 165–204).[7] Currently, IHD (45%), stroke (34%) and hypertensive heart disease (HHD) (11%) are the three leading causes of CVD deaths in Ethiopia, with about 170 Ethiopians dying each day.[8] Diet and systolic blood pressure (SBP) were the most predominant risk factors for CVD, accounting for over 50% of CVD-related disability-adjusted life years (DALYs), followed by air pollution.[7]

The trend in CVD-related death rate (age standardised) in Ethiopia is consistent with that of Kenya, Tanzania and Uganda, however, the prevalence is consistent with Tanzania

but lower than Kenya and Uganda.[9] In comparison to the neighbouring country, Sudan, and the other African countries under investigation, Ethiopia's premature deaths attributable to CVD (30–70 years old) is the lowest, at 6%.[10] In 2017, the age-standardised total CVD death rate was 10.9%, which is lower than the global rate of 31.8%.[9] The percentage of DALYs resulting from CVD for men was 4.2% and for women 4.0%. The total RHD mortality rate was 0.2% of all deaths, while the prevalence of RHD was 1.0%.[9] In a study by Yadeta *et al.*,[11] a prevalence of 1.4% was found, while in rural Ethiopia, an even higher RHD prevalence was reported (37.5/1 000 of the population).[12] The prevalence of atrial fibrillation (AF) and atrial flutter was 0.1% (Table 1).[9]

Tobacco and alcohol

In 2016, the prevalence of tobacco use in adult men 15 years and older was 8.1%, while fewer adult women (1.8%) smoked, as reported in the Global Adult Tobacco Survey (GATS).[6] Data from the WHO survey, STEPS (step-wise survey for NCD risk factors), revealed 7.3 and 0.4% of men and women, 15–69 years old, respectively, made use of this habit.[13] In Ethiopia, the smoking prevalence for the youth (15 years median age) was 4.5% among boys and 1% in girls.[14] No data were available for the estimated annual direct cost of tobacco use.[6] The premature CVD mortality rate attributable to tobacco is 2% of the total mortality rate, which is much lower than the global 10%.[15] The three-year (2016–18) average recorded alcohol consumption per capita (≥ 15 years) was 0.9 litres (Table 1).[6]

Raised blood pressure and cholesterol

In 2015, the percentage of men and women, 18 years and older, with raised blood pressure (BP) (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) was 28.8 and 31.7%, respectively.[6] STEPS data provided a much lower prevalence of 15.5% for men and 16.3% for women, which possibly differed because of the different age range and sample size.[13,16] The percentage of DALYs lost because of hypertension was 2.2%, whereas the mortality rate caused by HHD was 1.1% in 2017 (Table 1).[9] In 2015, the total cholesterol (TC) prevalence measured 5.2% in adults, 15–69 years old, with more women than men (6.8 vs 3.9%, respectively) having a raised TC (≥ 5.0 mmol/l).[16]

Physical activity

No data were available for adolescents, 11–17 years old, who were insufficiently active [< 60 minutes of moderate- to vigorous-intensity physical activity (PA) daily]. For adults, however, the age-standardised estimate was 14.9% of those who were insufficiently active (< 150 minutes of moderate-intensity PA per week, or < 75 minutes of vigorous-intensity PA per week) in

Table 1. Cardiovascular disease indicators for Ethiopia

Indicators	*Male*	*Female*	*Total*	*Year*
Status of the national CVD epidemic				
Premature CVD mortality (30–70 years old) (% deaths)	–	–	6	2012
Total CVD mortality (% of deaths)	10.5	11.6	10.9 (31.8)*	2017
Total RHD mortality (% of deaths)	0.2	0.2	0.2 (.5)*	2017
DALYs attributable to CVD (%)	4.2	4.0	4.1 (14.7)*	2017
AF and atrial flutter (%)	0.1	0.1	0.1 (.5)*	2017
Prevalence of RHD (%)**	0.6	0.8	1.4 (.5)*	2016
Tobacco and alcohol				
Prevalence of adult tobacco use (≥ 15 years old) (%)#	8.1 (36.1)##	1.8 (6.8)##	5.0	2016
Prevalence of youth (13–15-year-olds) tobacco use (%)	4.5 (18.2)##	1.0 (8.3)##		2007
Estimated direct (healthcare-related) cost of tobacco use in the population (current US$)			–	2018
Proportion of premature CVD mortality attributable to tobacco (%)	–	–	2 (10)*	2004
Recorded alcohol consumption per capita (≥ 15 years) (in litres of pure alcohol) (three-year average)			0.9	2016–18
Raised blood pressure and cholesterol				
Population with raised BP (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) (%)δ	15.5 (24.1)*	16.3 (20.1)*	15.8 (22.1)*	2015
Population with raised TC (≥ 5.0 mmol/l) (%)δ	3.9	6.8	5.2 (38.9)##	2015
DALYs attributable to hypertension (%)	2.1	2.3	2.2 (8.7)*	2017
Mortality caused by HHD (% of deaths)	0.7	1.7	1.1 (1.7)*	2017
Physical activity				
Adolescents (11–17 years old) who are insufficiently active (< 60 minutes of moderate- to vigorous-intensity PA daily) (%)	–	–	(80.7)##	2010
Adults (age-standardised estimate) who are insufficiently active (< 150 minutes of moderate-intensity PA per week, or < 75 minutes of vigorous-intensity PA per week) (%)	11.3	18.3	14.9 (27.5)##	2016
Overweight and obesity				
Adults who are overweight (BMI ≥ 25–< 30 kg/m^2) (%)	13.4	28.0	20.9 (38.9)##	2016
Prevalence of obesity (BMI ≥ 30 kg/m^2) (%)	1.9	6.9	4.5 (13.1)##	2016
Diabetes				
Defined population with fasting glucose ≥ 126 mg/dl (7.0 mmol/l) or on medication for raised blood glucose (age standardised) (%)	5.8 (9)*	5.0 (8)*	–	2014
Prevalence of diabetes (20–79 years old) (%)	–	–	4.3 (9.3)δδ	2019

CVD, cardiovascular disease; RHD, rheumatic heart disease; DALYs, disability-adjusted life years; AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HHD, hypertensive heart disease; PA, physical activity; BMI, body mass index.
*IHME Global data exchange;[9] **Yadeta *et al.*;[11] #Global Adult Tobacco Survey; ##WHO GHO data;[6] δGebreyes *et al.*;[16] δδ*IDF Diabetes Atlas*.[18]

2016 (Table 1).[6] In the 2015 STEP survey, 4% of men and 7.9% of women were reported to be physically inactive, with an overall prevalence of 5.8%.[13]

Overweight and obesity

In 2016, the prevalence of overweight [body mass index (BMI) ≥ 25–< 30 kg/m^2] and obesity (BMI ≥ 30 kg/m^2) in adults 25 years and older was 20.9 and 4.5%, respectively (Table 1).[6] Women had a higher prevalence (28%) of overweight than men (13.4%), with a similar pattern for obesity (6.9 vs 1.9% in women and men, respectively). According to STEPS data, far fewer men (4.4%) and women (8.8%) were found to be overweight, while only 1.2% of these adults had a BMI ≥ 30 kg/m^2.[13,17]

Diabetes

The percentage of the population defined with a fasting glucose level of ≥ 7.0 mmol/l or on medication for raised blood glucose (age standardised) in 2014 was 5.8% for men and 5.0% for women.[6] In 2019, the age-adjusted prevalence (adults 20–79 years) of diabetes was 4.3%, which is lower than the global prevalence of 9.3% (Table 1).[18] Adults aged 15–69 years old who participated in the 2015 STEP survey had a higher diabetes rate of 5.8% using WHO criteria, and 3.2% according to criteria of the American Diabetes Association.[16,17] In their article of the STEP survey on NCD risk factors, Gebreyes *et al.*[16] reported 9.1% of the participants had impaired fasting glucose levels (IFG 100–125 mg/dl = 5.55–6.94 mmol/l) according to IDF criteria, whereas, per WHO criteria, only 3.8% had intermediate hyperglycaemia. Of these participants, 8.8% were men and 9.6% women, with 10.4% living in urban and 8.9% in rural areas. An increase in IFG from 9.1 to 12.1% was observed in the age groups 15–24 years and ≥ 65 years, respectively, while those 25–34 years old had the lowest prevalence (7.8%).

Part C: Clinical practice and guidelines

Health system capacity and guidelines for NCD risk factors

Ethiopia had an average of 0.8 physicians and 7.14 nurses per 10 000 of the population in 2018, and three hospital beds per 10 000 people in 2015.[6] In 2017, a locally relevant clinical tool to assess CVD risk had been partially developed.[19] Ethiopia was one of the lower-income countries to participate in the REMEDY study that reported a hospital-based registry for RHD and rheumatic fever.[20] Locally relevant clinical guidelines for the management of acute rheumatic fever (ARF) and RHD have been implemented.[21] In 2016, guidelines were developed to address AF, pharyngitis, ARF and RHD.[22] Guidelines for the treatment of tobacco dependence and a system to measure the quality of care provided to people who have suffered acute cardiac events had been noted in 2016.[22,23] Similarly, guidelines for the detection and management of diabetes are available.[22]

Essential medicines and interventions

Data on drug availability from a survey in September 2017 revealed Ethiopia had five of the eight essential medicines available at primary-care facilities in the public health sector.[24] These were aspirin (23.08%), angiotensin converting enzyme (ACE) inhibitors (46.15%), β-blockers (19.23%), metformin (38.46%) and insulin (7.69% short acting; 11.54% intermediate acting). However, insulin is possibly only available at primary hospitals (Gebremichael, pers commun). Statins were only available at 4% of Ethiopian health facilities.[25] According to the revised National Essential Medicine List, warfarin and clopidogrel were available.[26] National guidelines are available for CVD risk stratification at the primary healthcare level, however, TC measurement is only done at the secondary and tertiary levels.[22] Secondary prevention of ARF and RHD is available in public-sector health facilities.[27,28]

Secondary prevention and management

In a single study in Bedele town in south-west Ethiopia, 11.0% of hypertensive persons received medical treatment in 2014.[29] Among identified cases with hypertension in the STEP survey, only 2.8% received treatment, which is lower than that reported for other LICs.[16] In a study by Yadeta *et al.*,[30] 76.1% of high-risk patients with AF were being treated with oral anticoagulants (OAC) in 2016. In another hospital-based study on AF patients attending the cardiac clinic in 2019, 66% received OAC.[31] Using the stroke risk-stratification CHA_2DS_2-VASc score, about 70% of participants with AF (4.3%) were identified to take OAC in a community-based cross-sectional study in south-west Ethiopia.[32] However, these studies do not represent national data, as information regarding AF prevalence is scarce.[32] The percentage of people with a history of CVD taking aspirin, statin and at least one antihypertensive agent is unknown.

Part D: Cardiovascular disease governance

In 2010, the Federal Ministry of Health (FMoH) developed a national strategic framework through the Health Sector Development Program IV (HSDP IV) addressing NCD, while previous HSDPs paid little or no attention to the prevention and control of NCD and their risk factors.[33] The development of a detailed national strategic action plan (NSAP) was recommended, which was drawn up and published in 2014.[34] The strategic plan, specifically, the Health Sector Transformation Plan (HSTP),[35] has recently been revised and endorsed in 2020.[36] For implementing the NSAP, there is a budget and a unit in the national MoH.[34,37] There is a CVD focal point within the NCD unit of the MoH. Furthermore, a national surveillance system that includes CVD and their risk factors has been implemented.[17] A national tobacco-control strategic plan has been launched, along with a multi-sectoral co-ordination mechanism.[19] Collaborative projects between the MoH and non-governmental organisations and Addis Ababa University for CVD interventions have been reported.[38] Non-governmental expenditure on major NCD is to a certain extent allocated to CVD healthcare,[35] and the benefits of CVD prevention and control for population health and the economy have been modelled.[39,40]

Assessment of policy response

No legislation exists that mandates health financing for CVD or any specific diseases, as the healthcare financing strategy

is comprehensive and integrated.[28,37] Although legislation mandating essential CVD medicines at affordable prices have been introduced, these medicines are available at 30 to 40% of health centres in the primary healthcare level, with interruptions being common.[25,38] Court orders protecting patients' rights and mandating improved CVD interventions, facilities, health-system procedures or resources were also not available.

In February 2019, the strongest tobacco-control legislation in Africa was passed in Ethiopia, covering at least four of the WHO framework convention on tobacco control (FCTC) articles.[41,42] These are articles 8 (protection from exposure to tobacco smoke, including banning smoking in indoor work and public places), 11 (packaging and labelling of tobacco products), 13 (tobacco advertising, promotion and sponsorship) and 16 (sales to and by minors).[41]

Policies ensuring equitable nationwide access to healthcare professionals and facilities have been implemented,[43] whereas screening of high-risk CVD individuals has been suggested.[44] Currently, a CVD risk-prediction module is being developed, and a CVD risk-prediction chart will soon be adopted (Gebremichael, pers commun). No sustainable funding for CVD from so-called 'sin' taxes was noted. In 2008, the percentage of excise tax on sugar-sweetened beverages was 30%, while that of the final consumer price of tobacco and alcohol products was 75%.[45] Parliament recently endorsed a proclamation for increasing excise taxes on alcohol and tobacco products [30% *ad valorem* plus US$0.25 (8 ETB) specific excise tax for cigarettes].[46,47]

No legislation is available banning the marketing of unhealthy foods to minors or mandating clear and visible warnings on unhealthy foods.[22] However, policy interventions by the Ethiopian Food and Drug Administration (EFDA) and MoH (sugar, salt, trans fats and saturated fats) are under development for promoting a diet to reduce CVD risk.[46]

Stakeholder action

As part of the HSDP IV, initiatives were formulated to implement an integrated approach for the prevention and control of NCD through the advocacy of risk factors such as smoking, diet and PA.[33] Advocacy for CVD policies and programmes by non-governmental organisations was addressed by the NCD Alliance, and particularly, the Consortium of Ethiopian NCD Associations (CENDA).[48] More recently, Ethiopia established the NCD and Injuries (NCDI) commission that was tasked with reviewing the NCDI situation and produced a report in 2018.[49] This report forms the basis for the NCD initiatives and advocacy campaigns in the country, which extensively contributes to curbing these diseases.[49] Health professionals at six universities have been working with the FMoH on raising awareness and training health workers on RHD since 2016 through a project, Improving RHD Care in Ethiopia.[50] Patient engagement groups for RHD are also in progress, as indicated in a study by Yadeta *et al*.[30]

In 2019, the WHO and the inter-agency task force on NCD conducted an investment case study for NCD and risk factors for NCD in Ethiopia, recommending that an effective multi-sectoral co-ordination mechanism be developed involving various partners.[49] Until now, the only involvement that has been invested is in the national tobacco-control plan.[19] The MoH is working with different professional societies such as the Ethiopian Society of Cardiac Professionals on developing guidelines, raising community awareness and training health workers.[51] In a study on civil servants, hypertension screening by businesses at workplaces was suggested, and a repeated call was made in 2019 to curb the high prevalence.[52,53]

The FMoH introduced an integrated management package for diabetes and hypertension at health centres and hospitals throughout the country.[54] Currently, about 691 health facilities are implementing PACK [maintained by Population Services International (PSI)-Ethiopia, with support from HHA (Healthy Heart Africa), CUAMM (*Collegio Universitario Aspiranti Medici Missionari*) with funding from the World Diabetes Federation (WDF); and the Tropical Health and Education Trust (UK-based, often DFID-funded NGO), with support from Novartis and Vital Strategies/Resolve to Save Lives].[54] The country has adopted the South African PACK global programme and developed the Ethiopian primary healthcare guidelines, which is currently implemented in more than 500 health centres, with NCD care adequately addressed.

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

Strengths

Through the HSDP IV and HSTP, Ethiopia has outlined strategies to combat the growing incidence of NCD, of which CVD ranks the highest.[33] An NCD unit was established to co-ordinate national NCD prevention and control activities, including the development of protocols for each of the main NCD, such as CVD, diabetes, asthma and cancer, along with identifying essential services for each of these.[34]

To improve data usage at all levels of the healthcare system, Ethiopia launched an information revolution strategy. The FMoH has one autonomous regulatory body to enforce regulations on harmful products such as tobacco, alcohol and an unhealthy diet.[43] This body, the EFDA, is funded by the FMoH, issues licenses and monitors all professionals and facilities in the public and private sector.[43]

The government has an NCD interest within the FMoH that is included in the HSDP IV and HSTP I.[33,35] Community-based health insurance coverage includes services for NCD prevention and treatment for the rural people and informal sector, which is relatively active although coverage and sustainability are still uncertain.[34] The other scheme, social health insurance for the formal sector, is pending because of refusal by this sector, while disease surveillance systems at national and sub-national levels strengthen NCD management.[34]

Guidelines to reduce the incidence of CVD and other related NCD, such as hypertension and RHD, have already been developed and are being implemented.[22] National guidelines to treat tobacco dependence are integrated within the national guidelines for clinical and programmatic management of NCD, and training manuals on healthy lifestyle counselling (including tobacco cessation) have been developed for primary healthcare workers.[22] Ethiopia has developed and launched a national tobacco-control strategic plan, although the smoking prevalence is relatively low.[19] Ethiopia, a LIC, also participated in the REMEDY study, a prospective, international, multi-centre, hospital-based registry for RHD.[20] Through the project, Improving RHD Care in Ethiopia, with support from the Minneapolis Heart Foundation and other donors, improved registration of cases, training of health workers

and awareness and advocacy of RHD are happening.[50] A national surveillance system (the STEP survey) that includes risk factors for CVD has also been undertaken and a report disseminated.[17]

According to the WHO FCTC, civil society is mainly responsible for advocacy for the development and enforcement of tobacco-control laws.[19] The implementation or enforcement of a national tobacco-control plan is the responsibility of government entities such as the EFDA, and excise tax is charged.[19] In February 2019, the Ethiopian parliament passed a new law on tobacco products, which claims to be 'one of the strongest tobacco-control legislations in Africa.'[41] Among other things, this new law will require work and public places to be tobacco free.[41] Legislation mandating essential CVD medicines at affordable prices has also been implemented.[38]

In summary, the strengths of the NCD programme in general and CVD in particular include:

- evolving interest and commitment of the FMoH and regional health bureaus on prevention and control of CVD
- an NCD agenda (including CVD) incorporated within the HSTP I and II
- strategic and annual plans regularly being developed on NCD (including CVD)
- guidelines, training materials and client and provider education materials developed on CVD
- awareness-raising campaigns being conducted, though not in a structured manner
- NCD issues (including CVD) integrated into the health-extension programme
- NCD programme (including CVD) integrated into the Ethiopian primary healthcare guideline
- national STEPS on NCD risk factors and GATS conducted and results launched
- national NCDI commission produced a report on NCDI situation and developed recommendations and cost-effective CVD interventions
- NCD investment case report produced by WHO and inter-agency task force on NCD (including CVD).

Threats

In 2008 the FMoH, and in 2014 the WHO Regional Office, showed that NCD such as CVD, diabetes mellitus and cancer were contributors to the high level of mortality and morbidity.[33,55] Other increasing threatening risk factors are raised BP, unhealthy diets, air pollution, high low-density lipoprotein cholesterol levels, high fasting plasma glucose levels, overweight, physical inactivity and tobacco use.[7,55] In 2017, CVD accounted for almost 11% of the mortality rate,[9] while the diabetes prevalence among 15- to 69-year-old adults was 5.8% in 2015, which is higher than the 4.3% recently reported for the country by the IDF.[13,18] The prevalence of raised BP in Ethiopia for men and women is higher than that of the global data (22.1%) and most of the other sub-Saharan countries included in this project.[6] Although slightly lower compared to the global figure (1.65%), deaths caused by HHD were 1.1% in 2017.[9]

As mentioned, overweight and obesity, as in most African countries, tend to be a problem, although these figures are lower than the global data at 38.9 and 13.1%, respectively.[6] Less than 15% of the adult population is insufficiently physically active.[6]

As per the NSAP/HSTP-II 2020–2025,[36] the following threats have been identified by the core committee:

- unregulated transnational (global) trade leading to imported products and behaviours
- proliferation of industrial/commercial food processing and brewery
- globalisation with resultant lifestyle changes (smoking, alcohol, physical inactivity, foods with added salt, sugar and saturated or trans fats)
- poor health-seeking behaviour among the public
- economic gain by the government from the booming industry, which predisposes to NCD risk factors (alcohol, khat, soft drinks)
- rapidly expanding urban centres and industries related to urbanisation.

Weaknesses

In Ethiopia, no comprehensive, nationally representative study had been done before the nationwide step-wise survey in 2014,[55] however, raised BP was found to be the most prevalent CVD risk factor in a few urban and rural studies.[22] Data on NCD and their risk factors were lacking, while there is also a lack of comprehensive management at health facilities.[34] Although the mean TC level among all STEPS participants, including those on current medication for increased TC was 130.9 mg/dl (> 7.2 mmol/l) in 2015,[17] country data for raised TC were not available.

While the new tobacco law should make a difference in protecting the public against its devastating effects, its enforcement in main cities of the country is far from the expected, except for the Tigrai region.[41] Although improved taxation of tobacco-control products is being implemented, Ethiopia is not yet making use of tax income to fund a national plan for a tobacco-control and CVD programme.[56]

Although the WHO supports countries such as Ethiopia in developing health-finance policies, no policy exists specifically for CVD.[55] Another weakness is the lack of sustainable funding for CVD, and the triple burden of diseases is still consuming the resources with little left for NCD. The little global funding for NCD, with enormous out-of-pocket expenditures, is widening the gap between the rich and poor. Furthermore, low awareness of NCD could have catastrophic effects on the health and economy of the country. Policies and legislation banning the marketing of unhealthy foods to minors and mandating clear and visible warnings on foods, similar to most countries, are not yet endorsed, nor are those promoting diets and PA to reduce CVD risk. There are also no policies for screening individuals at high risk of CVD. However, new initiatives on PA by the prime minister are underway, and the new HSTP (2020–2024/25) has indicated CVD risk stratification.[36]

Some of the CVD targets to be achieved by the year 2025 are far from being realised. The prevalence of diabetes and obesity has increased, and the availability of essential drugs is low.[57] Mainly, however, there is no adequate budget allocation for the CVD programme.

In summary, the following weaknesses have been identified by the core committee for the NSAP development:

- poor prioritisation of the CVD programme at all levels of the health system, especially in regions and woredas (districts)
- inadequate high-level advocacy for political leaders on CVD and risk factors

Cardiovascular Disease Scorecards – Africa

ETHIOPIA – NOVEMBER 2020

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

Country Demographics

World Bank Classification

Low income

79%

of population living in rural areas

60% (Sub-Sahara Africa)

ETHIOPIA

0.19%

of total mortality caused by **RHD**

Global data: **0.51%**

1.4%

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

Global data: **0.53%**

2%

of premature CVD mortality attributable to **tobacco**

Global data: **10%**

MALE **8.1** % **1.8** FEMALE

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

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

1.1%

of deaths caused by **hypertensive heart disease**

Global data: **1.65%**

15.5% **16.3%**

MALE FEMALE

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

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

4.5%

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

Global data: **13.1%**

10.94%

of **deaths** caused by CVD

Global data: **31.8%**

5.2%

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

Global data: **38.9%**

4.3%

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

3.9% (Africa)

WORLD HEART FEDERATION

www.worldheart.org
www.pascar.org

ETHIOPIA

Health System Capacity

0.8
Number of physicians (per 10,000 population)

7.14
Number of nurses (per 10,000 population)

3
Number of hospital beds (per 10,000 population)

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

Clinical Practice and Guidelines

Locally-relevant (national or subnational level):

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

Clinical Guidelines for:

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

ETHIOPIA

Cardiovascular Disease Governance

A national strategy or plan that addresses:

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

Stakeholder action

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

For more information, please email info@worldheart.org info@pascar.org cardiacprofessionalse@gmail.com

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

- lack of financial and technical resources for programme implementation
- poor recording of CVD-related indicators in the health-management information system with the resultant paucity of planning data
- low awareness and misconceptions about the burden and consequences of CVD of the community, healthcare providers and political leaders
- limited availability and affordability of high-quality, safe and effective basic technologies and medicines for screening, diagnosis, treatment and monitoring of CVD
- inadequate mix and capacity of the health workforce
- inadequately staffed regional health bureaus
- poor partnership between the public and private health systems
- poor or no regulation on khat, oils and fats, sugar, salt and environmental pollution
- non-existent multi-sectoral co-ordination mechanism for prevention and control of CVD
- inadequate resources for CVD (competing priorities of major infectious diseases).

Table 2. Indicators for Ethiopia to reach a reduction in premature CVD and related mortality by 2025

Indicators	*Baseline*	*Target by 2025*
Reduce overall premature mortality from CVD		25% relative reduction
Reduce prevalence of current tobacco use in persons ≥ 15 years	5%	30% relative reduction
Reduce harmful use of alcohol in persons ≥ 15 years	12.5% NCD STEPS in 2015*	10% relative reduction
Reduce prevalence of current khat use in persons ≥ 15 years	16% NCD STEPS in 2015*	20% relative reduction
Reduce prevalence of insufficient PA in persons ≥ 15 years	5.8% NCD STEPS in 2015*	10% relative reduction
Reduce mean population salt intake to < 5 g per day in persons ≥ 15 years	8.3 g NCD STEPS in 2015*	30% relative reduction
Reduce insufficient fruit and vegetable consumption in persons ≥ 15 years	97.6% STEPS in 2015*	25% relative reduction
Reduce the percentage of people who are obese or overweight	6.3% STEPS in 2015*	15% relative reduction
Reduce the age-standardised prevalence of raised TC among persons ≥ 18 years	5.6% STEPS in 2015*	10% relative reduction
Reduce prevalence of raised BP in persons ≥ 15 years	16% STEPS in 2015*	25% relative reduction
Reduction in the prevalence of ARF/RHD in the 4–24-year-old age group	17/1 000 school children and young adults**	25% relative reduction
Increase treatment (pharmacological and non-pharmacological) coverage for patients with hypertension	Baseline 28% of diagnosed based on the NCDI commission report**	50%
Increase the proportion of people with hypertension with controlled BP	26% based on the NCDI commission report**	60%
Halt increase in prevalence of raised blood sugar in persons ≥ 15 years	3.2% STEPS in 2015*	0% increase
Increase the proportion of people with diabetes with controlled blood glucose level	24% based on the NCDI commission report**	60%
Increase treatment coverage for patients with diabetes (pharmacological and non-pharmacological)	3% STEPS 2015*	50%
Increase availability of basic technologies and essential medicines (including generics) required to treat CVD in public and private facilities	Availability based on the SARA 2018 report#	80%
Decrease household air pollution from biomass fuel use	Baseline > 90% households use biomass fuel	< 60%

CVD, cardiovascular diseases; NCD, non-communicable diseases; STEPS, step-wise survey; PA, physical activity; TC, total cholesterol; BP, blood pressure; ARF/RHD, acute rheumatic fever/rheumatic heart disease.
*STEPS report;[12] **NCDI commission report;[49] #SARA 2018 report.[25]

Priorities

According to the NSAP,[34] four priority areas guide the implementation of NCD activities, which have also been incorporated into the HSTP-II.[36] These are to:

- strengthen the national response through policy, governance and leadership
- intensify health promotion and disease prevention, targeting behavioural and environmental risk factors
- develop comprehensive and integrated clinical interventions for NCD and their risk factors, and CVD in particular
- determine progress in the prevention and control of NCD through monitoring, evaluation and research.

Comprehensive interventions or programmes are needed to address unhealthy diets, physical inactivity, alcohol, obesity and air pollution among adults and children, as has been done for tobacco control.[41] Also, addressing the mentioned weaknesses through specific actions and stakeholders in the fight against NCD and CVD, such as RHD, HHD, heart failure and atherosclerotic CVD, which are emerging and will probably flood the country in a decade or so.

Total annual government expenditure should set a percentage apart for cardiovascular healthcare, and sustainable funding for CVD (for example, from taxation of tobacco and or other 'sin' products).

Recommendations by the Ethiopia NCDI commission to combat the NCD-related burden of disease include policy, planning and oversight; finance; service integration; strategic information, target setting, monitoring and evaluation; and education and advocacy. By attending to these and to achieve a 25% reduction in CVD by 2025 (Table 2), prominence should be given to:

- improving and implementing the WHO's best buys
- strengthening the primary healthcare system
- improving access to and affordability of essential drugs and technology
- strengthening community screening to commence drug therapy early
- increasing the health taskforce capacity.

This publication was reviewed by the PASCAR governing council and approved by the president of the Society of Cardiac Professionals in Ethiopia.

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Yale study adds to evidence of diabetes drug's link to heart risk

Rosiglitazone was associated with a 33% increased risk of a composite cardiovascular event (heart attack, heart failure, cardiovascular and non-cardiovascular related death) compared with controls, found a Yale analysis of 130 trials involving 48,000 patients.

This study is the most comprehensive evaluation of the cardiovascular risk of rosiglitazone ever done. Rosiglitazone belongs to a class of drugs called thiazolidinediones. It helps control blood sugar levels in patients with type 2 diabetes, but it can also increase the risk of serious heart problems. This has led to suspension of the drug in Europe and previous restrictions on its use in the US.

However, since 2007, studies have reported conflicting findings about whether rosiglitazone increases the risk of heart attacks. But these studies didn't have access to the raw data, also known as individual patient level data (IPD), from clinical trials and mostly relied on summary level data (results reported in publications and clinical trial registries), which are not as reliable when estimating the true safety profile of drugs.

Recent efforts by GlaxoSmithKline (GSK) – the maker of rosiglitazone – to make IPD available to external investigators, prompted a team of US researchers at Yale School of Public Health and the Yale-New Haven Health System, to re-analyse the data and clarify some of the uncertainties about rosiglitazone's cardiovascular risk. They analysed the results of more than 130 trials involving over 48,000 adult patients that compared rosiglitazone with any control for at least 24 weeks. IPD were available for 33 trials, which included 21,156 patients; the remaining trials only had summary level data available.

When the researchers analysed the IPD from trials made available by GSK, they found rosiglitazone was associated with a 33% increased risk of a composite cardiovascular event (heart attack, heart failure, cardiovascular and non-cardiovascular related death) compared with controls. This was estimated from the 274 events among 11,837 rosiglitazone patients and 219 events among 9,319 control patients.

When examining cardiovascular events independently, the analyses of the 33 GSK trials with IPD resulted in higher estimates of the risk of heart attacks than the analyses of trials with IPD and summary level data.

These findings highlight the potential for different results derived from different data sources, and demonstrate the need for greater clinical trial transparency and data sharing to accurately assess the safety of drugs, say the researchers.

"Our study suggests that when evaluating drug safety and performing meta-analyses focused on safety, IPD might be necessary to accurately classify all adverse events," they write. "By including these data in research, patients, clinicians, and researchers would be able to make more informed decisions about the safety of interventions."

They add: "Our study highlights the need for independent evidence assessment to promote transparency and ensure confidence in approved therapeutics, and post-market surveillance that tracks known and unknown risks and benefits."

Source: Medical Brief 2020

South Africa Country Report

PASCAR and WHF Cardiovascular Diseases Scorecard project

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Abstract

Data collected by the Pan-African Society of Cardiology for the World Heart Federation's Cardiovascular Diseases Scorecard project in Africa are presented. We summarise the strengths, threats, weaknesses and priorities identified from the collected data for South Africa, which need to be considered in conjunction with the associated sections in the accompanying infographic. Data sets that were used include open-source data available online and government publications. In the section on priorities and the way forward, we highlight the multifactorial health challenges with which South Africa has had to deal and the progress that has been made.

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On behalf of the World Heart Federation (WHF), the Pan-African Society of Cardiology (PASCAR) co-ordinated data collection and reporting for the country-level Cardiovascular Diseases Scorecard to be used in Africa.[1-3] The South African Heart Association, members of PASCAR and the WHF assisted in collating and verifying these data. Based on the collected data, we summarise the strengths, threats, weaknesses and priorities identified, which need to be considered in conjunction with the associated sections in the accompanying infographic. We used open-source data sets from the World Bank, the World Health Organization (WHO), the Institute for Health Metrics and Evaluation, the International Diabetes Federation (IDF) and relevant government publications.

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Part A: Demographics

According to the World Bank (2018), South Africa is an upper-middle-income country (MIC), with 34% of its people living in rural areas. Despite its status as an upper MIC and to appreciate the country's health status and challenges, it is important to note that it also occupies the status as one of the most unequal societies worldwide. The official unemployment rate in 2019 was close to 30%, while there is a large income and wealth inequality (the bottom 60% of the population hold 7% of net wealth).[4,5] Almost 19% of the population were living below the US$1.9-a-day ratio in 2014.[5] Life expectancy at birth in 2018 was 60 years for men and 67 years for women.[5] The general government health expenditure was 4.4% of the gross domestic product (GDP) in 2017,[5] while the total government health expenditure was 8.8% of the GDP in 2014.[6] In 2019, the country's GDP per capita was US$6 001.40, and the gross national income per capita purchasing power parity (current international $) was US$12 530 in 2018.[5]

Part B: National cardiovascular disease epidemic

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

South Africa reports premature death based on the sustainable developmental goals (SDGs), target 3.4, and only addresses premature death above the age of 30 years.[7] Therefore, all premature deaths caused by, for example, unoperated or operated congenital heart disease (CHD), rheumatic heart disease (RHD), peripartum cardiomyopathy and other cardiomyopathies in children, adolescents and young adults, remain unreported. Given the significant burden of these disorders in under-30-year-olds, there may be a significant under-reporting of premature cardiovascular deaths in the country.

South Africa's premature death rate attributable to CVD (30–70 years old) was 14% in 2012, which is the highest of the countries under investigation.[8] Several data sources suggest that

the main burden of CVD is from heart failure (HF), ischaemic heart disease (IHD) and cerebrovascular disease.[9,10] Premature deaths (age 30–70 years) attributable to NCD, which included cancer, diabetes or chronic respiratory diseases, in addition to CVD, was 26% in 2016.[11] The age-standardised total CVD death rate was 16.1%, while the percentage of disability-adjusted life years (DALYs) resulting from CVD was 7.0% in 2017.[12]

RHD, which has an estimated prevalence of 1.01%, is one of the main causes of premature CVD-related morbidity and mortality in the youth. This prevalence is similar to that of Tanzania and slightly lower than Mozambique's 1.09%. The total RHD mortality rate in 2017 was 0.22% of all deaths, which is almost similar to that of Cameroon (0.2%), but lower than Namibia and Senegal (0.27 and 0.28%, respectively) and Sudan's 0.38% (Table 1).[12]

Tobacco and alcohol

The WHO age-standardised prevalence of tobacco use in adult men and women (≥ 15 years) in 2018 was 46.8 and 16%, respectively (Table 1).[13] Similar prevalence data suggest that 1.68% of 10–14-year-old boys and 0.81% of girls smoked,[13] while among the adolescents (13–15-year-olds), 24.3% of boys and 19% of girls used one form or another of tobacco (Table 1).[14] The estimated annual direct healthcare-related cost of tobacco use was R11.4 billion (about US$0.77 billion) in 2016.[15] In 2004, the premature CVD mortality rate attributable to tobacco in South Africa was 18%.[16]

Alcohol is a major contributor to the burden of disease in South Africa. The three-year (2016–18) average recorded alcohol consumption per capita (≥ 15 years) was 7.3 litres (Table 1).[14] Among risk factors that drive the most death and disability combined in 2017, alcohol ranked fourth highest, which is a slight improvement from 2007 when it ranked third.[17]

Raised blood pressure and cholesterol

The percentage of men and women with raised blood pressure (BP) [systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg] was 27.4 and 26.1%, respectively in 2015, which increased with age.[14] In the first South African National Health and Nutrition Examination Survey (SANHANES), the prevalence for raised SBP was 5.3% in persons < 25 years old, rising to 50.5% in the 55–64-year-old group, and 63.7% in those over 65 years.[18] The percentage of DALYs lost because of hypertension was 5.2%, whereas the mortality rate caused by hypertensive heart disease was 2.0% in 2017 (Table 1).[12]

According to Global Health Observatory data, the estimated age-standardised raised total cholesterol (TC; ≥ 5.0 mmol/l) level was 35.5% in 2008, while only Tunisia had a higher TC level at 40.7%.[14] Data from SANHANES, conversely, indicated a prevalence of elevated TC in men, 15–65 years and older, of 18.9% that varied widely by province (Limpopo 10.9% and Western Cape 34.8%). In women, 15–65 years and older, 28.1%

Table 1. Cardiovascular disease indicators for South Africa

Indicators	*Male*	*Female*	*Total*	*Year*
Status of the national CVD epidemic				
Premature CVD mortality (30–70 years old) (% deaths)	–	–	14	2012
Total CVD mortality (% of deaths)	13.9	18.8	16.1 (31.8)*	2017
Total RHD mortality (% of deaths)	0.23	0.21	0.22 (.5)*	2017
DALYs attributable to CVD (%)	6.8	7.2	7.0 (14.7)*	2017
AF and atrial flutter (%)	0.29	0.29	0.29 (.5)*	2017
Prevalence of RHD (%)	0.91	1.1	1.01 (.5)*	2017
Tobacco and alcohol				
Prevalence of adult tobacco use (≥ 15 years old) (%)	46.8 (36.1)**	16 (6.8)**	–	2018
Prevalence of youth (13–15-year-olds) tobacco use (%)	24.3 (18.2)**	19.0 (8.3)**		2011
Estimated direct (healthcare-related) cost of tobacco use in the South African population (current US$)	–	–	0.77	2016
Proportion of premature CVD mortality attributable to tobacco (%)	–	–	18.0 (10)*	2004
Recorded alcohol consumption per capita (≥ 15 years old) (litres of pure alcohol) (three-year average)		–	7.3	2016–18
Raised blood pressure and cholesterol				
Population with raised BP (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) (%)	27.4 (24.1)**	26.1 (20.1)**	-	2015
Population with raised TC (≥ 5.0 mmol/l) (%)#	18.9	28.1	23.5 (38.9)**	2012
DALYs attributable to hypertension (%)	5.1	5.3	5.2 (8.7)*	2017
Mortality caused by hypertensive heart disease (% of deaths)	1.4	2.8	2.0 (1.7)*	2017
Physical activity				
Adolescents (< 13– ≥ 19 years old) who are insufficiently active (< 60 minutes of moderate- to vigorous-intensity PA daily) (%)	37.7	47.5	42.8 (80.7)**	2011
Adults (age-standardised estimate) who are insufficiently active (< 150 minutes of moderate-intensity PA per week, or < 75 minutes of vigorous-intensity PA per week) (%)	28.5	47.3	38.2 (27.5)**	2016
Overweight and obesity				
Adults who are overweight (BMI ≥ 25–< 30 kg/m^2) (%)	40.5	65.4	53.8 (38.9)**	2016
Prevalence of obesity (BMI ≥ 30 kg/m^2) (%)	15.4	39.6	28.3 (13.1)**	2016
Diabetes				
Defined population with fasting glucose ≥ 126 mg/dl (7.0 mmol/l) or on medication for raised blood glucose (age-standardised) (%)	9.7 (9)*	12.6 (8)*	11.3	2014
Prevalence of diabetes (20–79 years old) (%)	–	–	12.7 (9.3)##	2019

CVD, cardiovascular disease; RHD, rheumatic heart disease; DALYs, disability-adjusted life years; AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; PA, physical activity; BMI, body mass index.
*IHME global data exchange;[12] **WHO global data;[14] #SANHANES;[18] ##*IDF Diabetes Atlas*.[20]

had raised TC levels (Table 1), with similar varied prevalence by province (Limpopo 15.9% and Western Cape 39.3%).[18]

Physical activity

The age-standardised estimate for adults who were insufficiently active [< 150 minutes of moderate-intensity physical activity (PA) per week, or < 75 minutes of vigorous-intensity PA per week] was 38.2% (Table 1). Data from the third Youth Risk Behaviour Survey were available for adolescents, < 13–≥ 19 years old, who were insufficiently active.[19] Of these 10 189 participants, 42.8% had done insufficient or no PA during the week preceding the survey, with more females (47.5%) practising a sedentary lifestyle than adolescent males (37.7%).[19]

Overweight and obesity

In 2016, more South Africans (53.8%) were overweight, compared to most other African countries under investigation. Only Tunisia recorded a higher prevalence rate at 61.6%. For obesity, South Africans ranked the highest at 28.3%, followed by Tunisia with a rate of 26.9%. These figures are also higher than the global mean prevalence rates of 38.9 and 13.1% for overweight and obesity, respectively.[14] Far more women than men, respectively, were overweight (65.4 vs 40.5%) and obese (39.6 vs 15.4%).[14]

Diabetes

The percentage of the population defined with a fasting glucose level ≥ 7.0 mmol/l or on medication for raised blood glucose (age-standardised) in 2014 was 11.3%. In 2019, the age-adjusted prevalence (20–79 years old) of diabetes was 12.7%, which is much higher than the rate of 3.9% for Africa (Table 1).[20]

Part C: Clinical practice and guidelines

Health system capacity and guidelines for NCD risk factors

South Africa had an average of 9.1 physicians and 13.08 nurses per 10 000 of the population in 2017, [14] with 18 hospital beds per 10 000 people in 2018.[21] Locally relevant clinical tools to assess CVD risk and recent clinical guidelines for CVD prevention are available.[22,23] National guidelines for the treatment of tobacco dependence were compiled by the South African Thoracic Society and endorsed by CANSA (Cancer Association of South Africa) and TAG (Tobacco Action Group).[24] Local guidelines are available for the management of dyslipidaemia,[25] type 2 diabetes mellitus,[26] hypertension[27] and HF,[28] with recent updates in 2018 and 2020 for the latter. These guidelines have all been drawn up through local associations and societies by specialists in their respective fields, as opposed to government health agencies. For communicable but preventable CVD, society guidelines exist for pharyngitis, acute rheumatic fever and RHD.[29,30] South Africa has been a leader in conducting global population studies on RHD,[31,32] for example, the REMEDY study, which provides a tool to measure the quality of care. Alternative models to assess care specific to acute cardiac events has been developed, using Discovery Health data.[33]

Essential medicines and interventions

The WHO has developed an essential list of medicines[34] for cardiovascular medication, which covers treatment for angina, arrhythmias, hypertension, elevated lipids, HF and essential antithrombotic, antiplatelet and thrombolytic agents. All treatments on the list are available in public and private health sectors. Guidance and therapy for secondary prevention of rheumatic fever and RHD, which are also on the national essential drugs lists, are widely available in the public health sector, including those for CVD risk stratification and cholesterol measurement.[30]

Secondary prevention and management

Although South Africa has programmes and guidelines in place for primary and secondary prevention and management of CVD, available data suggest that a significant proportion of patients who should be on appropriate secondary prevention therapy are not. Examples include (1) the low use of statin and antiplatelet treatment after myocardial infarction and stroke,[35] (2) the low use of penicillin prophylaxis in patients with a history of RHD demonstrated in the REMEDY study,[36] and (3) the finding that approximately 44% of people with hypertension were on any treatment in 2016.[37]

Part D: Cardiovascular disease governance

A national strategic plan for the prevention and control of NCD and their risk factors has been developed, which includes CVD as the most important of these diseases.[38] NCD have been identified as a priority area within the national strategy, as evidenced by the appointment of a separate deputy director general and staff dedicated to the area. The following strategic priorities have been identified within the NCD space in the national plan for the next decade:

- introducing legislation and regulation to reduce the modifiable risk factors for NCD
- reducing costs and increasing the efficiency of health interventions, including providing affordable medicines, devices and vaccines, essential NCD health services, including preventative services
- establishing comprehensive surveillance mechanisms, health information systems, and dissemination processes to assist policy, planning, management and evaluation of NCD prevention and control.[38]

Therefore, important national NCD surveys, such as the SANHANES and South African Demographic and Health Surveys (SADHS), include data on NCD risk factors such as hypertension, diabetes, anthropometry and tobacco smoking.[38] South Africa also tracks the CVD-related mortality rate through a regional and national death register, co-ordinated by Statistics South Africa.[39] Although preventative strategies have been developed for rheumatic fever and RHD, South Africa has fallen short in its control efforts, and implementation thereof has been inadequate.[40]

In South Africa, the Tobacco Products Control Act 83 of 1993 was the first tobacco-control law and has been amended over time, the latest being in 2018.[41,42] A summary of the latest Control Tobacco Products and Electronic Delivery Systems Bill, published in the Government Gazette on 9 May 2018, covers

gaps and exploited loopholes.[42] South Africa has been part of the WHO framework convention on tobacco control (FCTC) since 2005 when its national tobacco-control plan was approved.[43,44]

Collaborative projects for NCD interventions, which include CVD, have been implemented between the Ministry of Health and non-health ministries and civil societies.[38] These include organisations/institutions such as the South African Medical Research Council, Human Sciences Research Council and Statistics South Africa. The percentage of total annual government expenditure on cardiovascular healthcare is not known. South Africa was part of the WHO-CHOICE (CHOosing Interventions that are Cost Effective) project that assessed cost-effective health outcomes for CVD prevention and control using mathematical modelling.[45]

Assessment of policy response

The costs relating to CVD in South Africa have been discussed in various publications.[46,47] However, no legislation mandating health financing, specifically for CVD or other NCD risk factors, is available. Although legislation of affordable essential CVD medicines is available, South African pharmaceutical policies do not meet the lowest prices of those achieved internationally.[48] Indirectly, through the Constitution and the National Health Act (No. 61 of 2003),[49] as amended, patients' rights are protected and improved interventions, facilities and health-system procedures or resources, which could include CVD, are mandated.[50,51]

Legislation is employed in areas where smoking is banned. Advertising, promotion and sponsorship of all forms of tobacco, along with measures to protect tobacco-control policies from tobacco industry interference, have been implemented.[43] However, clear and visible warnings appear on less than half of the main display areas of tobacco packs.[43] Furthermore, the amended Act provides for control over smoking, advertising of tobacco products and other related matters.[42] In South Africa, the excise tax of the final consumer price of tobacco products in 2018 was 52%[43] and that for alcohol 23%.[52]

The national Department of Health (NDoH) commissioned the University of Cape Town's Lung Institute to develop a symptom-based integrated clinical management guideline that included the screening of individuals at high risk of CVD and other related NCD.[53] Finding sustainable funding for these diseases is challenging, and only available for research; consequently, none is available from taxation.[54] Equitable nationwide access to healthcare professionals and facilities are in progress, although at a slow pace.[55]

In 2016, National Treasury documented recommendations to implement taxes on unhealthy foods, and particularly sugar-sweetened beverages (SSB), which were introduced in 2018.[56] In South Africa, these taxes were passed at 11%, although 20% was proposed.[57] Legislation on banning the marketing of unhealthy foods to minors has been drafted but not yet tabled.[58] No legislation exists mandating clear and visible warnings on foods that are high in calories, sugar or saturated fats, mostly because there is no universal agreement on what these should be.[59] However, the South African Bureau of Standards oversees labelling and marketing in the food and health category.[60] Policy interventions that promote a diet to reduce CVD risk and those that facilitate PA have been introduced through the Healthy Lifestyle campaign of the NDoH.[61,62]

Stakeholder action

Non-governmental organisation advocacy for CVD policies and programmes in South Africa is visible and effective, as indicated in the 2018 annual report of the Heart and Stroke Foundation of South Africa (HSFSA).[63] Professional education for healthcare providers and patients is provided through participation at international and national conferences, which are organised by the South African Heart Association (SA Heart).[64] SA Heart has several specialised interest groups, such as the Heart Failure Society of South Africa (HeFFSA), South African Society of Cardiovascular Intervention (SASCI), and the Cardiac Arrhythmia Society of Southern Africa (CASSA), among others.[64] Continuing medical education can also be accessed online via the South African Medical Association and other bodies. RhEACH is a non-governmental organisation providing education for people living with RHD.[65]

Civil societies, such as the South African NCD Alliance (SANCDA), were involved in the development and implementation of a national tobacco-control plan.[43,66] The NDoH addresses NCD (and consequently CVD) in its National Development Plan,[62] which involves various stakeholders such as the SANCDA[67] and HSFSA.[63] These professional associations also aim at reducing premature CVD mortality by 25% in 2025.[63,67] SANCDA is involved in a national multi-sectoral co-ordination mechanism for NCD/CVD as discussed at their first stakeholder meeting held on 11–12 February 2014.[68] Kolbe-Alexander *et al*.[69] identified a need for worksite health promotion to address the prevalence of CVD and related risk factors, which were on the increase. These researchers proposed this strategy to be the better choice to reach at-risk persons.[69] Health/wellness screening, which includes BP measurement at workplaces, is promoted and encouraged by many companies and specifically the medical aid industry. The HSFSA, through its health promotion programme, offers services such as the employee wellness programme.[63]

The following strengths, weaknesses, threats and priorities are summarised as part of the scorecard data collected for South Africa.

Strengths

At the 2011 United Nations General Assembly meeting, the former minister of health, Dr Aaron Motsoaledi, said that South Africa had led efforts to implement tobacco-control legislation. He continued to mention the country had passed regulations in reducing the use of trans fats, along with those to reduce the salt content in processed food.[70] In the SANHANES, conducted in 2012, investigators noted substantial gains had been made to reduce tobacco use.[71] South Africa's national tobacco-control plan, as part of the FCTC, has been hailed by the WHO, among others.[43,44]

The 2015–2020 strategic plan of the NDoH was drafted to 'achieve measurable improvement in critical public health' in which requests were made for partnership with communities in disease prevention and promotion of health and wellness.[72] In this plan, NCD, of which CVD rank the highest, will be addressed as part of the strategic goals of the NDoH. These, among other things, are to prevent disease and reduce its burden, re-engineer primary healthcare and improve the quality of care.[72] A new updated strategic plan 2030 is being commissioned.

The vision of the National Development Plan is to have significantly reduced the prevalence of NCD by 28% in 2030 through health promotion and wellness strategies.[62,67,72] The NDoH's Healthy Lifestyle campaign aims to promote healthy lifestyles through interventions that address inadequate nutrition, physical inactivity, alcohol abuse, tobacco smoking, high BP and diabetes to reduce CVD risk.[61] Every 10 years, a national surveillance system such as the SADHS or SANHANES, which includes CVD and their risk factors, is implemented.[38]

Various clinical guidelines have been introduced to manage the underlying NCD risk factors in the prevention of CVD and other related diseases.[21-29] South Africa is one of the African countries that has introduced taxes on unhealthy foods or SSB.[73] This introduction of a tax on SSB in April 2018 was a small victory in the fight against obesity. According to Professor Hofman, director of PRICELESS SA (Priority Cost Effective Lessons for Systems Strengthening) at the Wits School of Public Health, taxing should reduce the intake of harmful products through increasing the price. Hofman also advocated that advertising to children, in particular, needs attention.[74]

South Africa has a well-developed regulatory standards system that oversees the labelling and marking requirements.[60] However, Hofman asks for clear front-of-package (FOP) labelling.[74] Hofman was quoted saying 'There are three ways to curb nutrition-related NCDs in South Africa: [the] tax on unhealthy foods, halting of marketing of unhealthy foods and transparency about what people are eating.'[74]

Threats

The use of reporting protocols designed for diseases prevalent in high-income countries has meant that conditions affecting the poorest billions in the world have been omitted or undercounted in low- and middle-income countries. The recently published Lancet NCDI Poverty Commission, 'Bridging the gap in universal health coverage for the poorest billion,'[75] highlights that reporting premature death based on the SDG target 3.4 is inadequate for most of Africa. The reason being that only premature deaths above age 30 years are reported.[7,75] This inadequate definition for premature death is pronounced in regions with high poverty levels and a high burden of deaths among children and young people younger than 30 years old. These premature deaths are mostly caused by CHD, RHD, peripartum cardiomyopathy[76] and other cardiomyopathies. Under-reporting remains a great threat to addressing CVD in South Africa because one cannot act on preventing future deaths if these are not reported.

South Africa's premature CVD mortality rate at 14% is higher than its neighbouring country, Mozambique (8%), and most other African countries under review. The WHO-CHOICE project that assists countries with health policy and planning has flagged South Africa's very high adult and high child CVD mortality rates as a foremost priority, which needs to be addressed.[77] Of concern is that premature mortality is not limited to CVD, the risk of premature NCD mortality is similar to that of Sudan (26%), and is also higher than most of the other countries and neighbouring Namibia (21%).[78]

Although dated, in 2004, the proportion of premature CVD mortality attributable to tobacco was very high at 18%, compared to the other African countries. The prevalence of tobacco use among men (46.8%) and women (16%) in 2018 was higher than the global levels at 36.1 and 6.8%, respectively.[14] In a recent article, researchers noted the total cost of smoking in South Africa in 2016 amounted to US$2.27 billion, of which about a third went to in- and out-patient healthcare.[15] In 2013, disease-related tobacco use was estimated to cost R1.2 billion.[24] The percentage of deaths caused by tobacco was 10.11% in 2016, killing 550 men every week, and requiring action by government and other related organisations.[13]

The data for alcohol consumption and its health consequences remain a concern and threat to the nation's health. A high alcohol-attributable fraction to road traffic injuries (25.2%), liver cirrhosis (43.4%),[79] along with being the fourth largest risk factor contributing to death and disability, all point to significant work needed to reduce the alcohol-related burden.

Raised BP of South African men and women is a concern for developing CVD, as the prevalence is higher than the global figure of 22.1%.[14] Although, the SANHANES researchers reported lower national TC levels, in some provinces such as the Western Cape, the women (39.3%) presented with levels higher than those of the WHO global data (38.9%) (Table 1).[14,18] Of the defined population, 11.3% had raised blood glucose levels, while the prevalence of diabetes more than doubled over two years in 2019 from 5.5 to 12.7%, also creating an increased risk for CVD.[14,20]

Obesity, which is not only the result of physical inactivity but also poor eating habits, gives rise to a high diabetes prevalence. In a recent joint statement, leaders of the WHF and the World Stroke Organization urged governments to move away from the widely adopted approach of addressing clinical factors such as hypertension, obesity and physical inactivity individually in isolation.[80] They advocate for a far broader approach by following the population-wide strategy.[80]

Vorster *et al.*[81] acknowledged that in light of starvation, the global obesity epidemic demonstrates a 'worldwide failure to attain the goal of optimal nutrition for everyone.' Focus on the food and beverage industry has increased because of food marketing to children being considered as partially responsible for childhood obesity.[82]

RHD remains a threat in Africa and developing countries. In a cost-effective strategy, it was suggested that all children presenting with pharyngitis be treated with penicillin without a throat culture, which could be costly.[83] A systematic review[9] and another on CVD, HF, IHD, cerebrovascular disease and other related risk factors, such as hypertension, pose even higher risks for developing CVD in South Africa and many other African countries.[10]

Professor Hofman mentioned that a study conducted by the American Chamber of Commerce determined that NCD will cost the South African economy 7% of the GDP by 2030. These diseases have debilitating effects on the quality of life and, ultimately, result in death.[84]

Weaknesses

South African pharmaceutical policies do not meet the lowest prices of those achieved internationally for affordable essential CVD medicines.[48] Although the Essential Medicines List at primary healthcare level contains diabetes type 1 and 2 medication (insulin, metformin), insulin is not available at most clinics.[67] Warfarin is the most widely used anticoagulant in the

Cardiovascular Disease Scorecards – Africa

SOUTH AFRICA – NOVEMBER 2020

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

SOUTH AFRICA

Country Demographics

World Bank Classification

Upper-middle income

34%

of population living in rural areas

60% (Sub-Sahara Africa)

0.22%

of total mortality caused by **RHD**

Global data: **0.51%**

1.01%

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

Global data: **0.53%**

18%

of premature CVD mortality attributable to **tobacco**

Global data: **10%**

MALE **46.8** % **16** **FEMALE**

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

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

2.03%

of deaths caused by **hypertensive heart disease**

Global data: **1.65%**

27.4% **26.1%**

MALE **FEMALE**

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

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

28.3%

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

Global data: **13.1%**

16.13%

of **deaths** caused by CVD

Global data: **31.8%**

23.5%

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

Global data: **38.9%**

12.7%

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

3.9% (Africa)

WORLD HEART FEDERATION

www.worldheart.org
www.pascar.org
www.saheart.org

SOUTH AFRICA

Health System Capacity

9.1
Number of physicians (per 10,000 population)

13.08
Number of nurses (per 10,000 population)

18
Number of hospital beds (per 10,000 population)

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

Clinical Practice and Guidelines

Locally-relevant (national or subnational level):

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

Clinical Guidelines for:

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

SOUTH AFRICA

Cardiovascular Disease Governance

A national strategy or plan that addresses:

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

Stakeholder action

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

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

public sector, with more people using it than in the private sector. However, in most provinces, it is only made available at designated international normalised ratio clinics and hospitals, as opposed to primary care clinics or community centres.[85,86]

In a report to inform the minister of health, SANCDA emphasised that although action plans to address diabetes and hypertension had been assembled, these were merely window dressing and without any support.[66]

Sustainable funding for CVD from the taxation of tobacco or other 'sin' products does not exist. Although legislation exists mandating clear and visible warnings on at least half of the principal display areas of tobacco packs, only 40% of the space is covered.[67]

In 2012, adjusted transparent alcohol excise tax was introduced that distinguished between alcoholic beverages (wine 23%, clear beer 25% and spirits 48%).[87] However, in 2018, excise taxes for alcohol were based on the rate of beer at 23% and lag behind those of tobacco products.[52] In May 2014, the Department of Health published draft regulations relating to the labelling of foodstuffs that will see severe restrictions on the advertising of unhealthy foods to children.[58] By 2016, this draft legislation was still under discussion.[88]

Priorities and the way forward

Twenty-five years after South Africa underwent a peaceful transition from apartheid to democracy, the country has a complex and two-tiered healthcare system that has not been able to address the health needs of most of its population.[89] The public system serves 84% of the population but is chronically underfunded and understaffed, with enormous challenges. The wealthiest 16% of the population has access to private healthcare, consuming 58% of the GDP expenditure on health.[89] Over 70% of doctors in the country are employed in the private sector. Furthermore, the healthcare system has to contend with multiple colliding epidemics, which include HIV and tuberculosis, CVD, mental health and other NCD such as injuries, substance abuse and violence, and unacceptably high mortality rates attributable to maternal and childhood diseases. More than 12% of the South African population of 57 million is HIV infected, having the world's largest antiretroviral therapy programme, subsidised by the government and provided free of charge. South Africa is one of the few African countries that has universal healthcare for people with HIV.[89]

South African priorities for dealing with CVD have to be seen in the overall context of all those colliding conditions,[89] and a simplified multi-sectoral approach is needed.[80] Because of the stretched and competing resources and limited health infrastructure, the following strategies are currently planned and partially underway:

- improvement in diagnosis and management of NCD/CVD at the primary care level, including via an integrative service with infectious diseases such as HIV/tuberculosis
- development of human resources including task sharing and task shifting (e.g. use of non-physician technicians)
- improving salaries for health professionals to retain them in the public workforce domain
- increased and easier access to essential medicines for CVD by promoting simplified regimens, generic drugs and combination tablets
- development of context-specific guidelines and algorithms for risk stratification and medical management appropriate to the South African context
- population-wide interventions to promote a healthy diet, physical activity, healthy environment and cessation of smoking and alcohol abuse
- strengthening surveillance and quality assurance systems[89]
- increasing the partnerships between industry and government to map out the promotion of healthy food options and a healthier work environment
- strengthening the Directorate for Chronic Diseases, Disability and Geriatrics that has produced and distributed several national guidelines for preventing and controlling NCD.

More effective collaboration between the medical and non-medical government sectors with the public and industry will facilitate better overall use of resources, tackling the larger burden of CVD affecting South Africans from childhood to old age.

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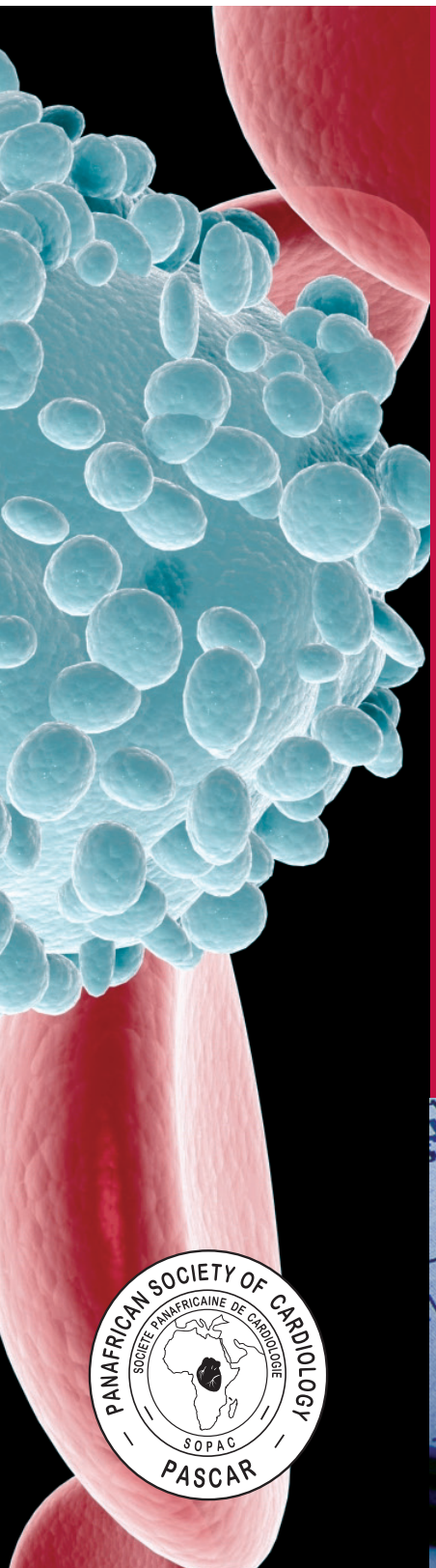

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