A multicentre cross-sectional descriptive study evaluating the cardiovascular risk profile of preoperatively identified patients with hypertension

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GVNSAR006

Submitted to the University of Cape Town in fulfilment of the requirements for the degree Masters of Medicine (MMed) in Anaesthesiology in the published paper format.

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Professor Robert Dyer

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Table of Contents

Declaration

I, Sarisha Govender, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
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Signed by candidate

Date: 18 May 2021

Publications and Presentations

Part of thesis was presented at the South African Society of Anaesthesiologists Congress on 12 March 2020 in Pretoria.
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Abstract

Background. The prevalence of hypertension in adults in South Africa (SA) is 35%. Hypertension is the most important modifiable risk factor for cardiovascular (CV) and chronic kidney disease (CKD) in sub-Saharan Africa. However, 49% of people are unaware of their blood pressure status. Screening for hypertension prior to surgery provides a unique opportunity to diagnose and treat affected individuals. Furthermore, assessing overall CV risk identifies patients at highest risk for complications, and improves the utilisation of scarce resources.

Objective. To evaluate the CV risk profile of hypertensive patients in the adult population of the Western Cape Province presenting for elective non-cardiac, non-obstetric surgery.

Methods. This report documents the CV risk profile of patients recruited to the HASS-2 study (Hypertension and Surgery Study 2), which was undertaken in seven Western Cape hospitals. Patients were screened for hypertension and pharmacological treatment was initiated or adjusted in patients with stages 1 and 2 disease. Stage 3 patients were referred to a physician. In the present substudy, patients with stages 1 and 2 hypertension were assessed for associated CV risk factors, the presence of target organ damage, and documented CV or kidney disease; they received an overall risk stratification according to the 2018 European Society of Cardiology and the European Society of Hypertension Guidelines.

Results. Sixty-one patients with stage 1 and 12 with stage 2 hypertension were analysed. Established CV disease was present in 13.7% of the study population, and CKD (eGFR <60 ml/min) in 10.8%. Seventy-one percent of the study group had a raised body mass index, and 55.9% underlying metabolic syndrome. Prediabetes and diabetes were present in 16.1% and 14.5% respectively. According to the 2018 European guidelines, 34.7% were at moderate, 33.3% at high and 16.7% at very high risk for a CV event in the following 10 years.

Conclusions. The perioperative period is a critical time during which surgeons, nurses and anaesthetists can influence patients' CV risk of adverse events. This involves appropriate screening, education and treatment. In this study population, nearly 9 out of 10 elective surgical patients with stage 1 or 2 hypertension had CV risk factors placing them at moderate to very high risk. The simultaneous assessment of these additional CV risk parameters, in addition to diagnosis and management of hypertension, may further decrease the health and financial burden in resource-limited facilities in SA, and improve CV outcomes.

Acknowledgements

I would like to thank the Department of Anaesthesia and Perioperative Medicine of the University of Cape Town, Provincial Government of Western Cape and the 7 participating hospitals for contributing to and supporting this multicentre research work. Much gratitude to the staff involved in data collection at each hospital.

Thank you to Claire Pfister for being a wonderful partner in this project and to Margot Flint and Liezel Loo for their guidance and support.

I thank and am grateful to my supervisors Professors Brian Rayner, Robert Dyer and Bruce Biccard for being my mentors in this process.

Tables and Figures

Table 1. Definition of hypertension according to the South African Hypertension Practice Guideline 2014

Stage	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Optimal	<120	<80
Normal	120 - 129	80 - 84
High-normal	130 - 139	85 - 89
Stage 1	140 - 159	90 - 99
Stage 2	160 - 179	100 - 109
Stage 3	≥180	≥110

Table 2. American Heart Association/National Cholesterol Education Program definition of metabolic syndrome (≥3 of the criteria below are required)

Risk factor	Diagnostic threshold
Abdominal obesity: men	>102 cm
Abdominal obesity: women	>88 cm
Triglycerides	>1.7 mmol/L
HDL cholesterol: men	<1.03 mmol/L
HDL cholesterol: women	<1.3 mmol/L
Blood pressure	≥130/≥85 mmHg
Fasting blood glucose	>5.55 mmol/L

Table 3. Stages of chronic kidney disease (CKD)		
Stage	**Classification**	**eGFR range** (mL/min/1.73 m^2)
Stage 1	Kidney damage with normal function	>90
Stage 2	Kidney damage with mild CKD	60 - 89
Stage 3A	Moderate CKD	45 - 59
Stage 3B	Moderate CKD	30 - 44
Stage 4	Severe CKD	15 - 29
Stage 5	Kidney failure	<15
eGFR = estimated glomerular filtration rate.		

Table 4. Baseline patient demographic details (*N*=73*)				
Parameter	**Overall**	**Stage 1 (*n*=61*)**	**Stage 2 (*n*=12*)**	***p*-value**
Age (y), mean (SD)	57 (13.4)	56 (13.1)	62 (14.5)	0.166
Sex, *n* (%) Female Male	 42 (57.5) 31 (42.5)	 36 (59.0) 25 (41.0)	 6 (50.0) 6 (50.0)	 0.751
Systolic BP (mmHg), mean (SD)	154 (11.8)	151 (10.6)	168 (5.2)	< 0.001
Diastolic BP (mmHg), mean (SD)	88 (10)	87 (9.7)	89 (11.3)	0.4
BMI (kg/m^2), *n* (%) Normal	 19/66 (28.8)	 16/54 (29.6) †	 3 (25.0)	 0.949
Overweight	16/66 (24.2)	13/54 (24.1) †	3 (25.0)	0.949
Obese	31/66 (47.0)	25/54 (46.3) †	6 (50.0)	0.949
Waist circumference: female ≥88 cm, *n* (%)	33/39 (84.6)	27/33 (81.8)‡	6 (100)	0.256
Waist circumference: male ≥102 cm, *n* (%)	10/27 (37)	9/21 (42.9) ‡	1 (16.7)	0.241
Metabolic syndrome, *n* (%)	33/59 (55.9)	26/47 (55.3) §	7 (58.3)	1.0

*Unless otherwise indicated.
†Missing data *n*= 7.
‡Missing data *n*= 3 females and 4 males in stage 1.
§Missing data *n*= 14.

Table 5. Key baseline laboratory parameters (*N*=73[*])				
Parameter	**Overall**	**Stage 1 (*n*=61[*])**	**Stage 2 (*n*= 12[*])**	***p*-value**
LDL (mmol/L), mean (SD)	1.91 (1.26)	1.70 (1.14)[†]	2.39 (1.61)	0.093
HDL (mmol/L), mean (SD)	1.08 (0.49)	1.11(0.52)[‡]	1.27 (0.35)	0.310
Triglycerides (mmol/L), mean (SD)	1.71 (0.91)	1.72 (0.95)[‡]	1.66 (0.93)	0.846
Pre-diabetes, n (%)	9/56 (16.1)	7/45 (15.6)[§]	2/11 (18.2)[¶]	0.832
Diabetes, n (%)	9/63 (14.5)	8/50 (16.0)[‖]	1 (8.3)	0.498
HbA1c %, mean (SD)	5.33 (2.25)	5.14 (2.03)[†]	5.52 (2.71)	0.591
Fasting blood glucose (mmol/L), mean (SD)	4.95 (2.05)	4.83 (2.04)[§]	4.58 (2.24)	0.711
Uric acid (mmol/L), mean (SD)	0.31 (0.13)	0.29 (0.12)[**]	0.37 (0.10)[¶]	0.58
eGFR (mL/min), median (IQR)	95 (77 - 109)	96 (84-112)	77 (64-95)	0.14
Dipstick proteinuria, n (%)	19/64 (29.7)	16/53 (30.2)[††]	3/11 (27.3)[¶]	0.847

SD = standard deviation, IQR = interquartile range, eGFR = estimated glomerular filtration rate.
[*]Unless otherwise indicated.
[†]Missing data *n*= 13.
[‡]Missing data *n*= 12.
[§]Missing data *n*= 16.
[¶]Missing data *n*= 1.
[‖]Missing data *n*= 11
[**]Missing data *n*= 15.
[††]Missing data *n*= 8.

Table 6. Baseline target organ damage and established CV disease (*N*=73[*])			
	Overall	**Stage 1 (*n*=61[*])**	**Stage 2 (*n*=12)**
CKD,[†] *n* (%)			
Stage 1	36/65 (55.4)	32/53 (60.4)	4 (33.3)
Stage 2	22/65 (33.9)	16/53 (30.2)	6 (50.0)
Stage 3	7/65 (10.8)	5/53 (9.4)	2 (16.7)
LVH, *n* (%)	12/60 (20.0)	10/48 (20.8)[‡]	2 (16.7)
Advanced retinopathy, *n* (%)	4 (5.5)	2 (3.3)	2 (16.7)
Established CV disease, *n* (%)	10 (13.7)	7 (11.5)	3 (25.0)

CKD = chronic kidney disease, LVH = left ventricular hypertrophy, established CV disease = stroke, transient ischaemic attack, coronary heart disease, heart failure and peripheral artery disease.

[*]Unless otherwise indicated.

[†]Missing data = 8 in stage 1 hypertension.

[‡]Missing data = 13.

Table 7. Risk stratification of patients, n (%)			
	Overall (*N*=72)	**Stage 1 (*n*=60) ***	**Stage 2 (*n*=12)**
Low risk <1%	11 (15.2)	11 (18.3)	0
Moderate risk 1 - <5%	25 (34.7)	21 (35.0)	4 (33.3)
High risk 5 - 10%	24 (33.3)	20 (33.3)	4 (33.3)
Very high risk ≥10%	12 (16.7)	8 (13.3)	4 (33.3)

* Missing data = 1.

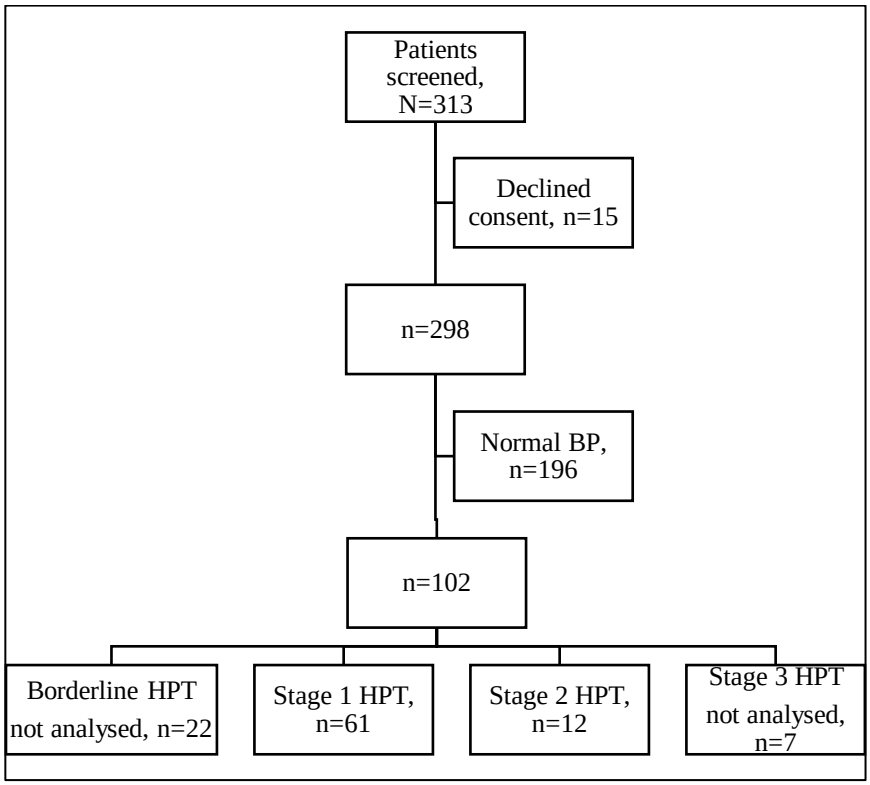

Figure 1: Flow chart of patient recruitment in seven hospitals(BP=blood pressure; HPT=hypertension).

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A multicentre cross-sectional descriptive study evaluating the cardiovascular risk profile of preoperatively identified patients with hypertension

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Background. The prevalence of hypertension in adults in South Africa (SA) is 35%. Hypertension is the most important modifiable risk factor for cardiovascular (CV) and chronic kidney disease (CKD) in sub-Saharan Africa. However, 49% of people are unaware of their blood pressure status. Screening for hypertension prior to surgery provides a unique opportunity to diagnose and treat affected individuals. Furthermore, assessing overall CV risk identifies patients at highest risk for complications, and improves the utilisation of scarce resources.
Objective. To evaluate the CV risk profile of hypertensive patients in the adult population of the Western Cape Province presenting for elective non-cardiac, non-obstetric surgery.
Methods. This report documents the CV risk profile of patients recruited to the HASS-2 study (Hypertension and Surgery Study 2), which was undertaken in seven Western Cape hospitals. Patients were screened for hypertension and pharmacological treatment was initiated or adjusted in patients with stages 1 and 2 disease. Stage 3 patients were referred to a physician. In the present substudy, patients with stages 1 and 2 hypertension were assessed for associated CV risk factors, the presence of target organ damage, and documented CV or kidney disease; they received an overall risk stratification according to the 2018 European Society of Cardiology and the European Society of Hypertension Guidelines.
Results. Sixty-one patients with stage 1 and 12 with stage 2 hypertension were analysed. Established CV disease was present in 13.7% of the study population, and CKD (eGFR <60 mL/min) in 10.8%. Seventy-one percent of the study group had a raised body mass index, and 55.9% underlying metabolic syndrome. Prediabetes and diabetes were present in 16.1% and 14.5% respectively. According to the 2018 European guidelines, 34.7% were at moderate, 33.3% at high and 16.7% at very high risk for a CV event in the following 10 years.
Conclusions. The perioperative period is a critical time during which surgeons, nurses and anaesthetists can influence patients' CV risk of adverse events. This involves appropriate screening, education and treatment. In this study population, nearly 9 out of 10 elective surgical patients with stage 1 or 2 hypertension had CV risk factors placing them at moderate to very high risk. The simultaneous assessment of these additional CV risk parameters, in addition to diagnosis and management of hypertension, may further decrease the health and financial burden in resource-limited facilities in SA, and improve CV outcomes.

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Cardiovascular (CV) disease is the leading cause of death worldwide.[1] In 2013 in sub-Saharan Africa alone, there were approximately 1 million associated deaths.[2] Hypertension is the most important modifiable risk factor for preventing CV disease in Africa, but there is a considerable unmet need. According to the late Prof. Bongani Mayosi, it was the 'number one best buy' for preventing heart disease in Africa.[3]

There is an estimated 35.1% prevalence of hypertension in the South African (SA) adult population. However, there are significant deficiencies in management, as 48.7% of the adult population have never been screened, are unaware of their hypertension status, and are at risk for adverse CV events.[4] Identifying people with hypertension is an important step towards improving treatment of the disease and preventing adverse CV events.

The perioperative period is an ideal opportunity to screen for hypertension, as measuring blood pressure (BP) before surgery is mandatory. In a recent study, approximately 50% of patients presenting for non-cardiac elective surgery were identified as having hypertension, of whom 10% were newly diagnosed, and 40% were found to have poorly controlled hypertension.[5] Furthermore, there has been a burgeoning epidemic of other CV risk factors (obesity, dyslipidaemia, and dysglycaemia) that cluster with hypertension.

Although there is a direct relationship between adverse CV outcome and raised BP, this is modified by the presence of CV risk factors (advanced age, smoking, dyslipidaemia, obesity, and diabetes), target organ damage (e.g. left ventricular hypertrophy (LVH), as evidenced by electrocardiogram (ECG) changes), and established CV or kidney disease. For example, a patient with stage 1 hypertension with no risk factors may have a predicted risk of an adverse CV event in the next 10 years of <1%, but a diabetic patient with end organ damage may have a risk of >10%.[6]

CV risk stratification is fundamental to all hypertension guidelines, since in absolute terms treatment of patients at highest risk will yield the greatest number of events prevented, and those at lowest risk the least. This enables a limited-resource healthcare system to use funds optimally and target other risk factors. The perioperative period presents an ideal opportunity to identify and educate these patients, and improve their treatment.

The primary objective was to describe the comorbid risk profile of hypertensive patients identified in the recent Hypertension and Surgery Study 2 (HASS-2) conducted in Western Cape Province, SA[7] This substudy involved identifying CV risk factors, target organ damage, and established CV and kidney disease, in newly diagnosed or poorly controlled hypertensive patients.

Methods

This is a substudy of HASS-2. Briefly, HASS-2 was a multicentre cross-sectional study conducted at seven hospitals in Western Cape Province, SA: Groote Schuur (a tertiary referral hospital); and six level two institutions, namely George, Mitchells Plain, New Somerset, Paarl, Victoria and Worcester hospitals. Data were collected over a period of 5 working days by anaesthesia medical officers, registrars and specialists, as well as personnel from nursing and surgical departments involved in patient management. Adult patients presenting for elective non-cardiac and non-obstetric surgery were recruited. The inclusion criteria were age ≥18 years, and stage 1 and stage 2 hypertension as defined by the South African Hypertension Practice Guideline 2014 (Table 1).[8]

Patients were excluded if they declined to participate in the study, were scheduled for day case procedures, local ophthalmic procedures, obstetric or cardiac surgery, or had normal, high-normal BP or stage 3 hypertension as defined by the South African Hypertension Guideline 2014. Stage 3 patients were referred to a physician for further management.

All consenting patients presenting at the in-hospital preoperative visit the day before their surgery were screened for hypertension, using a validated automated device. The BP measurements were conducted by both nursing staff and anaesthetists the day prior to surgery, to mitigate the effect of anxiety. This was done in accordance with recommendations in the Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British Hypertension Society.[9]

The present substudy was approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (ref. no. HREC REF 830/2018), and the Western Cape Department of Health. All centres involved had institutional approval granted. The study was registered on ClinicalTrials.gov (ref. no. NCT03921086). All patients provided written informed consent and the Revised Standards for Quality Improvement Reporting (SQUIRE) were followed.[10]

Height, weight, and waist circumference were measured, and body mass index (BMI) calculated. Normal weight was defined as BMI <25, overweight 25 - 30, and obese >30 kg/m^2.

The following investigations were performed on patients included in the study, to assess overall CV risk prior to surgery: fasting lipogram, fasting blood glucose, $HbA1_C$, sodium, potassium, creatinine, haemoglobin, urine dipsticks for proteinuria, and ECG.

The American Diabetes Association criteria were used to classify prediabetes and diabetes. Diabetes was defined as HBA1c ≥6.5% or fasting glucose ≥7 mmol/L, and prediabetes as HbA1c between 5.7% and 6.4% or fasting glucose between 5.6 mmol/L and 6.9 mmol/L. The American Heart Association/The National Heart, Lung, and Blood Institute criteria were used to define metabolic syndrome (Table 2).[11]

The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease-epidemiology collaboration equation (CKD-EPI), and kidney disease was staged from 1 to 5 (Table 3). Urine dipsticks detecting proteinuria 1+ or more

Table 1. Definition of hypertension according to the South African Hypertension Practice Guideline 2014[8]

Stage	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Optimal	<120	<80
Normal	120 - 129	80 - 84
High-normal	130 - 139	85 - 89
Stage 1	140 - 159	90 - 99
Stage 2	160 - 179	100 - 109
Stage 3	≥180	≥110

Table 2. American Heart Association/National Cholesterol Education Program definition of metabolic syndrome (≥3 of the criteria below are required)

Risk factor	Diagnostic threshold
Abdominal obesity: men	>102 cm
Abdominal obesity: women	>88 cm
Triglycerides	>1.7 mmol/L
HDL cholesterol: men	<1.03 mmol/L
HDL cholesterol: women	<1.3 mmol/L
Blood pressure	≥130/≥85 mmHg
Fasting blood glucose	>5.55 mmol/L

Table 3. Stages of CKD

Stage	Classification	eGFR range (mL/min/1.73 m^2)
Stage 1	Kidney damage with normal function	>90
Stage 2	Kidney damage with mild CKD	60 - 89
Stage 3A	Moderate CKD	45 - 59
Stage 3B	Moderate CKD	30 - 44
Stage 4	Severe CKD	15 - 29
Stage 5	Kidney failure	<15

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

were regarded as significant. Left ventricular hypertrophy (LVH) on ECG was defined according to the Framingham criteria: R in AVL >1.1 mV; R in V5 or V6 ≥2.5 mV, S in V1 or V2 ≥2.5 mV, S in V1 or V2 + R in V5 or V6 ≥3.5 mV, or S in III + R in I ≥2.5 mV.[12]

The 10-year CV risk was calculated using the SCORE system of the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) risk stratification guidelines, which combine elevated BP measurements, risk factors, target organ damage and overt CV or kidney disease. Low risk was a calculated 10-year SCORE of <1%, moderate risk 1 - 5%, high risk 5 - 10% and very high risk >10%.[6,13]

Data were anonymously recorded on data capture forms designed for the study, and thereafter captured electronically onto the secured Research Electronic Data Capture (REDCap) data base, with no random verification. Hard copies were filed in the Department of Anaesthesia and Perioperative Medicine of the University of Cape Town.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp., USA). Categorical variables were reported as proportions and compared using the χ^2 test and Fisher's exact test, as appropriate. Continuous variables were described as mean and standard deviation (SD) or median and interquartile range (IQR) and compared using the *t*-test or one-way analysis of variance.

Results

The patient recruitment flow chart is shown in Fig. 1. Analysis of CV risk was confined to patients with stages 1 and 2 hypertension. Stage 3 patients were excluded because they were at high risk based on their BP measurements alone.[6] Forty-two (57.5%) of the 73 patients were known hypertensives and 31 (42.5%) were newly diagnosed.

The overall baseline demographic details are shown in Table 4. The mean age was 57 years and 57.5% were females. Patients with stage 2 hypertension had a higher mean systolic BP (168 v. 151 mmHg, p=0.001) compared with those with stage 1. There was no difference in diastolic BP between stages 1 and 2. With regard to CV risk factors, 47% were obese (BMI >30 kg/m^2), and 24.2% were overweight (BMI 25 - 30 kg/m^2). Metabolic syndrome was diagnosed in 55.9%, and prediabetes and diabetes were present in 16.1% and 14.5% respectively (9 patients in each stage). Increased waist circumference was found in 84.6% of females compared with 37.0% of males.

Key baseline laboratory data pertaining to dyslipidaemia, diabetes and chronic kidney disease are shown in Table 5. The overall mean low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels were 1.91 and 1.08 mmol/L respectively. The median eGFR was 96 in stage 1 and 77 mL/min in stage 2 hypertension (p=0.14).

The presence of target organ damage (TOD), and overt CV and kidney disease is shown in Table 6. Seven patients (10.8%) had stage 3 CKD and 19 (29.7%) proteinuria.

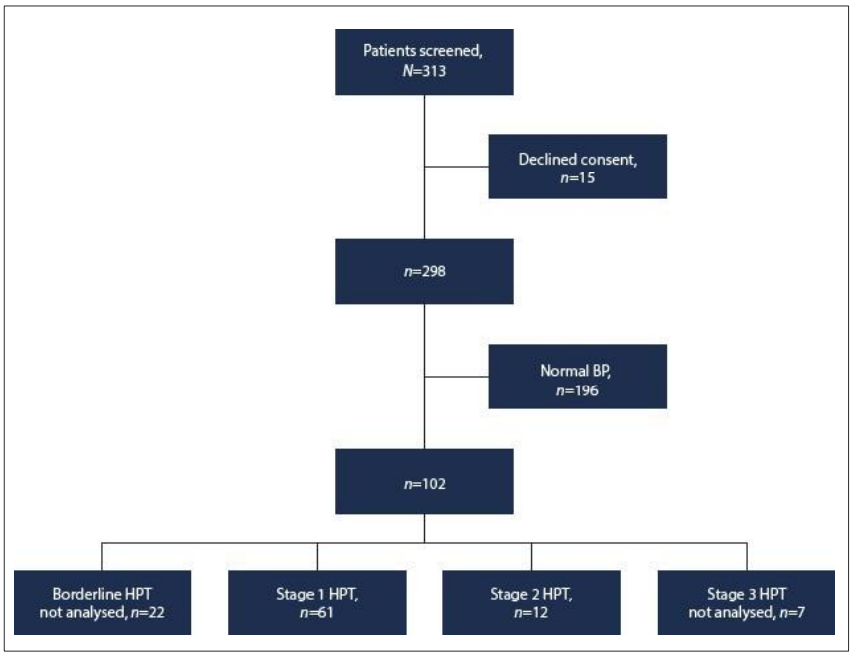

Fig. 1. Flow chart of patient recruitment in seven hospitals (BP = blood pressure; HPT = hypertension).

Table 4. Baseline patient demographic details (*N*=73*)

Parameter	Overall	Stage 1 (*n*=61*)	Stage 2 (*n*=12*)	*p*-value
Age (y), mean (SD)	57 (13.4)	56 (13.1)	62 (14.5)	0.166
Sex, *n* (%)				
Female	42 (57.5)	36 (59.0)	6 (50.0)	
Male	31 (42.5)	25 (41.0)	6 (50.0)	0.751
Systolic BP (mmHg), mean (SD)	154 (11.8)	151 (10.6)	168 (5.2)	< 0.001
Diastolic BP (mmHg), mean (SD)	88 (10)	87 (9.7)	89 (11.3)	0.4
BMI (kg/m^2), *n* (%)				
Normal	19/66 (28.8)	16/54 (29.6)†	3 (25.0)	0.949
Overweight	16/66 (24.2)	13/54 (24.1)†	3 (25.0)	0.949
Obese	31/66 (47.0)	25/54 (46.3)†	6 (50.0)	0.949
Waist circumference: female ≥88 cm, *n* (%)	33/39 (84.6)	27/33 (81.8)‡	6 (100)	0.256
Waist circumference: male ≥102 cm, *n* (%)	10/27 (37)	9/21 (42.9)‡	1 (16.7)	0.241
Metabolic syndrome, *n* (%)	33/59 (55.9)	26/47 (55.3)§	7 (58.3)	1.0

*Unless otherwise indicated.
†Missing data *n*=7.
‡Missing data *n*=3 females and 4 males in stage 1.
§Missing data *n*=14.

Table 5. Key baseline laboratory parameters (*N*=73*)

Parameter	Overall	Stage 1 (*n*=61*)	Stage 2 (*n*=12*)	*p*-value
LDL (mmol/L), mean (SD)	1.91 (1.26)	1.70 (1.14)†	2.39 (1.61)	0.093
HDL (mmol/L), mean (SD)	1.08 (0.49)	1.11(0.52)‡	1.27 (0.35)	0.310
Triglycerides (mmol/L), mean (SD)	1.71 (0.91)	1.72 (0.95)‡	1.66 (0.93)	0.846
Pre-diabetes, *n* (%)	9/56 (16.1)	7/45 (15.6)§	2/11 (18.2)¶	0.832
Diabetes, *n* (%)	9/63 (14.5)	8/50 (16.0) ‖	1 (8.3)	0.498
HbA1c %, mean (SD)	5.33 (2.25)	5.14 (2.03)†	5.52 (2.71)	0.591
Fasting blood glucose (mmol/L), mean (SD)	4.95 (2.05)	4.83 (2.04)§	4.58 (2.24)	0.711
Uric acid (mmol/L), mean (SD)	0.31 (0.13)	0.29 (0.12)**	0.37 (0.10)¶	0.58
eGFR (mL/min), median (IQR)	95 (77 - 109)	96 (84 - 112)	77 (64 - 95)	0.14
Dipstick proteinuria, *n* (%)	19/64 (29.7)	16/53 (30.2)††	3/11 (27.3)¶	0.847

SD = standard deviation, IQR = interquartile range, eGFR = estimated glomerular filtration rate.
*Unless otherwise indicated.
†Missing data *n*=13.
‡Missing data *n*=12.
§Missing data *n*=16.
¶Missing data *n*=1.
‖ Missing data *n*=11.
**Missing data *n*=15.
††Missing data *n*=8.

Table 6. Baseline target organ damage and established CV disease (*N*=73*)

	Overall	Stage 1 (*n*=61*)	Stage 2 (*n*=12)
CKD,† *n* (%)			
Stage 1	36/65 (55.4)	32/53 (60.4)	4 (33.3)
Stage 2	22/65 (33.9)	16/53 (30.2)	6 (50.0)
Stage 3	7/65 (10.8)	5/53 (9.4)	2 (16.7)
LVH, *n* (%)	12/60 (20.0)	10/48 (20.8)‡	2 (16.7)
Advanced retinopathy, *n* (%)	4 (5.5)	2 (3.3)	2 (16.7)
Established CV disease, *n* (%)	10 (13.7)	7 (11.5)	3 (25.0)

CKD = chronic kidney disease, LVH = left ventricular hypertrophy, established CV disease = stroke, transient ischaemic attack, coronary heart disease, heart failure and peripheral artery disease.
*Unless otherwise indicated.
†Missing data *n*=8 in stage 1 hypertension.
‡Missing data *n*=13.

There were no cases of stages 4 or 5 CKD. LVH on ECG, according to Framingham criteria, was present in 20% of patients.

The risk stratification of patients according to the SCORE system of the ESH/ECS is shown in Table 7. Overall 16.7% were at very high, 33.3% high, 34.7% moderate and 15.2% low risk for CV events. There were no differences between stages 1 and 2 hypertension, except that there were no low-risk cases in stage 2 patients, since their BP automatically defines them as moderate risk.

Table 7. Risk stratification of patients

	Overall (*N*=72)	Stage 1 (*n*=60)*	Stage 2 (*n*=12)
Low risk <1%, *n* (%)	11 (15.2)	11 (18.3)	0
Moderate risk 1 - <5%, *n* (%)	25 (34.7)	21 (35.0)	4 (33.3)
High risk 5 - 10%, *n* (%)	24 (33.3)	20 (33.3)	4 (33.3)
Very high risk ≥10%, *n* (%)	12 (16.7)	8 (13.3)	4 (33.3)

*Missing data *n*=1.

Discussion

Principal findings

This substudy showed that the coexistence of CV risk factors influences the overall risk stratification of patients with hypertension. Using the SCORE system from the ESH/ESC hypertension guidelines we found that nearly 9 out of 10 elective surgical patients with stages 1 or 2 hypertension have a moderate to very high risk of experiencing CV events, and 5 out of 10 patients have a high or very high risk. Only 15% of participants with stage 1 hypertension were classified as low risk according to the SCORE system. The South African Hypertension Practice Guideline[8] advises that these patients may only require lifestyle modification for 3 - 6 months, and antihypertensive therapy if uncontrolled after this period of time. In stage 1 hypertension, 46% of patients were classified as high or very high risk; this underscores the importance of risk stratification, even in patients with so-called mild hypertension. Recent guidelines have suggested that patients at high risk should be targeted for more intensive BP control if resources permit. In addition, our findings may underestimate CV risk, as ESH/ESC guidelines recommend multiplying the SCORE risk by 1.3 for people residing in sub-Saharan Africa. However, multiplying the SCORE by 1.3 should be individualised, considering the diverse population of sub-Saharan Africa.

Overall, 7 out of 10 patients were overweight or obese, and 6 out of 10 had underlying metabolic syndrome. Interestingly, abdominal obesity was present in 84.6% of females v. 37.0% of males. The high prevalence of these CV risks suggests that there is considerable opportunity for improving the lifestyle of patients in terms of diet and physical activity. Prediabetes and diabetes were present in 16.1% and 14.5% respectively, and the mean HbA1c level of diabetic patients was suboptimal, which highlights poor disease control and increased risk, in those already diagnosed with diabetes. The mean LDL cholesterol was 1.91 mmol/L, which is a surprising result that is not entirely explained. It may represent a negative phase reaction in patients undergoing surgery,[14] or possibly high levels of statin use in the public sector in the Western Cape.

CV risk is potentially modifiable if risk factors are identified and treated appropriately. In this study established CV disease was

present in 14% of patients, unrecognised CKD (eGFR <60 mL/min) in 11%, proteinuria in 30%, and 1 in 5 patients fulfilled criteria for LVH on ECG. This emphasises the importance of screening patients preoperatively to decrease morbidity.

Implications of the study

Hypertension is one of the most common comorbidities associated with elective non-cardiac surgery.[5] This, together with additional CV risk factors, significantly increases the perioperative risk of these patients.[6,13] CV risk stratification is fundamental to all hypertension guidelines, since in absolute terms treatment of patients at highest risk will yield the greatest number of events prevented, and those at lowest risk the least. This enables a limited-resource healthcare system to use funds optimally and target treatment of these risk factors to prevent CV disease.

In a recent study in the Western Cape,[5] the importance was shown of identifying poorly controlled hypertension and diagnosing new disease in the perioperative period. The present substudy indicates that screening for additional CV risk factors in the perioperative period may improve morbidity and mortality.

CV disease is a leading cause of death,[1] and in SA the majority of patients are initially assessed in a primary healthcare setting. Excluding age, CV risk factors are generally modifiable. This study has shown that the perioperative period is a key opportunity for the identification of goal-directed screening parameters which can substantially influence the overall health of patients. Initiation of therapy based on abnormalities detected at this time could reduce the burden on already strained secondary and tertiary institutions.

Our findings have particular relevance in view of the increasing burden of non-communicable diseases in sub-Saharan Africa from 1990 to 2017, which includes significant increases in hypertensive and ischaemic heart disease, stroke and CKD.[15]

Study strengths and limitations

A strength of this multicentre investigation was that data collection was performed prior to surgery. This allowed identification of those patients at risk, provided education to both patients and surgical staff, and if necessary, allowed for the referral of patients for further management (specifically stage 3 hypertension) and follow-up.

A limitation of this study was missing data of some of the parameters used to classify CV risk (inadequate data for diagnosis of metabolic syndrome in 19%, absent baseline laboratory data in 11 - 18%, and no ECG diagnosis of LVH in 18%). eGFR results from the laboratory were not corrected for body surface area. In addition, the data entered into REDCap had no random verification. We do not expect these factors to have resulted in major errors of risk classification, although some minor misclassifications may have been possible. Importantly, we do not believe this would have changed the fundamental message of this work, which is that hypertensive patients who present for elective surgery in the Western Cape predominantly have an important CV risk profile.

Further limitations of the study were that there were no data captured on the prevalence of smoking, and use of statins was not recorded in the questionnaire. Day case surgery was also excluded in the screening process of HASS-2, thereby possibly missing undiagnosed or poorly controlled hypertension. Further research involving larger study populations would be beneficial to substantiate the findings of this substudy.

Conclusions

The perioperative period is a significant period during which surgeons, nurses and anaesthetists can influence patients' CV risk of adverse events. This involves appropriate screening, education and treatment. The ultimate goal is to improve the overall lifestyle, pharmacological management and health of the SA population. The simultaneous assessment of CV risk factors, in addition to diagnosis and management of hypertension, may further decrease the health and financial burden in resource-limited facilities in SA, and improve CV outcomes.

Declaration. None.

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Author contributions. Tis submission has 17 authors from a multicentre cross-sectional observational study conducted at seven Western Cape hospitals. All authors (SG, CP, BR, RD, MF, FR, JD, MN, JS, EC, EC, VK, TP, ZF, JR, RvZ and BB) were involved in the overall conception and execution of the study, as well as the interpretation, drafing and critical revision of the work, and final approval of the version to be published, and agreed to be accountable for all aspects, accuracy and integrity of the work. FR and JD were responsible for data collection at George Hospital, EC and EC at Somerset Hospital, VK and TP at Paarl Hospital, ZF at Victoria Hospital, SG and CP at Groote Schuur Hospital, JR at Mitchell's Plain Hospital, and RvZ at Worcester Hospital.

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Conflicts of interest. None.

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Appendices

a) Protocol

Protocol for **H**ypertension **A**nd **S**urgery **S**tudy (HASS) 2: Substudy

A multicentre cross-sectional descriptive study evaluating the risk profile of hypertensive patients identified perioperatively over a period of one week. (HASS 2)

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Study Summary

1. Introduction

There is an estimated 30% prevalence of hypertension in the South African adult population. In the perioperative period, there is a 20-25% prevalence of hypertension found in elective non-cardiac surgery patients.

Hypertension is a well known component of metabolic syndrome and the prevalence of metabolic syndrome has increased over the past few decades. Hypertension together with metabolic syndrome increases the risk of morbidity and increases the burden on an already limited health care system.

The perioperative period presents a key opportunity to identify, educate and optimise treatment of these patients. This may diminish the strain on the healthcare system.

This is a descriptive substudy analysing co-morbidities associated with hypertension, in order to better stratify this population with the ultimate aim of improving patients' health and reducing the financial burden on health care.

2. **Background**

Hypertension affects over 1 billion people worldwide [2].

In patients presenting for elective non-cardiac surgery, hypertension is one of the most commonly encountered co-morbidities, with an estimated prevalence of 20-25% [4]. In a recent study (HREC Ref: 661/2016; 708/2016 and NHRD WC_2016RP55_876), approximately 50% of patients presenting for non-cardiac elective surgery were identified as having hypertension [3]. Importantly, about 10% of all patients presenting for elective surgery were newly diagnosed with hypertension. Furthermore, 40% of those patients identified as hypertensive, were found to have poorly controlled hypertension [3].

Metabolic syndrome has become a worldwide major public health problem and has increased in prevalence over the past few decades. Features of metabolic syndrome include hypertension, dyslipidaemia, elevated fasting blood glucose and abdominal obesity. [5]

South Africans in particular, are at high risk of cardiovascular disease, since this country has among the highest prevalences of smoking, dyslipidaemia, undiagnosed diabetes mellitus and obesity in Africa. [6] The WHO estimates the prevalence of hypercholesterolaemia to be 40% in men and 37% in women. [7] The prevalence of obesity is higher in the African population compared to the rest of the world. [7] According to the International Diabetes Federation World Atlas, it is predicted that the prevalence of diabetes in Africa will rise from 14 million at present to 34 million in 2040. [7]

Cardiovascular disease and its complications include coronary heart disease, myocardial infarction, stroke, heart failure, arrhythmias, chronic kidney disease, peripheral vascular disease and retinopathy [7] [8]. Cardiovascular disease is the leading cause of death worldwide. [1] In 2013 in sub-Saharan Africa alone, there were approximately 1 million associated deaths. [7]

Patients with diabetes mellitus, hypertension, dyslipidaemia, kidney disease (with or without proteinuria) and established atherosclerotic disease are considered to be very high risk for cardiovascular events.[7] The risk of morbidity and mortality increases as risk factors increase.
The risk of morbidity and mortality in this population makes them a vulnerable group. This, together with the added physiological stress of surgery, may dramatically increase cardiovascular risk and complications in this population.

There is therefore a crucial opportunity for perioperative clinicians to diagnose and treat these aspects of metabolic syndrome found in hypertensive patients. Through screening, educating and treating these patients, cardiovascular risk and associated morbidity and mortality may be reduced. Identifying and treating these factors early in the perioperative period will also decrease the financial burden on an already resource-limited health care system.

Ultimately, this cross sectional descriptive substudy aims to decrease short and long term morbidity and mortality, through education of clinicians and patients.

Aim:
Describe the co-morbid risk profile of hypertensive patients identified in the HASS 2 study.

Objective:

Identify diabetes mellitus, dyslipidaemia, renal impairment, obesity, ECG changes in newly diagnosed or poorly controlled hypertensive patients identified in the HASS 2 study.

Educate these identified patients and encourage follow up at their primary health care facility.

Primary outcome:
Description of the co-morbidities of hypertensive patients presenting for elective surgery.

3. **Methodology**

Study design:
This will be a multicentre cross-sectional study. It will include Groote Schuur-, George-, Mitchells Plain-, New Somerset-, Paarl-, Victoria- and Worcester Hospitals as for the primary HASS 2 study.

Adult patients fulfilling the inclusion criteria who are presenting for elective non-cardiac and non-obstetric surgery will be recruited. Patients who are newly diagnosed hypertensives or poorly controlled hypertensives will be identified by the anaesthetist at the preoperative consultation. It is this identified group of patients in whom the cardiovascular risk factors diabetes mellitus, dyslipidaemia, obesity, renal impairment and ECG changes will be identified and analysed.

Patient population:

We will recruit approximately 100 hypertensive patients, either newly diagnosed or poorly controlled.

Inclusion criteria:

- Adult (older than 18 years)
- Elective surgery at preoperative in-hospital visit
- All stage 1 and stage 2 hypertensive patients as defined by the South African Hypertension Practice Guideline 2014

Exclusion criteria:

- Patient refusal
- Day case surgery
- Obstetric and cardiac surgery

- Patients with severe hypertension (>180/110 mmHg) (Stage 3) as defined by the South African Hypertension Practice Guideline 2014
- Patients with blood pressures within normal ranges.

Recruitment:

Patients will be recruited at the preoperative in-hospital anaesthesia consultation. Those patients identified as hypertensives will be classified as newly diagnosed, poorly controlled or well controlled hypertensives. According to the HASS 2 algorithm, the first 2 groups will have treatment initiated or escalated. Patients with normal blood pressure will not be recruited for the study.

Patients recruited for this substudy will have the following routine tests done:

Fasting lipogram

Fasting blood glucose level

HBA1C level

Serum sodium, potassium, creatinine and calculation of eGFR (CKD-EPI equation)

Urine dipstix

Serum uric acid level

ECG

Waist circumference and body mass index (BMI)

This will be a part of routine screening of the preoperative patient for the HASS 2 study, with the exception of the serum uric acid level, lipogram, and routine HbA1C level. Blood will be sampled from the patient in theatre by the anaesthetist during induction, after insertion of an IV line, so that no additional blood sampling will be experienced by the patients. Tests will be sent to the NHLS laboratory for processing and the results obtained will kept strictly confidential.

Informed consent:
Written informed consent will be obtained from all participants. This will be a short addition to the approved HASS 2 study consent form, in connection with an approximately 10 ml increase in blood sampled. Forms will be available in English and explained to the participants in the language of their choice. A translator will assist with interpretation if required.

Data collection:

Anaesthesia Registrars, Medical Officers and Specialists will collect data over a period of one working week at the seven hospitals in the Western Cape. All patients presenting at the in-hospital preoperative visit will have their blood pressure measured and classified into the above-mentioned groups by the attending anaesthetist. All patients identified as having stage 1 and 2 hypertension will be recruited for the study.

Data confidentiality:
Participants will be assigned a study number and any data captured will be stored and analysed using the study number only, to protect confidentiality. A record of hospital admission numbers will be maintained, to follow up patients. Study records that identify a patient will be kept confidential as required by law. Privacy regulations provide safeguards for anonymity, security and authorised access. Except when required by law, no data will identify the patient in the study records. The data collected remains the intellectual property of the University of Cape Town.

All demographic data pertaining to a participant will be collected on a standardised form as detailed above.

Data analysis:
All data will be collected electronically from NHLS, entered electronically into the secure RedCap application, and analysed with the help of statisticians appointed by the Department. Data will be kept anonymous, as no patient-identifying data will be recorded on the standardised forms at the preoperative visit.

The relevant definitions for the risk factors are as follows:

1 LVH:

Framingham criteria *(Circulation,1990; 81:815-820)*

R in AVL > 1.1 mV

R in V5 or V6 (left precordial leads) ≥ 2.5 mV

S in V1 or V2 (right precordial leads) ≥ 2.5 mV

S in V1 or V2 + R in V5 or V6 ≥ 3.5 mV

S in III + R in 1 ≥ 2.5 mV

2 Stages of CKD and GFR for each stage:

Stage 1 with normal or high GFR (GFR > 90 mL/min)

Stage 2 Mild CKD (GFR = 60-89 mL/min)

Stage 3A Moderate CKD (GFR = 45-59 mL/min)

Stage 3B Moderate CKD (GFR = 30-44 mL/min)

Stage 4 Severe CKD (GFR = 15-29 mL/min)

Stage 5 End Stage CKD (GFR <15 mL/min)

3 Metabolic syndrome: ≥3 of the below criteria are required

Risk Factor	Diagnostic threshold
Abdominal obesity	
Men	>102 cm
Women	>88 cm
Triglycerides	>1.77 mmol/L
HDL Cholesterol	
Men	<1 mmol/L
Women	<1.3 mmol/L
Blood pressure	≥130/≥85 mmHg
Fasting glucose	> 6 mmol/L

Ref: NCEP JAMA 2001, 285: 2486-97

4 BMI:

Category	BMI (kg/m^2)	
	from	to
Very severely underweight		15
Severely underweight	15	16
Underweight	16	18.5

Normal (healthy weight)	18.5	25
Overweight	25	30
Obese Class I (Moderately obese)	30	35
Obese Class II (Severely obese)	35	40
Obese Class III (Very severely obese)	40	45
Obese Class IV (Morbidly Obese)	45	50
Obese Class V (Super Obese)	50	60
Obese Class VI (Hyper Obese)	60	

Statistical Analysis:

Descriptive statistics (mean and standard deviation) will be used to analyse the relative contribution of the co-morbidities identified, as well as the laboratory results.

Timeline:

Data collection scheduled for 14 January-18 January 2018

5. Dissemination of results:

Study results will be recorded and submitted in the form of a M. Med dissertation to the University of Cape Town for assessment as per postgraduate requirements. These results will be made available to the public. The results of the study will also be submitted to a peer-reviewed journal for consideration for publication.

Resources and Costs:

Funding for the running of the study (data collection, storage and analysis) will be obtained from the Department of Anaesthesia and Perioperative Medicine of the University of Cape Town.

Ethics

Risks and Benefits:
This study poses no potential risk as the bloods taken for the required tests will be a part of routine perioperative screening and care. Should a patient be newly diagnosed with a cardiovascular risk factor they will be counseled appropriately and their initiation and follow up of new treatment will be ensured. A discharge educational letter for the patient and a referral letter for the patient's primary health care facility will be given.

Benefits include:

- Early detection of cardiovascular risk factors of metabolic syndrome.
- Optimization of patient's health condition to decrease morbidity and mortality risk in both the short and long term.
- Decrease in financial burden on healthcare system.
- Information from this study may be used for future working models in the health care system.

The ongoing ethical conduct of the trial remains the responsibility of the Principal Investigator. The trial will conform to the principles outlined in the Helsinki Declaration (2013).

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b) Data collection

Hypertension and Surgery Study 2: Data Collection Form

Patient Name: Folder Number: Date of birth: (Place patient sticker here)

Nurses blood pressure readings:

1. SBP:	DBP:
2. SBP:	DBP:
3. SBP:	DBP:
4. SBP:	DBP:
5. SBP:	DBP:

Doctor's blood pressure readings:

1. SBP:	DBP:
2. SBP:	DBP:
3. SBP:	DBP:
4. SBP:	DBP:
5. SBP:	DBP:

Blood results:

Sodium:
Potassium:
Creatinine:
Hb:
Fasting glucose
HbA1C:
Total cholesterol:
LDL:
HDL:
Triglycerides:
Urine dipstix:
Uric Acid:

c) Consent form

INFORMED CONSENT FORM

Title of Study:

A multicentre, cross-sectional quality improvement project: evaluating the implementation of a hypertension guideline protocol by perioperative clinicians.

Investigators: Dr Claire-Louise Pfister, Dr Margot Flint, Dr Marcin Nejthardt, Dr Francois Roodt, Prof Robert Dyer, Prof Justiaan Swanevelder, Prof Bruce Biccard, Dr Sarisha Govender

Department of Anaesthesia and Perioperative Medicine, University of Cape Town, South Africa

Information:
You are being approached to be a part of a research study on blood pressure. The doctors that are running this study are trying to improve the management of your blood pressure if they identify that it is higher than normal. High blood pressure is commonly part of a condition called metabolic syndrome. Metabolic syndrome is the term for a group of conditions that can put you at risk of complications such as: stroke, heart attack and kidney disease. Metabolic syndrome has become more common in the past few decades. High blood pressure with metabolic syndrome increases the risk of serious health complications.

If you have no objection, the doctors would appreciate your permission to collect information relating to your blood pressure measured in the ward, any medication you are currently taking to control your blood pressure, and any medication which is started during the study to control your blood pressure. This study will benefit you, as your high blood pressure will be treated timeously. You will be given some more information about your blood pressure and a letter for follow up at your local clinic to continue your medication in the future.

At the same time, we would like to screen you for features of metabolic syndrome which includes Diabetes (high blood sugar), high cholesterol, being overweight and kidney disease. These are conditions which are known to be associated with high blood pressure.
These tests will include;

- Some blood tests to check:
    - o Your kidney function (urea and electrolytes and uric acid)
    - o Diabetes (HbA1C and glucose)
    - o Cholesterol (Lipogram), and
- ECG to check your heart.

The ECG that we do routinely to check your heart function will be done before your surgery in the ward and will not cause any pain or discomfort. The blood tests will be done when we put the drip up for your operation. We will take a small amount of blood (approximately 2 table spoons) for the blood tests. The results of these tests will give the doctors more information about your health in order to improve your long-term health and treatment.

Any relevant results will be shared with you and managed appropriately according to the South African Hypertension Guideline of 2014. Should we pick up any abnormal results you will be handed an information sheet on metabolic syndrome as well as a letter that you should take to your doctor on your next visit to help him or her monitor and treat your condition. The study doctors will also be available should you have any questions.

This information will be stored both on paper and on computer. To protect your privacy, the information will be labelled in a way that you are not identified. If the results of these studies are published, your identity will be kept confidential.

"If you agree to be a part of this study, Dr Flint will collect your hospital number. If you are put onto tablets for high blood pressure, or your tablets for this are changed, Dr Flint will follow-up on the internet pharmacy database to see if you collect the medications at three and six months after you leave the hospital."

By signing this form, you are allowing the use of this information for the research study. These research projects have been approved by the Human Research Ethics Committee of the University of Cape Town. If you have any ethical concerns or questions about your rights or welfare as a participant in this research, the Human Research Ethics Committee can be contacted on 021 406 6338.

Please read this form carefully and ask the investigator (study doctor) to explain any words or information that are not clear to you. This will help to ensure that you understand the details of your participation before you give your consent. You will be given a copy of this consent form to take home with you. The doctors will answer any questions you may have about this consent form and about the study.

What will happen if I sign this form but don't want to be in the study later on?
If you decide at any time that you don't want to be a part of this study, you can let one of the doctors know. Taking part is purely voluntary and by not agreeing to take part will not affect your normal care for surgery.
The UCT's Faculty of Health Sciences Human Research Ethics Committee can be contacted on 021 406 6338 in case you have any ethical concerns or questions about your rights or welfare as a participant on this research study.

CONSENT STATEMENT
I therefore certify the following:
• I have read the above information form and understand that the study involves research.
• I understand that the doctors will make a copy of some of my routinely recorded data from my standard patient care.

• I have had the opportunity to ask questions. All my questions have been answered to my satisfaction.
• I understand that any information that leaves the doctor's office will be deidentified
(i.e., identifying information will be removed from the documents).
_____YES _____ NO

Name of Participant/Legal Representative (printed) Signature

Name of person obtaining consent (printed) Signature Date:

d) Ethics Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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20 December 2018

HREC REF: 830/2018

Prof B Rayner
Division of Nephrology & Hypertension
E13, Renal Unit
NGSH

Dear Prof Rayner

PROJECT TITLE: A MULTICENTRE CROSS-SECTIONAL DESCRIPTIVE STUDY EVALUATING THE RISK PROFILE OF HYPERTENSIVE PATIENTS IDENTIFIED PERIOPERATIVELY OVER A PERIOD OF ONE WEEK. (HASS 2) Sub-study linked to 489/2018 (MMED Candidate - Dr S Govender)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 December 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Sarisha Govender will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

e) Journal Instructions to Author

Author Guidelines taken from http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been

published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice

- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style

- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ*therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.

- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.

- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

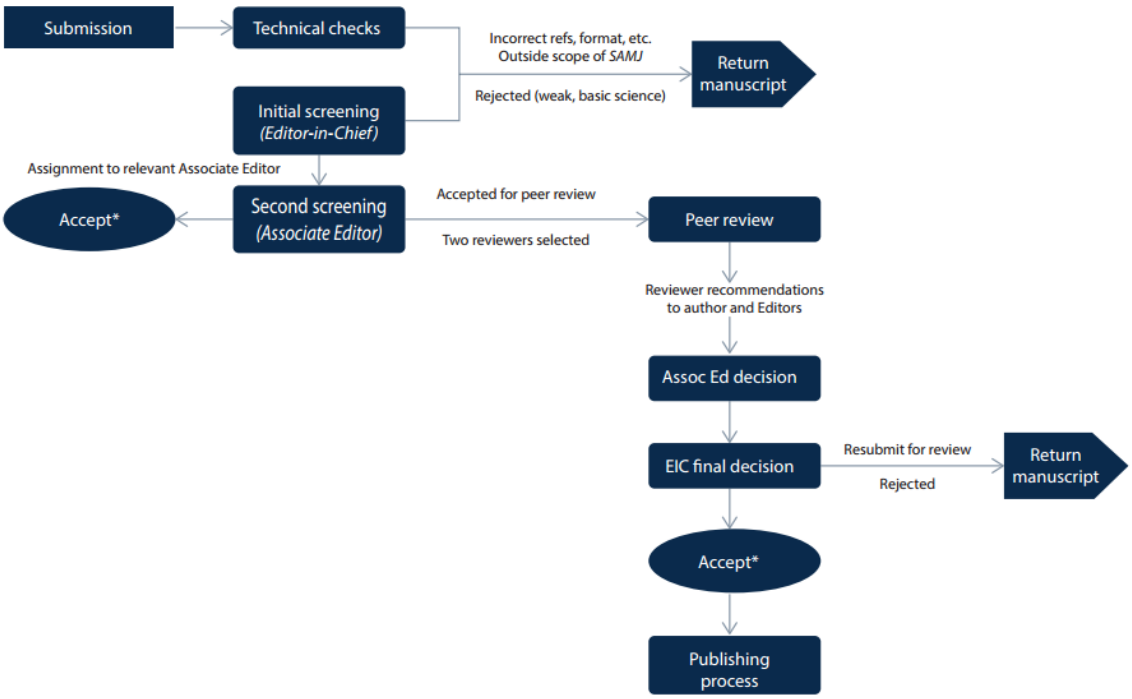
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts, CME
**Some minor revisions may be requested

Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of SAMA. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@samedical.org for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Copyright Notice

main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement.

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f) Correspondence with Journal

Ref.: SAMJ14640
A multicentre cross-sectional descriptive study evaluating the cardiovascular risk profile of preoperatively identified patients with hypertension
South African Medical Journal

Dear Dr Govender,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript.

For your guidance, reviewers' comments are appended below.

If you are prepared to undertake the work required, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by Mar 31, 2020. Please let us know if you require additional time.

To submit a revision, go to https://www.editorialmanager.com/samj/ and log in as an Author. You will see a menu item called Submission Needing Revision.

Best wishes

Bridget Farham, PhD
Editor
South African Medical Journal

Reviewers' comments:

Reviewer's Responses to Questions

Please comment on your General impression of this manuscript - bear the following in mind:

Is the article relevant?

Does it offer anything new?

Are there similar studies in our region/outside the region?

Does it add to the existing medical body of knowledge?

On first glance, are the methods, results and conclusions reasonable?

Do the conclusions actually draw on the results?

Does the article have a clear message?

Will it help SAMJ readers make better clinical decisions and, if so, how?

Is a general medical journal the right place for it?

Reviewer #1: This article is highly relevant. It offers a novel approach to making the best use of the preoperative assessment of patients before surgery. Instead on focusing on the immediate short-term (as is "normally" the case it offers to use the data gathered by anaesthetists and their team to influence the long-term of patients with hypertension. I do not know of other articles proposing to use the preoperative assessment data to "inform" the long-term. I can say yes to all the other questions listed under this heading.

Reviewer #2: The article is relevant though contextual WC study.

Yes it is novel peri-operative/ preoperative research question being described.

Hypertension studies are done worldwide and cardiovascular risk assessment tools are continuously evaluated in the literature

It will definitely add to the medical body of knowledge, although it is contextual and a small sample.

Every aspect reasonable.

Yes the conclusion draw on the result. Not sure about the financial benefit that it wants to claim. This screening might be better done at primary care level- but at present it is not done, so it is a very valid method in performing it.

Yes a very clear message.

The manuscript and research show that the preoperative assessment of hypertension and the cardiovascular risk that goes with it is a worthwhile intervention, and could lead to reduction of morbidity and mortality, if applied in a province and eventually countrywide.

Yes a general medical journal is the correct place for publishing this research as; this is a diagnosis that can be made by all HCP and their proxies and the risk assessment tools is general medicine guidelines and general clinical assessments used everyday by generalists. The preoperative assessment is only one of many intervention time points at which this strategy could be used to identify and categorize a patient as low, medium, high or extreme high risk of developing cardiovascular complications within 10 years of diagnosis.

Please comment on the Methods and analysis presented in this manuscript

Study design

Is the research question and planned outcomes clearly defined?

Was the sample adequate and sufficiently described?

Are the methods adequately described and appropriate to the study objectives?

Statistical considerations

Are simple statistical methods applied appropriately?

Reviewer #1: I can say yes to all of the questions.

Reviewer #2: This is a substudy of a larger study, should the larger multicenter primary study be published first.

It is a descriptive study of 102 patients, worrying to me as reviewer is the amount of missing data. Looking at risk factors and medication questions- mentioned by the authors in the limitation section self. The cardiovascular risk is assessed using laboratory tests not regularly performed and this show in the missing data. Bedside tests like urine dipsticks was not available or not done in 9 patients out of 102= 8,8% of patients. I am asking in the result section how does this influence the results and influence the conclusion to the study.

Adequately described.

It is very simple and appropriately applied statistics without any statistical errors. Saying that, my question to the authors is, with the amount of missing data in some subsets of the data (ex. laboratory data- lipogram, Uric acid and dipsticks) should they use probability to explain the subset or can normal and abnormal "tests" in the missing data influence the true probability of the risk in the population to much??

Please comment on the Results, Discussion and Conclusions presented in this manuscript

Results

Is the population/sample adequately described?

Are the results clearly presented?

Are they credible and do they answer the research question?

Are tables clear and useful, not simply mirroring data discussed in the Results text?

Reviewer #1: I can say yes to all the questions. There is however a limitation because of the number of patients included in the study.

Reviewer #2: yes, substudy, and performed over one working week in WC hospitals.

well presented results.

yes they do, except for the missing data- how much does it influence the final conclusion to the data, please see my attached word document. There is a definite difference in very high risk between stage 1 and 2 patients 13.3% vs 33.3%.

Tables used perfectly.

Discussion

Are the results well discussed in light of previous evidence and the literature?

Are the limitations of the study sufficiently discussed?/ Are the strengths and weakness discussed?

Is the meaning and relevance of the study discussed?

Reviewer #1: I can aslo say yes to all the questions

Reviewer #2: There is a definite difference in very high risk between stage 1 and 2 patients 13.3% vs 33.3%, not mentioned in the discussion. This is rather obvious but worthwhile to mention.

In discussing the SCORE risk in sub Saharan countries: The reviewer believes, it really depends on the individual patient being from a specific group within the diverse population whether - 1x or 1,3x SCORE risk should be used. Sub Saharan Africa and especially the WC is a very diverse population.

Do the authors think the Balci article is a correct reference?? Maybe, but maybe worthwhile to seek a better explanation or reference. Conclusion of Balci et al: really referring to ACS: Lipid modification after ACS should be taken into account and the fasting lipid profile assessment should be performed as soon as possible after admission to the hospital. Increasing evidence suggest that statin therapy reduces morbidity and mortality in patients experiencing an acute coronary event, when initiated immediately after patients' admission. The reduction of LDL following ACS is supported by the evidence based data. Therefore, interventions on the lipid

profile of patients diagnosed with ACS should be initiated as soon as possible. In addition, statins should be given to patients with a metabolic status that does not pose a risk, according to guidelines. The fluctuations in lipid and lipoprotein levels should be monitored for a few months after ACS and any clinical decision should be based on them.
Maybe look at: Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res. 2004;45:1169–1196. [PubMed]

Conclusion

Are the implications of the research summarised?

Do the authors make relevant recommendations for future research or application?

Reviewer #1: The implications are stated and could even be strengthned

Reviewer #2: Implications- and the strong reasoning why this should be published come out in the conclusion.

Yes they do state the necessity of larger number and ongoing research in the field.

Reviewer #1: To make the best use of data on blood pressure at the time of assessment before surgery makes great sense bearing in mind than in many patients hypertension is not recognised and not treated or inadequately controlled. It is important that the diagnosis of hypertension is made. Investigations and identification of complications and risk factors make it possible to determine the long-term risk in individual patients. Your study demonstrates that some patients with stages 1 or 2 hypertension are at high risk. This is a significant contribution to the literature on hypertension with practical implications as far as preoperative assessment is concerned. Probably what should be emphasized the most is the role of cardiovascular risk factors, over and above the level of blood pressure itself. This is well recognised in the 2018 ESC/ESH guideline

However, there is a problem: only 73 patients with stage 1 and 12 patients with stage 2 hypertension were found (plus 7 with stage 3 hypertension) in a cohort of 313 patients screened (a prevalence of hypertension of 25%). Because of the small numbers of patients, in the patients' characteristics only systolic blood pressures were significantly different. The same is true of all basic laboratory parameters where there a no significant differences for the same reason.

One finding stands out: with stage 2 hypertension, no patients was at low risk but this is expected as the scoring system itself gives moderate risk for stage 2 hypertension. What is important is that the same proportion of stage 1 and stage 2 had moderate or high risk. This should be emphasized more in the discussion as there could be a view that stage 1 hypertension does not matter that much when picked-up at pre-assessment. This may be true of the immediate perioperative period (the main concern of the AAGBI guideline) but not in the long-term which is

more important.

Page 5, lines 50-58. "Patients were excluded if they declined to participate in the study, were scheduled for day case procedures, local ophthalmic procedures". If the aim is to use data for identifying patients who are at risk why exclude day case and ophthalmic? In the long-term they are as much at risk as those undergoing other types of surgeries. As you state: "Identifying people with hypertension is an important step to improving treatment of the disease and preventing adverse CV events." I suppose that it was felt that for these patients the investigations were "excessive" I think this should be specified in the paper.

Table 1. This is also the ESC/ESH classification of 2018.

Reviewer #2: Dear Author/s
Thank you for the submission, this research is very applicable to the readers of SAMJ as this 'model' can be implemented at any contact point with a HCP, not only preoperatively.
I have questions, suggestions and comments that I would like you to answer and make before publication of the manuscript, see attached word document with comments.
Publication of this substudy before the primary/ main study is up to the discretion of the Editor of the Journal.
I would like to review a revision of the manuscript.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.
View Attachments

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Dr Bridget Farham
Editor in Chief, SAMJ

Revision: Manuscript: SAMJ14640
A multicentre cross-sectional descriptive study evaluating the cardiovascular risk profile of preoperatively identified patients with hypertension

Thank you for the opportunity to revise our manuscript. We have addressed each point made by the reviewers, including a detailed response to the annotated word document of Reviewer 2. Our responses are in italics in each case, following the comments of the reviewers. We have attached a revised manuscript with all revisions in red font.

Response to reviewers:

General impression of the manuscript

Reviewer #1: This article is highly relevant. It offers a novel approach to making the best use of the preoperative assessment of patients before surgery. Instead of focusing on the immediate short-term (as is "normally" the case it offers to use the data gathered by anaesthetists and their team to influence the long-term of patients with hypertension. I do not know of other articles proposing to use the preoperative assessment data to "inform" the long-term. I can say yes to all the other questions listed under this heading.

Response: The comments are appreciated.

Reviewer #2: The article is relevant though contextual WC study.
Yes it is novel peri-operative/ preoperative research question being described.
Hypertension studies are done worldwide and cardiovascular risk assessment tools are continuously evaluated in the literature
It will definitely add to the medical body of knowledge, although it is contextual and a small

sample.
Every aspect reasonable.
Yes the conclusion draw on the result. Not sure about the financial benefit that it wants to claim. This screening might be better done at primary care level- but at present it is not done, so it is a very valid method in performing it.
Yes a very clear message.
The manuscript and research show that the preoperative assessment of hypertension and the cardiovascular risk that goes with it is a worthwhile intervention, and could lead to reduction of morbidity and mortality, if applied in a province and eventually countrywide.
Yes a general medical journal is the correct place for publishing this research as; this is a diagnosis that can be made by all HCP and their proxies and the risk assessment tools is general medicine guidelines and general clinical assessments used everyday by generalists. The preoperative assessment is only one of many intervention time points at which this strategy could be used to identify and categorize a patient as low, medium, high or extreme high risk of developing cardiovascular complications within 10 years of diagnosis.

Response: The comments are appreciated.

Methods and analysis (study design and statistical analysis)

Reviewer #1: I can say yes to all of the questions.

Response: The comments are appreciated.

Reviewer #2: This is a sub-study of a larger study, should the larger multicentre primary study be published first.

Response: We have addressed this issue below in our response to the annotated word document with appended comments by Reviewer 2. We feel that is not necessary to delay publication of the sub-study.

It is a descriptive study of 102 patients, worrying to me as reviewer is the amount of missing data. Looking at risk factors and medication questions- mentioned by the authors in the limitation section self. The cardiovascular risk is assessed using laboratory tests not regularly performed and this show in the missing data. Bedside tests like urine dipsticks was not available or not done in 9 patients out of 102= 8,8% of patients. I am asking in the result section how does this influence the results and influence the conclusion to the study.

Response: These concerns have been addressed in detail in our responses to the annotated word document of Reviewer 2, below.

It is very simple and appropriately applied statistics without any statistical errors. Saying that, my question to the authors is, with the amount of missing data in some subsets of the data (ex. laboratory data- lipogram, Uric acid and dipsticks) should they use probability to explain the subset or can normal and abnormal "tests" in the missing data influence the true probability of the risk in the population to much??

Response: We have addressed these concerns in our response to the annotated word document of Reviewer 2, below.

Results

Reviewer #1: I can say yes to all the questions. There is however a limitation because of the number of patients included in the study.

Response: We agree and this has been highlighted in the revised Discussion.

Reviewer #2: yes, sub-study, and performed over one working week in WC hospitals; well-presented results.
Yes they do, except for the missing data- how much does it influence the final conclusion to the data, please see my attached word document. There is a definite difference in very high risk between stage 1 and 2 patients 13.3% vs 33.3%. Tables used perfectly.

Response: We address all these points in our response to Reviewer 2's annotated document, below. The comments are appreciated.

Discussion

Reviewer #1: I can also say yes to all the questions.

Response: The comment is appreciated.

Reviewer #2: There is a definite difference in very high risk between stage 1 and 2 patients 13.3% vs 33.3%, not mentioned in the discussion. This is rather obvious but worthwhile to mention.

Response: The comment is appreciated, but as the subgroup is very small, we believe that this signal is fragile[1] and therefore would prefer not to draw the reader's attention to this point.

In discussing the SCORE risk in sub Saharan countries: The reviewer believes, it really depends on the individual patient being from a specific group within the diverse population whether - 1x or 1,3x SCORE risk should be used. Sub Saharan Africa and especially the WC is a very diverse population.

Response: This is addressed in our response to the annotated paper of Reviewer 2, below.

Do the authors think the Balci article is a correct reference?? Maybe, but maybe worthwhile to seek a better explanation or reference. Conclusion of Balci et al: really referring to ACS: Lipid modification after ACS should be taken into account and the fasting lipid profile assessment should be performed as soon as possible after admission to the hospital. Increasing evidence suggest that statin therapy reduces morbidity and mortality in patients experiencing an acute coronary event, when initiated immediately after patients' admission. The reduction of LDL following ACS is supported by the evidence-based data. Therefore, interventions on the lipid profile of patients diagnosed with ACS should be initiated as soon as possible. In addition, statins should be given to patients with a metabolic status that does not pose a risk, according to guidelines. The fluctuations in lipid and lipoprotein levels should be monitored for a few months after ACS and any clinical decision should be based on them.
Maybe look at: Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res. 2004;45:1169–1196. [PubMed]

Response: Thank you for providing a more appropriate reference than the one we provided. This reference will be used instead to help explain the low LDL levels in this population. The issues related to ACS are beyond the scope of the article and are not really pertinent to patients admitted for elective surgery.

Conclusion

Reviewer #1: The implications are stated and could even be strengthened.
Reviewer #2: Implications- and the strong reasoning why this should be published come out in the conclusion.
Yes they do state the necessity of larger number and ongoing research in the field.

Response: These comments are appreciated.

Response to annotated paper sent by Reviewer 2:

Abstract
Comment in Abstract on potentially delaying publication of this sub-study until the publication of the Hass-2 paper:

Response: The present paper addresses different issues from those that are the main focus of Hass-2, and it is an independent sub-study, so that it is not necessary to delay publication of this sub-study.

Methods
Comment on clarification of the exact subject of the present manuscript:

Response: We have clarified the exact subject at the end of the introduction and the beginning of the methods, with all changes in red font:

"The primary objective was to describe the co-morbid risk profile of hypertensive patients identified in the recent Hypertension and Surgery Study (HASS-2) conducted in the Western Cape (unpublished, personal communication Dr C Pfister). This sub-study involved identifying cardiovascular risk factors, target organ damage, established CV and kidney disease, in newly diagnosed or poorly controlled hypertensive patients.

Methods

This is a sub-study of HASS-2. HASS-2 was a perioperative hypertension quality improvement project, which is currently in the process of publication. Briefly, HASS-2 was a multicentre cross-sectional study that was conducted at 7 hospitals in the Western Cape, South Africa: Groote Schuur (a tertiary referral hospital) and six level two institutions, namely George, Mitchells Plain, New Somerset, Paarl, Victoria and Worcester Hospital."

Under Framingham Criteria:

Response: Changed from R in 1 to R in I (Roman numeral, as suggested).

Comment on quality assurance of data capture:

Response: There was no random verification of the data entered into REDCap. This has been added to the Methods, and listed as a limitation in the discussion.

Results
Comment on Legend of Table 4, concerning the sex of the patients, and missing data:

Response: For the readers' interpretation, we would prefer to retain the information on male/female demographics. We agree that missing data in patients as regards the metabolic syndrome is a limitation of our study, and have included this in the Discussion.

Comments on legend of Table 5, concerning missing data:

Response: The mean (SD) of the available data on HDL is 1.8 (0.49). It is unlikely that elevated HDL in a percentage of the missing cases would result in a major re-classification of risk. We feel that further statistical analysis would not add value. However, we agree with the reviewer that the missing data is a limitation, and this is now included in comments in the Discussion (please see below, and in the revised manuscript). It was not the intention of this study to create a classification system with great accuracy, but rather to indicate the potential value of the simultaneous assessment of CV risk factors in addition to hypertension.

Comment on the legend of Table 6:

Response: We agree that missing data as regards LVH may be significant, and have included this limitation in the Discussion.

Comment on Table 7 – risk stratification.

Response: Major incorrect classification is unlikely, but occasional misclassification is possible (please see Discussion section on limitations). All these points (REDCap validation, and missing data points) have all been addressed in this new paragraph in the discussion;

'A limitation of this study is some missing data of the parameters used to classify CV risk (inadequate data for diagnosis of metabolic syndrome in 19%, absent baseline laboratory data in 11-18%, and no ECG diagnosis of LVH in 18%). In addition, the data entered into REDCap had no random verification. We do not expect these factors to have resulted in major errors of risk classification, although some minor misclassifications may have been possible. Importantly, we do not believe this would have changed the fundamental message of this work, which is that hypertensive patients who present for elective surgery, in the Western Cape, predominantly have an important CV risk profile.'

Comment on difference in very high risk between Stage 1 and 2 hypertension:

Response: The comment is appreciated, but as the subgroup is very small, we believe that this signal is fragile[1] and therefore would prefer not to draw the reader's attention to this point.

Discussion

Comment on use of the SCORE risk:

Response: This is a statement made in the Guideline – it may be that there are areas in sub-Saharan Africa in which multiplying by 1.3 may overestimate risk, but as a general rule, we feel that the statement holds true. We have now added this to the Discussion:
"However, multiplying the SCORE by 1.0 or 1.3 should be individualised, considering the diverse population of sub-Saharan Africa."

Comment on Balci article: *Please see above*

Response: We have accepted the preferred reference. Thank you for this reference.

Comment on urine dipsticks:

Response: This missing data is unlikely to significantly change the result. We have discussed the limitations of the missing data in the discussion.

The following statement has been added to the Discussion in the section on limitations, to address the concerns about missing data:

"A limitation of this study is some missing data of the parameters used to classify CV risk (inadequate data for diagnosis of metabolic syndrome in 19%, absent baseline laboratory data in 11-18%, and no ECG diagnosis of LVH in 18%). In addition, the data entered into REDCap had no random verification. We do not expect these factors to have resulted in major errors of risk classification, although some minor misclassifications may have been possible. Importantly, we do not believe this would have changed the fundamental message of this work, which is that hypertensive patients who present for elective surgery, in the Western Cape, predominantly have an important CV risk profile.

Further limitations of the study were that was no data was captured on the prevalence of smoking, and use of statins was not recorded in the questionnaire. Day case surgery was also excluded in the screening process of HASS-2, thereby possibly missing undiagnosed or poorly controlled hypertension. *Further research involving larger study populations would be beneficial to substantiate the findings of this sub-study."*

<u>Final general comments of the 2 reviewers:</u>

Reviewer #1: To make the best use of data on blood pressure at the time of assessment before surgery makes great sense bearing in mind than in many patients hypertension is not recognised and not treated or inadequately controlled. It is important that the diagnosis of hypertension is made. Investigations and identification of complications and risk factors make it possible to determine the long-term risk in individual patients. Your study demonstrates that some patients with stages 1 or 2 hypertension are at high risk. This is a significant contribution to the literature on hypertension with practical implications as far as preoperative assessment is concerned. Probably what should be emphasized the most is the role of cardiovascular risk factors, over and above the level of blood pressure itself. This is well recognised in the 2018 ESC/ESH guideline.

Response: Thank you for these comments. We feel that we have appropriately emphasised the importance of the CV risk factors.

However, there is a problem: only 73 patients with stage 1 and 12 patients with stage 2 hypertension were found (plus 7 with stage 3 hypertension) in a cohort of 313 patients screened (a prevalence of hypertension of 25%). Because of the small numbers of patients, in the patients' characteristics only systolic blood pressures were significantly different. The same is true of all basic laboratory parameters where there a no significant differences for the same reason.

Response: These points are well taken. The sample size was small, and a much larger study would be required to show differences with narrow confidence intervals. The statement is made in the limitations section of the Discussion: "Further research involving larger study populations would be beneficial to substantiate the findings of this sub-study."

One finding stands out: with stage 2 hypertension, no patients was at low risk, but this is expected as the scoring system itself gives moderate risk for stage 2 hypertension. What is

important is that the same proportion of stage 1 and stage 2 had moderate or high risk. This should be emphasized more in the discussion as there could be a view that stage 1 hypertension does not matter that much when picked-up at pre-assessment. This may be true of the immediate perioperative period (the main concern of the AAGBI guideline) but not in the long-term which is more important.

Response: We agree that the finding of moderate or high risk in Stage 1 patients is important, and have emphasised this in the first paragraph of the Discussion: "In stage 1 hypertension, 46% of patients were classified as high- or very high risk; this underscores the importance of risk stratification even in patients with so-called mild hypertension."

Page 5, lines 50-58. "Patients were excluded if they declined to participate in the study, were scheduled for day case procedures, local ophthalmic procedures". If the aim is to use data for identifying patients who are at risk why exclude day case and ophthalmic? In the long-term they are as much at risk as those undergoing other types of surgeries. As you state: "Identifying people with hypertension is an important step to improving treatment of the disease and preventing adverse CV events." I suppose that it was felt that for these patients the investigations were "excessive" I think this should be specified in the paper.

Response: We understand and agree with this valid viewpoint. The reason for exclusion was that day case procedures were excluded for the main HASS-2 study, because there would have been no opportunity to provide the prescribed BP assessment, to implement the algorithm for initiation of anti-hypertensive therapy by the anaesthesiologist, and in-hospital follow-up. The sub-study was thus limited by the inclusion/exclusion criteria of the main study.

Table 1. This is also the ESC/ESH classification of 2018.

Response: Thank you. We have added this to the Table legend.

Reviewer #2: Dear Author/s
Thank you for the submission, this research is very applicable to the readers of SAMJ as this 'model' can be implemented at any contact point with a HCP, not only preoperatively.
I have questions, suggestions and comments that I would like you to answer and make before publication of the manuscript, see attached word document with comments.
Publication of this substudy before the primary/ main study is up to the discretion of the Editor of the Journal.
I would like to review a revision of the manuscript.

Response: Thank you for your detailed comments in the word document, to each of which we have responded, above.

We look forward to your and the reviewers' response to our revision.

Yours sincerely,

Sarisha Govender
On behalf of all co-authors

SAMJ 14640 ORIGINAL RESEARCH

A multicentre cross-sectional descriptive study evaluating the cardiovascular risk profile of preoperatively identified patients with hypertension

S Govender,[1] MB ChB, DA (SA); **C Pfister,**[1] MB ChB, BSc, DA, DCH; **B Rayner,**[2] MB ChB, FCP (SA), MMed, PhD; **R A Dyer,**[1] MB ChB, FCA (SA), PhD; **M Flint,**[1] BSc (Medical Physiology), HSc, MSc, PhD; **F Roodt,**[3] MB ChB, FCA (SA); **J Davids,**[3] MB ChB, DA (SA), FCA (SA), MMed (Anaes); **M B Nejthardt,**[1] BSc Hons (Physiology), MB ChB, DA (SA), FCA (SA); **J L Swanevelder,**[1] MB ChB, DA (SA), FCA (SA), MMed, FRCA; **E Chiu,**[1,4] MB ChB, DA; **E Cloete,**[1,4] MB ChB, DA (SA), FCA (SA); **V Koller,**[5] MB ChB, FCA (SA)**; T Pretorius,**[5] MB ChB, DA (SA), FCA (SA), MMed (Anaesth); **Z Fullerton,**[6] MB ChB, DA (SA), FCA (SA), MMed (Anaesth); **J Roos,**[7] MB ChB, DA (SA),

MMed (Anaesth), FCA (SA); **R van Zyl,**[8] MB ChB, DA (SA), FCA (SA); **B M Biccard,**[1] MB ChB, MMedSci, FCA (SA), PhD

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Corresponding author: *S Govender (govsar@hotmail.com)*

Background. The prevalence of hypertension in adults in South Africa (SA) is 35%. Hypertension is the most important modifiable risk factor for cardiovascular (CV) and chronic kidney disease (CKD) in sub-Saharan Africa. However, 49% of people are unaware of their blood pressure status. Screening for hypertension prior to surgery provides a unique opportunity to diagnose and treat affected individuals. Furthermore, assessing overall CV risk identifies patients at highest risk for complications, and improves the utilisation of scarce resources.
Objective. To evaluate the CV risk profile of hypertensive patients in the adult population of the Western Cape Province presenting for elective non-cardiac, non-obstetric surgery.
Methods. This report documents the CV risk profile of patients recruited to the HASS-2 study (Hypertension and Surgery Study 2), which was undertaken in seven Western Cape hospitals. Patients were screened for hypertension and pharmacological treatment was initiated or adjusted in patients with stages 1 and 2 disease. Stage 3 patients were referred to a physician. In the present substudy, patients with stages 1 and 2 hypertension were assessed for associated CV risk factors, the presence of target organ damage, and documented CV or kidney disease; they received an overall risk stratification according to the 2018 European Society of Cardiology and the European Society of Hypertension Guidelines.
Results. Sixty-one patients with stage 1 and 12 with stage 2 hypertension were analysed. Established CV disease was present in 13.7% of the study population, and CKD (eGFR <60 ml/min) in 10.8%. Seventy-one percent of the study group had a raised body mass index, and 55.9% underlying metabolic syndrome. Prediabetes and diabetes were present in 16.1% and 14.5% **(Query: see query in Table 5)** respectively. According to the 2018 European guidelines, 34.7% were at moderate, 33.3% at high and 16.7% at very high risk for a CV event in the following 10 years.
Conclusions. The perioperative period is a critical time during which surgeons, nurses and anaesthetists can influence patients' CV risk of adverse events. This involves appropriate screening, education and treatment. In this study population, nearly 9 out of 10 elective surgical patients with stage 1 or 2 hypertension had CV risk factors placing them at moderate to very high risk. The simultaneous assessment of these additional CV risk parameters, in addition to diagnosis and management of hypertension, may further decrease the health and financial burden in resource-limited facilities in SA, and improve CV outcomes.

S Afr Med J 2021;111(1):xxx. https://doi.org/10.7196/SAMJ.2020.v111i1.14640

Cardiovascular (CV) disease is the leading cause of death worldwide.[1] In 2013 in sub-Saharan Africa alone, there were approximately 1 million associated deaths.[2] Hypertension is the most important modifiable risk factor for preventing CV disease in Africa, but there is a considerable unmet need. According to the late Prof. Bongani Mayosi, it was the 'number one best buy' for preventing heart disease in Africa.[3]

There is an estimated 35.1% prevalence of hypertension in the South African (SA) adult population. However, there are significant deficiencies in management, as 48.7% of the adult population have never been screened, are unaware of their hypertension status, and are at risk for adverse CV events.[4] Identifying people with hypertension is an important step towards improving treatment of the disease and preventing adverse CV events.

The perioperative period is an ideal opportunity to screen for hypertension, as measuring blood pressure (BP) before surgery is mandatory. In a recent study, approximately 50% of patients presenting for non-cardiac elective surgery were identified as having hypertension, of whom 10% were newly diagnosed, and 40% were found to have poorly controlled hypertension.[5] Furthermore, there has been a burgeoning epidemic of other CV risk factors (obesity, dyslipidaemia, and dysglycaemia) that cluster with hypertension.

Although there is a direct relationship between adverse CV outcome and raised BP, this is modified by the presence of CV risk factors (advanced age, smoking, dyslipidaemia, obesity, and diabetes), target organ damage (e.g. left ventricular hypertrophy (LVH), as evidenced by electrocardiogram (ECG) changes), and established CV or kidney disease. For example, a patient with stage 1 hypertension with no risk factors may have a predicted risk of an adverse CV event in the next 10 years of <1%, but a diabetic patient with end organ damage may have a risk of >10%.[6]

CV risk stratification is fundamental to all hypertension guidelines, since in absolute terms treatment of patients at highest risk will yield the greatest number of events prevented, and those at lowest risk the least. This enables a limited-resource healthcare system to use funds optimally and target other risk factors. The perioperative period presents an ideal opportunity to identify and educate these patients, and improve their treatment.

The primary objective was to describe the comorbid risk profile of hypertensive patients identified in the recent Hypertension and Surgery Study 2 (HASS-2) conducted in the Western Cape Province, SA (Pfister CL, Govender S, Dyer RA, Rayner BL, et al. A multi-center, cross-sectional quality improvement project: the perioperative implementation of a hypertension protocol by anesthesiologists. Anesth Analg. 2020;131:1401–1408)[7]. This substudy involved identifying CV risk factors, target organ damage, and established CV and kidney disease, in newly diagnosed or poorly controlled hypertensive patients.

Methods

This is a substudy of HASS-2. Briefly, HASS-2 was a multicentre cross-sectional study conducted at seven hospitals in the Western Cape Province, SA: Groote Schuur (a tertiary referral hospital); and six level two institutions, namely George, Mitchells Plain, New Somerset, Paarl, Victoria and Worcester hospitals. Data were collected over a period of 5 working days by anaesthesia medical officers, registrars and specialists, as well as personnel from nursing and surgical departments involved in patient management. Adult patients presenting for elective non-cardiac and non-obstetric surgery were recruited. The inclusion criteria were age ≥18 years, and stage 1 and stage 2 hypertension as defined by the South African Hypertension Practice Guideline 2014 (Table 1).[8]

Patients were excluded if they declined to participate in the study, were scheduled for day case procedures, local ophthalmic procedures, obstetric or cardiac surgery, or had normal, high-normal BP or stage 3 hypertension as defined by the South African Hypertension Guideline 2014. Stage 3 patients were referred to a physician for further management.

All consenting patients presenting at the in-hospital preoperative visit the day before their surgery were screened for hypertension, using a validated automated device. The BP measurements were conducted by both nursing staff and anaesthetists the day prior to surgery, to mitigate the effect of anxiety. This was done in accordance with recommendations in the Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British Hypertension Society.[9]

Query: refs 9 – 11 not cited in sequence. Renumber from here?

The present substudy was approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (ref. no. HREC REF 830/2018), and the Western Cape Department of Health. All centres involved had institutional approval granted. The study was registered on ClinicalTrials.gov (ref. no. NCT03921086). All patients provided written informed consent and the Revised Standards for Quality Improvement Reporting (SQUIRE) were followed.[10]

Height, weight, and waist circumference were measured, and body mass index (BMI) calculated. Normal weight was defined as BMI <25, overweight 25 - 30, and obese >30 kg/m^2.

The following investigations were performed on patients included in the study, to assess overall CV risk prior to surgery: fasting lipogram, fasting blood glucose, HbA1C, sodium, potassium, creatinine, haemoglobin, urine dipsticks for proteinuria, and ECG.

The American Diabetes Association criteria were used to classify prediabetes and diabetes. Diabetes was defined as HBA1c ≥6.5% or fasting glucose ≥7 mmol/L, and prediabetes as HbA1c between 5.7% and 6.4% or fasting glucose between 5.6 mmol/L and 6.9 mmol/L. The American Heart Association/The National Heart, Lung, and Blood Institute criteria were used to define metabolic syndrome (Table 2).[11]

The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease-epidemiology collaboration equation (CKD-EPI), and kidney disease was staged from 1 to 5 (Table 3). Urine dipsticks detecting proteinuria 1+ or more were regarded as significant. Left ventricular hypertrophy (LVH) on ECG was defined according to the Framingham criteria: R in AVL >1.1 mV; R in V5 or V6 ≥2.5 mV, S in V1 or V2 ≥2.5 mV, S in V1 or V2 + R in V5 or V6 ≥3.5 mV, or S in III + R in I ≥2.5 mV.[12]

The 10-year CV risk was calculated using the SCORE system of the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) risk stratification guidelines, which combine elevated BP measurements, risk factors, target organ damage and overt CV or kidney disease. Low risk was a calculated 10-year SCORE of <1%, moderate risk 1 - 5%, high risk 5 - 10% and very high risk >10%.[6,13]

Data were anonymously recorded on data capture forms designed for the study, and thereafter captured electronically onto the secured Research Electronic Data Capture (REDCap) data base, with no random verification. Hard copies were filed in the Department of Anaesthesia and Perioperative Medicine of the University of Cape Town.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 25 (SPSS, USA). Categorical variables were reported as proportions and compared using the χ^2 test and Fisher's exact test, as appropriate. Continuous variables were described as mean and standard deviation (SD) or median and interquartile range (IQR) and compared using the *t*-test or one-way analysis of variance.

Results

The patient recruitment flow chart is shown in Fig. 1. Analysis of CV risk was confined to patients with stages 1 and 2 hypertension. Stage 3 patients were excluded because they were at high risk based on their BP measurements alone.[6] Forty-two (57.5%) of the 73 patients were known hypertensives and 31 (42.5%) were newly diagnosed.

The overall baseline demographic details are shown in Table 4. The mean age was 57 years and 57.5% were females. Patients with stage 2 hypertension had a higher mean systolic BP (168 v. 151 mmHg, *p*=0.001) compared with those with stage 1. There was no difference in diastolic BP between stages 1 and 2. With regard to CV risk factors, 47% were obese (BMI >30 kg/m^2), and 24.2% were overweight (BMI 25 - 30 kg/m^2). Metabolic syndrome was diagnosed in 55.9%, and prediabetes and diabetes were present in 16.1% and 14.5% **(Query: as above and in Table 5)** respectively (9 patients in each stage). Increased waist circumference was found in 84.6% of females compared with 37.0% of males.

Key baseline laboratory data pertaining to dyslipidaemia, diabetes and chronic kidney disease are shown in Table 5. The overall mean low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels were 1.91 and 1.08 mmol/L respectively. The median eGFR was 96 in stage 1 and 77 ml/min in stage 2 hypertension (*p*=0.14).

The presence of target organ damage (TOD), and overt CV and kidney disease is shown in Table 6. Seven patients (10.8%) had stage 3 CKD and 19 (29.7%) proteinuria. There were no cases of stages 4 or 5 CKD. LVH on ECG, according to Framingham criteria, was present in 20% of patients.

The risk stratification of patients according to the SCORE system of the ESH/ECS is shown in Table 7. Overall 16.7% were at very high, 33.3% high, 34.7% moderate and 15.2% low risk for CV events. There were no differences between stages 1 and 2 hypertension, except that there were no low-risk cases in stage 2 patients, since their BP automatically defines them as moderate risk.

Discussion

Principal findings

This substudy showed that the coexistence of CV risk factors influences the overall risk stratification of patients with hypertension. Using the SCORE system from the ESH/ESC hypertension guidelines we found that nearly 9 out of 10 elective surgical patients with stages 1 or 2 hypertension have a moderate to very high risk of experiencing CV events, and 5 out of 10 patients have a high or very high risk. Only 15% of participants with stage 1 hypertension were classified as low risk according to the SCORE system. The South African Hypertension Practice Guideline[8] advises that these patients may only require lifestyle modification for 3 - 6 months, and antihypertensive therapy if uncontrolled after this period of time. In stage 1 hypertension, 46% of patients were classified as high or very high risk; this underscores the importance of risk stratification, even in patients with so-called mild hypertension. Recent guidelines have suggested that patients at high risk should be targeted for more intensive BP control if resources permit. In addition, our findings may underestimate CV risk, as ESH/ESC guidelines recommend multiplying the SCORE risk by 1.3 for people residing in sub-Saharan Africa. However, multiplying the SCORE by 1.3 should be individualised, considering the diverse population of sub-Saharan Africa.

Overall, 7 out of 10 patients were overweight or obese, and 6 out of 10 had underlying metabolic syndrome. Interestingly, abdominal obesity was present in 84.6% of females v. 37.0% of males. The high prevalence of these CV risks suggests that there is considerable opportunity for improving the lifestyle of patients in terms of diet and physical activity.

Prediabetes and diabetes were present in 16.1% and 14.5% **(Query: as above and in Table 5)** respectively, and the mean HbA1c level of diabetic patients was suboptimal, which highlights poor disease control and increased risk, in those already diagnosed with diabetes.

The mean LDL cholesterol was 1.91 mmol/L, which is a surprising result that is not entirely explained. It may represent a negative phase reaction in patients undergoing surgery,[14] or possibly high levels of statin use in the public sector in the Western Cape.

CV risk is potentially modifiable if risk factors are identified and treated appropriately. In this study established CV disease was present in 14% of patients, unrecognised CKD (eGFR <60

ml/min) in 11%, proteinuria in 30%, and 1 in 5 patients fulfilled criteria for LVH on ECG. This emphasises the importance of screening patients preoperatively to decrease morbidity.

Implications of the study

Hypertension is one of the most common comorbidities associated with elective non-cardiac surgery.[5] This, together with additional CV risk factors, significantly increases the perioperative risk of these patients.[6,13] CV risk stratification is fundamental to all hypertension guidelines, since in absolute terms treatment of patients at highest risk will yield the greatest number of events prevented, and those at lowest risk the least. This enables a limited-resource healthcare system to use funds optimally and target treatment of these risk factors to prevent CV disease.

In a recent study in the Western Cape,[5] the importance was shown of identifying poorly controlled hypertension and diagnosing new disease in the perioperative period. The present substudy indicates that screening for additional CV risk factors in the perioperative period may improve morbidity and mortality.

CV disease is a leading cause of death,[1] and in SA the majority of patients are initially assessed in a primary healthcare setting. Excluding age, CV risk factors are generally modifiable. This study has shown that the perioperative period is a key opportunity for the identification of goal-directed screening parameters which can substantially influence the overall health of patients. Initiation of therapy based on abnormalities detected at this time could reduce the burden on already strained secondary and tertiary institutions.

Our findings have particular relevance in view of the increasing burden of non-communicable diseases in sub-Saharan Africa from 1990 to 2017, which includes significant increases in hypertensive and ischaemic heart disease, stroke and CKD.[15]

Study strengths and limitations

A strength of this multicentre investigation was that data collection was performed prior to surgery. This allowed identification of those patients at risk, provided education to both patients and surgical staff, and if necessary, allowed for the referral of patients for further management (specifically stage 3 hypertension) and follow-up.

A limitation of this study was missing data of some of the parameters used to classify CV risk (inadequate data for diagnosis of metabolic syndrome in 19%, absent baseline laboratory data in 11 - 18%, and no ECG diagnosis of LVH in 18%). eGFR results from the laboratory were not corrected for body surface area. In addition, the data entered into REDCap had no random verification. We do not expect these factors to have resulted in major errors of risk classification, although some minor misclassifications may have been possible. Importantly, we do not believe this would have changed the fundamental message of this work, which is that hypertensive patients who present for elective surgery in the Western Cape predominantly have an important CV risk profile.

Further limitations of the study were that there were no data captured on the prevalence of smoking, and use of statins was not recorded in the questionnaire. Day case surgery was also excluded in the screening process of HASS-2, thereby possibly missing undiagnosed or poorly controlled hypertension. Further research involving larger study populations would be beneficial to substantiate the findings of this substudy.

Conclusions

The perioperative period is a significant period during which surgeons, nurses and anaesthetists can influence patients' CV risk of adverse events. This involves appropriate screening, education and treatment. The ultimate goal is to improve the overall lifestyle, pharmacological management and health of the SA population. The simultaneous assessment of CV risk factors, in addition to diagnosis and management of hypertension, may further decrease the health and financial burden in resource-limited facilities in SA, and improve CV outcomes.

Declaration. None.
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Author contributions.
This submission has 17 authors from a multicentre cross-sectional observational study conducted at 7 Western Cape hospitals. All authors (SG, CP, BR, RD, MF, FR, JD, MN, JS, EC, E Cloete, VK, TP, ZF, JR, RvZ and BB) were involved in the overall conception and execution of the study, as well as the interpretation, drafting and critical revision of the work, and final approval of the version to be published, and agreed to be accountable for all aspects, accuracy and integrity of the work. FR and JD were responsible for data collection at George-, EC and EC at Somerset-, VK and TP at Paarl-, ZF at Victoria-, SG and CP at Groote Schuur-, JR at Mitchell's Plain-, and RvZ at Worcester Hospital.

Note to author: Please include a short description of authors' roles in preparing the manuscript.

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Conflicts of interest. None.

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Fig. 1. Flow chart of patient recruitment in seven hospitals (BP = blood pressure; HPT = hypertension).

Table 1. Definition of hypertension according to the South African Hypertension Practice Guideline 2014[7]

Stage	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Optimal	<120	<80
Normal	120 - 129	80 - 84
High-normal	130 - 139	85 - 89
Stage 1	140 - 159	90 - 99
Stage 2	160 - 179	100 - 109
Stage 3	≥180	≥110

Table 2. American Heart Association/National Cholesterol Education Program definition of metabolic syndrome (≥3 of the criteria below are required)	
Risk factor	**Diagnostic threshold**
Abdominal obesity: men	>102 cm
Abdominal obesity: women	>88 cm
Triglycerides	>1.7 mmol/L
HDL cholesterol: men	<1.03 mmol/L
HDL cholesterol: women	<1.3 mmol/L
Blood pressure	≥130/≥85 mmHg
Fasting blood glucose	>5.55 mmol/L

Table 3. Stages of chronic kidney disease (CKD)		
Stage	**Classification**	**eGFR range** (mL/min/1.73 m^2)
Stage 1	Kidney damage with normal function	>90
Stage 2	Kidney damage with mild CKD	60 - 89
Stage 3A	Moderate CKD	45 - 59
Stage 3B	Moderate CKD	30 - 44
Stage 4	Severe CKD	15 - 29
Stage 5	Kidney failure	<15
eGFR = estimated glomerular filtration rate.		

Table 4. Baseline patient demographic details (*N*=73*)

Parameter	**Overall**	**Stage 1 (*n*=61*)**	**Stage 2 (*n*=12*)**	***p*-value**
Age (y), mean (SD)	57 (13.4)	56 (13.1)	62 (14.5)	0.166
Sex, *n* (%) Female Male	 42 (57.5) 31 (42.5)	 36 (59.0) 25 (41.0)	 6 (50.0) 6 (50.0)	 0.751
Systolic BP (mmHg), mean (SD)	154 (11.8)	151 (10.6)	168 (5.2)	< 0.001
Diastolic BP (mmHg), mean (SD)	88 (10)	87 (9.7)	89 (11.3)	0.4
BMI (kg/m^2), *n* (%) Normal	 19/66 (28.8)	 16/54 (29.6) †	 3 (25.0)	 0.949
Overweight	16/66 (24.2)	13/54 (24.1) †	3 (25.0)	0.949
Obese	31/66 (47.0)	25/54 (46.3) †	6 (50.0)	0.949
Waist circumference: female ≥88 cm, *n* (%)	33/39 (84.6)	27/33 (81.8)‡	6 (100)	0.256
Waist circumference: male ≥102 cm, *n* (%)	10/27 (37)	9/21 (42.9) ‡ **Author: Please check highlighted figures – see comments below**	1 (16.7)	0.241
Metabolic syndrome, *n* (%)	33/59 (55.9)	26/47 (55.3) ⁋	7 (58.3)	1.0

*Unless otherwise indicated. **(I have added the new totals from which %s were calculated to avoid confusion. Please see query in your original footnote below)**
†Missing data = 7.
‡Missing data = 3 females and 4 males in stage 1.
⁋Missing data = 14.

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missing data: * = 7, ** = 28 females and 40 males in stage 1 **(36 females - 28 = 8??); (there are only 25 males in stage 1)**, and 6 in stage 2,
*** = 14.

Table 5. Key baseline laboratory parameters (*N*=73[*])				
Parameter	**Overall**	**Stage 1 (*n*=61[*])**	**Stage 2 (*n*= 12[*])**	***p*-value**
LDL (mmol/L), mean (SD)	1.91 (1.26)	1.70 (1.14)[†]	2.39 (1.61)	0.093
HDL (mmol/L), mean (SD)	1.08 (0.49)	1.11(0.52)[‡]	1.27 (0.35)	0.310
Triglycerides (mmol/L), mean (SD)	1.71 (0.91)	1.72 (0.95)[‡]	1.66 (0.93)	0.846
Pre-diabetes, n (%)	9/56 (16.1)	7/45 (15.6)[§]	2/11 (18.2)[‖]	0.832
Diabetes, n (%)	9/63 (14.5)	8/50 (16.0)	1 (8.3)	0.498
HbA1c %, mean (SD)	5.33 (2.25)	5.14 (2.03)[†]	5.52 (2.71)	0.591
Fasting blood glucose (mmol/L), mean (SD)	4.95 (2.05)	4.83 (2.04)[§]	4.58 (2.24)	0.711
Uric acid (mmol/L), mean (SD)	0.31 (0.13)	0.29 (0.12)[**]	0.37 (0.10)[‖]	0.58
eGFR (mL/min), **(Query: different in Table 3? Add /1.73 m^2?)** median (IQR)	95 (77 - 109)	96 (84-112)	77 (64-95)	0.14
Dipstick proteinuria, n (%)	19/64 (29.7%)	16/53 (30.2)[††]	3/11 (27.3)[‖]	0.847
SD = standard deviation, IQR = interquartile range, eGFR = estimated glomerular filtration rate. [*]Unless otherwise indicated. [†]Missing data = 13. [‡]Missing data = 12. [§]Missing data = 16. [‖]Missing data = 1. [**]Missing data = 15. [††]Missing data = 8.				
#Missing data = 10				

Table 6. Baseline target organ damage and established CV disease (*N*=73[*])			
	Overall	**Stage 1 (*n*=61[*])**	**Stage 2 (*n*=12)**
CKD,[†] *n* (%)			
Stage 1	36/65 (55.4)	32/53 (60.4)	4 (33.3)
Stage 2	22/65 (33.9)	16/53 (30.2)	6 (50.0)
Stage 3	7/65 (10.8)	5/53 (9.4)	2 (16.7)
LVH, *n* (%)	12/60 (20.0)	10/48 (20.8)[‡]	2 (16.7)
Advanced retinopathy, *n* (%)	4 (5.5)	2 (3.3)	2 (16.7)
Established CV disease, *n* (%)	10 (13.7)	7 (11.5)	3 (25.0)

CKD = chronic kidney disease, LVH = left ventricular hypertrophy, established CV disease = stroke, transient ischaemic attack, coronary heart disease, heart failure and peripheral artery disease.

[*]Unless otherwise indicated.

[†]Missing data = 8 in stage 1 hypertension.

[‡]Missing data = 13.

Table 7. Risk stratification of patients, n (%)			
	Overall (*N*=72)	**Stage 1 (*n*=60) ***	**Stage 2 (*n*=12)**
Low risk <1%	11 (15.2)	11 (18.3)	0
Moderate risk 1 - <5%	25 (34.7)	21 (35.0)	4 (33.3)
High risk 5 - 10%	24 (33.3)	20 (33.3)	4 (33.3)
Very high risk ≥10%	12 (16.7)	8 (13.3)	4 (33.3)
* Missing data = 1.			

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