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Stroke as the index presentation of traditional cardiovascular risk factors and Human Immunodeficiency Virus in a South African population

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ABSTRACT

Objectives: We sought to identify what proportion of each cardiovascular risk factor and Human Immunodeficiency Virus (HIV) was first diagnosed at the time of stroke, compared to those that were diagnosed prior to the event, and to explore if this had any impact on the severity of stroke.
Methods: Adult patients presenting with a new stroke to a quaternary hospital in Johannesburg between 2014 and 2017 were prospectively recruited. Patients were investigated for undiagnosed traditional cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, obesity and smoking), as well as HIV infection. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).
Results: 346 patients were included. Stroke was the index presentation for at least one risk factor in 199 (57.5 %) patients. Dyslipidaemia was newly diagnosed in 76.0 % of all dyslipidaemics (95 out of 125). Newly-diagnosed dyslipidaemia was associated with a more severe neurological deficit (Median NIHSS of 12 (8-16) vs 7 (4-12), p=0.0007) and younger age on presentation (53 (44-63) years vs 62 (51-71) years, p=0.02) as compared to previously-diagnosed dyslipidaemia.
Conclusions: More than half of patients had previously undiagnosed modifiable risk factors at the time of their stroke. Dyslipidaemia was undiagnosed in a very high proportion, and this was associated with a higher stroke severity and younger age of presentation.

Introduction

Stroke is the second leading cause of mortality worldwide, behind only ischemic heart disease.[1] The burden of disease falls disproportionately on lower and lower-middle income countries (LMICs) such as South Africa, with 80 % of the world's burden of stroke-related deaths and 90 % of its disability adjusted life years.[2,3] Stroke patients in LMICs have poorer access to diagnostic and treatment modalities and greater severity of stroke,[4] and as such have higher 3-month mortality than those in high-income countries.[5] Despite this disproportionately large burden of disease, LMICs have access to fewer resources to both prevent and treat stroke.[6]

Large multinational studies affirm that traditional cardiovascular risk factors (RFs) are responsible for the majority of the population risk for stroke.[4,7–9] These include hypertension (HPT), diabetes mellitus (DM), dyslipidaemia, atrial fibrillation (AF), obesity and smoking. Evidence suggests that the increased burden of stroke in LMICs may in part be due to worse control of modifiable RFs and reduced access to healthcare.[10] In order to address the increasing incidence and burden of disease due to stroke, detailed analysis of the identification and control of modifiable stroke RFs, individualised to specific regions and countries, is required.

It is inappropriate to consider stroke risk factors in South Africa without discussing the contribution of Human Immunodeficiency Virus

Abbreviations: AF, atrial fibrillation; AI, artificial intelligence; ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; Dx, diagnosed; ELISA, enzyme-linked immunosorbent assay; HDL, high density lipoprotein cholesterol; HIV, Human Immunodeficiency Virus; HPT, hypertension; ICH, intracerebral haemorrhage; IQR, interquartile range; IS, ischaemic stroke; LDL, low density lipoprotein cholesterol; LMICs, lower-middle income countries; MAP, mean arterial pressure; NIHSS, National Institutes of health stroke scale; PLWH, people living with Human Immunodeficiency Virus; RF, risk factor; SSA, Sub-Saharan Africa; TOD, target organ damage; US$, United States Dollar.

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(HIV). As of 2020, it was estimated that 7.8 million South Africans are living with HIV, making it the country with the most people living with HIV (PLWH) in the world.[11] HIV has been shown to independently contribute to stroke risk, with HIV positive patients having higher incidence of stroke and at younger ages than those who are HIV negative.[12–15] There is now good evidence to suggest that HIV may be considered an independent risk factor for stroke.[15–18] In Sub-Saharan Africa, this increased stroke risk in PLWH appears to be independent of traditional RFs[15] though some recent studies have shown a similar traditional RF profile in PLWH and HIV negative stroke patients.[19]

Problem statement

It is clear that traditional RFs and HIV contribute to a large number of strokes in South Africa. It is however unclear how well these conditions are screened for and managed in the public healthcare sector, with its enormous resource constraints and very large patient load.

We thus sought to identify what proportion of each RF was first diagnosed at the time of stroke, compared to those that were diagnosed prior to the event, and to explore if this had any impact on stroke severity. The identification of potential shortcomings in RF screening and diagnosis is the first step in implementing strategies to decrease and control the RF burden which has been shown to contribute to major cardiovascular disease such as stroke.

Methods

This cross-sectional study took place at the Charlotte Maxeke Johannesburg Academic Hospital, a 1000-bed quaternary-level hospital in Johannesburg, South Africa, from August 2014 to November 2017 (40 months).

We recruited consecutive patients aged 18 years and older who presented with a new stroke. Stroke was defined as per the World Health Organization case definition: "a clinical syndrome consisting of rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting >24 h or leading to death with no apparent cause other than a vascular origin".[20] Exclusion criteria were the diagnosis of meningitis based on cerebrospinal fluid examination, or the presence of intracranial mass lesions on radiographic imaging, or other stroke mimics. Full informed consent was obtained as per the Helsinki Declaration. Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Certificate number M140429, renewed as M190688).

All patients were assessed and examined by the same specialist neurologist (ES), who then co-ordinated and interpreted all relevant investigations. A detailed clinical history and review of medical records was used to establish the presence of a pre-diagnosed RF. Computed tomography scans were performed on all patients. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).

HPT was defined as having 3 or more blood pressure readings greater than 140/90 mm Hg beyond the first 72 h post-stroke, with or without the presence of the following target organ damage (TOD): hypertensive retinopathy on direct ophthalmoscopy, left ventricular hypertrophy on electrocardiogram, echocardiogram or chest X-ray, or renal dysfunction (defined as estimated glomerular filtration rate less than 60 ml/min/1.73m2 with no other cause). Acute post-stroke elevated blood pressure (BP) was not used as diagnostic for HPT due to the well-described transient increase in BP seen acutely post-stroke.[21] Atrial fibrillation was diagnosed on standard 12-lead electrocardiography according to the criteria in the 2014 AHA/ACC/HRS Guideline.[22]

DM was defined as a fasting glucose ≥7.0mmol/l, or a random glucose ≥11.1mmol/l, or an HbA1c >6.5 %. Patients with anaemia were not diagnosed as diabetic solely on HbA1c measurement, to avoid false positives.[23]

Dyslipidaemia was defined as a total cholesterol ≥ 5.2 mmol/L, and/or Low Density Lipoprotein Cholesterol (LDL) ≥ 3.3mmol/L.[24] Blood for lipogram assessment was taken in a non-fasting state. Current evidence suggests that for cardiovascular risk assessment, non-fasting total cholesterol, and LDL are equivalent to a fasting sample.[24–27] Acute post-stroke transient decreases in cholesterol levels were accounted for by taking blood for lipograms within 24 h of the stroke onset, where possible, and by not considering a low post-stroke High Density Lipoprotein Cholesterol (HDL) to be diagnostic for dyslipidaemia.[28–30]

Obesity was defined as a body mass index (BMI) of ≥30 kg/m^2. This was obtained by measuring the patient's height using a stadiometer and the weight using a calibrated mechanical column scale where BMI = weight ÷ height^2. This was not possible in patients unable to stand unaided.

HIV testing (ELISA) was performed in all consenting patients.

Statistical analysis

Data was analysed using Excel (Microsoft) and Graphpad Prism (Graphpad Software V9.5). Continuous variables were evaluated for normality using Shapiro-Wilk and Kolmogorov-Smirnov tests. Chi square, Fisher's exact test and Mann-Whitney statistical tests were then performed for parametric and non-parametric variables where appropriate. Data are reported as median with interquartile ranges (IQR) unless otherwise specified. Only available data was analysed. Missing data was not imputed. P values of less than 0.05 were considered significant.

Results

346 patients presenting with stroke met inclusion criteria. (Fig. 1) Basic demographic data is shown in Table 1. The proportion of male to female patients was exactly 1:1, by random chance. Most patients were black African, with the proportions of different ethnicities being in keeping with the national population of South Africa.[11] 309 patients (89.3 %) had ischaemic stroke (IS), with 37 (10.7 %) having intracerebral haemorrhage (ICH).



Fig. 1. Study flowchart
Blocks shaded in grey indicate patients not included in the study.

Table 1
Demographic characteristics of included patients.

		N (%)
Patients Included		346
Age		
	Median (IQR)	52 (42-63)
Sex	Male	173 (50)
	Female	173 (50)
Ethnicity		
	African	273 (78.9)
	Caucasian	45 (13.0)
	Mixed	17 (4.9)
	Indian/Asian	11 (3.2)
HIV Status		
	Positive	87 (25.1)
	Negative	234 (67.6)
	Unknown	25 (7.2)
Traditional RFs	HPT	229 (66.2)
	Dyslipidaemia (n=339)	125 (36.9)
	Obesity (n= 215)	76 (35.3)
	Smoking	91 (26.3)
	DM	73 (21.1)
	Atrial fibrillation	24 (6.9 %)

DM: diabetes mellitus, **HIV**: Human Immunodeficiency Virus, **HPT**: hypertension, **IQR**: interquartile range

Cardiovascular risk factors

The commonest RF was HPT, which was present in 66.2 % of the cohort, followed by dyslipidaemia in 36.9 % of the 339 patients for whom blood lipid profiles were available (Table 1) The median total cholesterol was 4.4 (3.7 - 5.1) mmol/L, LDL 2.7 (2.1 - 3.4) mmol/L, HDL 1.1 (0.9 - 1.4) mmol/L and triglycerides 1.0 (0.8 - 1.41) mmol/L.

Of those patients who had body mass index measured (n = 215), 35.3 % were clinically obese with BMI > 30 kg/m^2 (Table 1). Amongst this group the median BMI was 35.4 kg/m^2 (32.1 - 40.1 kg/m^2) as compared to 27.9 kg/m^2 (24.0 - 32.9 kg/m^2) for the cohort as a whole.

73 patients (21.1 %) had diabetes mellitus, of which only 2 (2.7 %) had Type 1 DM, whilst the remaining 71 patients had Type 2 DM. Amongst diabetic patients the median HbA1c was 7.9 % (6.9 - 10.9 %). Atrial fibrillation was detected in 24 patients (6.9 %).

25.1 % of patients were HIV positive, which was significantly higher than the expected HIV prevalence rate in the general South African population of 13.1 %[11] (χ^2, p <0.0001). 7.2 % of patients refused testing for HIV or were unable to consent.

Out of the total of 346 stroke patients, 44.2 % had one known RF, whilst 27.2 % and 9.2 % of the population were known with two and three RFs respectively (Fig. 2A).

Stroke as the index presentation for risk factors

We further analysed those patients for whom the following RFs were newly diagnosed on admission: HPT, DM, dyslipidaemia, atrial fibrillation (AF) as well as HIV (as a non-traditional RF). Obesity and smoking are difficult to define as "newly diagnosed" RFs and were thus not analysed further.

In our cohort, stroke was the index presentation for at least 1 RF in 199 patients (57.5 %) (Fig. 2B). Amongst those patients with newly-diagnosed RFs on presentation, 72.4 % were newly-diagnosed with one new RF, 24.6 % were diagnosed with two and 3.0 % had three new RFs diagnosed.

Of the 281 patients known with RFs prior to their stroke, 162 (57.7 %) were newly diagnosed with one or more additional RFs on presentation with stroke (Fig. 2C).

The greatest proportion of newly-diagnosed patients compared to those with a pre-existing diagnosis was in dyslipidaemia (76.0 % of dyslipidaemics were newly diagnosed as such) followed by AF (50 %), DM (39.7 %) and HIV (37.9 %). HPT was newly-diagnosed in only 20.5 % of hypertensive patients. These proportional differences were statistically significant (Fig. 2D, χ2, p <0.0001).

The proportion of patients with newly diagnosed HPT and HIV was higher in males compared to females. There was no sex difference in newly diagnosed DM, dyslipidaemia and AF (Table 2).

Newly-diagnosed dyslipidaemia is associated with younger age and more severe stroke

Patients newly diagnosed with dyslipidaemia were significantly younger and had a higher NIHSS on presentation than those who were previously-diagnosed (Table 3). Those patients previously-diagnosed with dyslipidaemia were all on statin treatment, and had lower total and LDL cholesterol. BMI was similar between the groups.

Table 4 shows the relationships between RF and NIHSS on univariate regression analysis and on multivariate regression analyses. Univariate regression analyses revealed that a new diagnosis of dyslipidaemia as well as smoking were the only RFs having a significant effect on NIHSS. Multivariate linear regression models including age and all RFs with p≤0.25 on univariate regressions (sex, smoking, DM, HIV and newly diagnosed dyslipidaemia) demonstrated the only significant effect on NIHSS to be from those with newly diagnosed dyslipidaemia. Similarly multivariate regression models including age and all RF's with p≤0.25 on univariate analysis, but including all patients with dyslipidaemia (and not only those who were newly diagnosed as such), revealed the diagnosis of dyslipidaemia (known and newly diagnosed combined) as having no effect on NIHSS. This confirms that it is newly diagnosed dyslipidaemia (and not all dyslipidaemia) which influences stroke severity. Smoking and DM were the only 2 RFs affecting stroke severity in this analysis. The coefficient for smoking indicates a lower stroke severity in smokers (Table 4).

Newly diagnosed hypertension is associated with greater odds of ICH

A greater proportion of patients with ICH had HPT than patients with IS (97.3 % vs 62.46 %, Fischer's exact test, p <0.0001). Patients being diagnosed for the first time with HPT (n = 47) had a greater proportion of ICH than those patients (n=182) with known HPT (25.53 % vs 13.19 %, Odds Ratio 2.57 (1.00 - 4.81), Fishers exact test, p =0.045).

In comparing newly-diagnosed and established hypertensive patients (Table 5), the newly diagnosed patients had higher admission blood pressures than the patients who were already known with HPT. The age of presentation was similar between the groups.

Whilst the median NIHSS score for patients with ICH was greater than that for patients with IS (14[10–20] vs 11[7–16], p =0.0074), being newly-diagnosed with HPT was not associated with a higher NIHSS score than being known with the diagnosis (Table 5).

We found no significant difference between the two groups when comparing any individual markers of hypertensive heart disease, or renal dysfunction (Table 4). Patients with established HPT were more likely to have 1 of the above features of TOD present than those newly diagnosed (Odds ratio 2.1 (1.1-3.9), p = 0.03). However, it was still notable that 44.7 % of newly diagnosed hypertensive patients had evidence of TOD, other than the stroke (Table 5).

With regards to AF, there was no difference in age, sex, other RFs or stroke severity between those known with AF and those newly diagnosed (Table S1 in online supplement). All known AF patients were found to be sub-therapeutically anticoagulated at the time of stroke.

New diagnosis of HIV on presentation with stroke had a higher median age than those with pre-existing diagnosis

Of the 87 patients who were HIV positive, 33 were newly diagnosed (37.9 %). Patients with newly diagnosed HIV were older than those with established HIV, and more likely to be male (Table 6). There were no differences in other RFs, NIHSS or BMI.

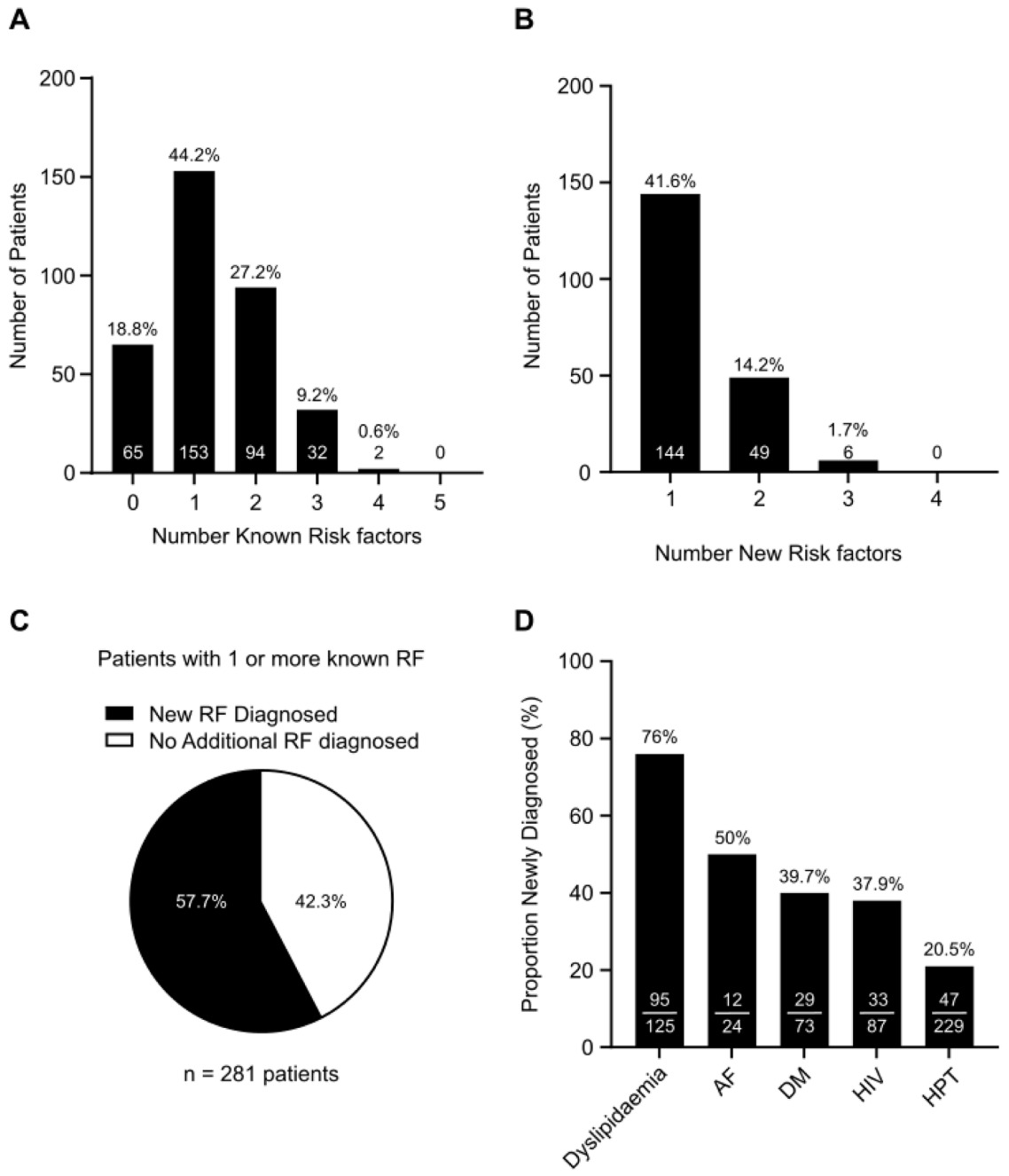


Fig. 2. Stroke is the index presentation for a number of risk factors
A Bar chart showing the number of previously identified cardiovascular risk factors (RF) within the patient population. Included risk factors are : Atrial aibrillation (AF), Diabetes Mellitus (DM), dyslipidaemia, obesity, infection with Human Immunodeficiency Virus (HIV), hypertension (HPT) and smoking. Chart shows absolute number of patients (bottom) and percentage of the cohort (top) with each number of RF. **B** Bar chart showing the number of newly diagnosed risk factors. Included risk factors are : AF, DM, Dyslipidemia, HPT and HIV. Chart shows absolute number of patients (bottom) and percentage of total population (top) with each number of newly identified RF **C** Pie Chart showing the proportion of patients (as percentage) with 1 or more known risk factor who were diagnosed with additional risk factors on presentation with stroke. **D** Bar chart showing the proportion of patients with each RF for whom stroke was the index presentation for that RF.

Newly diagnosed diabetic patients were younger than those with a pre-existing diagnosis

Newly diagnosed diabetic patients were younger on presentation than those with a known prior diagnosis (Table 7). There was no significant difference in HbA1c between newly diagnosed and existing diabetic patients with pre-diagnosed patients with DM having a median HbA1C of 9.0 %. There was also no difference in other RFs, NIHSS, BMI or sex between the two groups.

Discussion

The identification and management of cardiovascular RFs remains the most valuable tool in stroke prevention at a community level.

From our cohort of 346 stroke patients seen at a major treatment centre in Johannesburg over a 40-month period, we found stroke to be the index presentation of at least one RF in 199 patients (57.5 % of our cohort). Over a quarter of these had two or more new RFs identified which may have contributed to the stroke pathogenesis. It is unknown whether these patients had ever sought healthcare in the past. However,

Table 2
Comparison of newly diagnosed RF between males and females.

	Proportion of each RF which is newly diagnosed		
RF	Males	Females	P-value
HPT	30/114 (26.3 %)	17/115 (14.8 %)	0.03
DM	17/40 (42.5 %)	12/33 (36.4 %)	0.59
Dyslipidaemia	45/58 (77.6 %)	50/67 (74.6 %)	0.70
Atrial fibrillation	3/10 (30.0 %)	9/14 (64.3 %)	0.11
HIV	21/43 (48.8 %)	12/44 (27.3 %)	0.04

DM: diabetes mellitus, **HIV**: Human Immunodeficiency Virus, **HPT**: hypertension, **RF**: Risk factor

Table 3
Comparison between newly diagnosed and known dyslipidaemic patients.

	Newly Diagnosed n = 95 (IQR)	Known Dyslipidaemia n = 30 (IQR)	P value
Age (years)	53 (44 - 63)	62 (51 - 71)	0.02
Male (%)	47.4	43.3	0.70
HPT (%)	26.3	16.7	0.28
DM (%)	27.4	20.0	0.42
Smoking (%)	17.9	40.0	0.012
Total Cholesterol (mmol/L)	5.4 (5.1 - 6.2)	3.8 (3.2 - 4.7)	<0.0001
LDL (mmol/L)	3.7 (3.4 - 4.3)	2.2 (1.7 - 3.0)	<0.0001
BMI (kg/m^2)	n = 62 29.5 (25.4 - 35.6)	n = 17 29.7 (26.8 - 34.1)	0.64
Obesity (%)	n = 62 43.6	n = 17 41.2	0.86
NIHSS	12 (8-16)	7 (4-12)	0.0007

BMI: Body Mass Index, **DM**: diabetes mellitus, **HPT**: hypertension, **LDL**: Low Density Lipoprotein, **NIHSS**: National Institutes Of Health Stroke Scale

of the 281 patients with at least 1 established RF, who are thus assumed to have accessed healthcare, 57.7 % had an additional RF identified on presentation with stroke. We do not know how many of these RFs were previously screened for (negatively) at the healthcare centre the patient was accessing. If they were not screened, this may represent a relatively easily accessible, high cardiovascular risk population which will potentially benefit greatly from the identification and treatment of all major RFs before they lead to stroke and other cardiovascular disease.

Our findings of a significantly younger age in patients with newly diagnosed dyslipidaemia and DM (when compared to those with a pre-existing diagnosis) is of great interest. Such diseases are considered "diseases of the elderly", thus younger individuals may be less likely to be screened for them. On the contrary, our finding of a higher median age in those with newly diagnosed HIV compared to those with a pre-stroke HIV diagnosis may indicate how HIV screening may be neglected in an older population, who may be considered to be at lower risk for acquiring the disease. Male patients had a significantly higher proportion of undiagnosed HPT and HIV when compared to female patients. Previous studies have suggested that males are less likely than females to seek healthcare, particularly for screening purposes.[31] Our described age and sex differences are indicative of potential shortcomings in the screening of RFs and may assist in the targeting of screening towards specific demographics for particular diseases.

Dyslipidaemia was the most commonly undiagnosed RF. A striking 76 % of dyslipidaemics were only diagnosed as such on presentation with a stroke. This likely directly reflects the deficiencies of dyslipidaemia screening in South Africa at primary healthcare level, despite the South African Dyslipidaemia Guidelines recommending screening for dyslipidaemia in all adults from the age of 40 years.[24] A recent cohort from rural South Africa diagnosed 2860 participants with dyslipidaemia, of which only 30 (1 %) were aware of their diagnosis prior to

Table 5
Comparison of newly diagnosed and established hypertensive patients.

	Newly Diagnosed HPT n = 47 (IQR)	Established HPT n = 182 (IQR)	P-value
Age (years)	56 (45-64)	57(49-69)	0.15
Male (%)	63.8	46.2	0.03
DM (%)	21.2	30.8	0.20
Dyslipidaemia (%)	34.0	43.7	0.23
Smoking (%)	27.7	25.3	0.74
Obesity (%)	30.4	43.9	0.23
Presentation Systolic BP (mmHg)	184 (167 - 199)	156 (135-188)	<0.0001
Presentation Diastolic BP (mmHg)	116 (102 – 133)	94 (82 – 114)	<0.0001
Presentation MAP (mmHg)	141 (128 - 154)	115 (100 - 137)	<0.0001
Presentation Heart rate (bpm)	89 (75 – 103)	90 (78 – 100)	0.90
NIHSS	12 (7-15)	11(7.75-17)	0.95
Any evidence of TOD	21 (44.7 %)	114 (62.6 %)	0.03
Features of HHD on Echo	n=33 13 (39.4 %)	n =128 57 (44.5 %)	0.69
Decreased EF on Echo	n = 32 3 (9.4 %)	n=127 27 (21.3 %)	0.20
Atrial fibrillation	0 (0 %)	6 (3.3 %)	0.35
Renal dysfunction	n = 45 11(24.4 %)	n =173 57 (32.9 %)	0.37

BP: Blood pressure, **Echo**: Echocardiogram **EF**: Ejection Fraction, **HHD**: Hypertensive Heart Disease, **HPT**: Hypertension, **MAP**: Mean arterial pressure, **IQR**: Interquartile range, **NIHSS**: National Institutes of Health Stroke Scale, **TOD**: Target organ damage

Table 4
Risk factors (RF) associated with NIHSS on univariate and multivariate regression analyses.

	Univariate regression (n=346**)		Multivariate regression*† (n=114**)		Multivariate regression*†† (n=314**)	
RF	β-Coefficient±SEM	P value	β-Coefficient±SEM	P value	β-Coefficient±SEM	P value
Age	-0.014±0.020	0.51	-0.069±0.039	0.078	-0.016±0.023	0.487
Sex	0.896±0.632	0.16	1.438±1.099	0.194	0.201±0.704	0.776
Smoking	-2.042±0.712	**0.004**	-2.643±1.341	0.051	-2.116±0.799	**0.009**
HPT	-0.397±0.670	0.55	-	-	-	-
Newly Dx HPT	-0.069±0.956	0.94	-	-	-	-
DM	1.195±0.775	0.12	1.933±1.261	0.128	1.720±0.836	**0.041**
Newly Dx DM	0.491±1.411	0.73	-	-	-	–
Dyslipidaemia	-1.126±0.657	0.09	-	-	-1.155±0.774	0.088
Newly Dx Dyslipid	3.879±1.181	**0.001**	3.281±1.350	**0.017**	-	-
BMI	-0.013±0.045	0.77	-		-	-
HIV	0.835±0.730	0.25	-1.068±1.323	0.421	0.908±0.675	0.241
Newly Dx HIV	0.210±1.307	0.87	-	-	-	-
Atrial fibrillation	-0.958±1.247	0.44	-	-	-	-
Newly Dx Atrial fibrillation	1.750±2.538	0.50	-	-	-	-

BMI: Body Mass Index, **DM**: diabetes mellitus, **Dx**: diagnosed, **HIV**: Human Immunodeficiency Virus, **HPT**: hypertension,
*Age and only those RF where p≤0.25; †Newly diagnosed dyslipidaemia included in model; ††Dyslipidaemia included in model; significant RF are shown in bold type
**Differences in sample size are due to missing data regarding lipograms (n=7) and HIV status (n=25 did not consent to testing)

Table 6
Comparison of newly diagnosed and known HIV patients.

	Newly Diagnosed HIV n = 33 (IQR)	Known HIV n = 54 (IQR)	P-value
Age (years)	47 (37.5 - 55.5)	39.6 (31-49.25)	0.02
Male (%)	63.6	40.7	0.04
HPT (%)	10.0	15.8	0.59
DM (%)	9.1	3.7	0.29
Dyslipidaemia (%)	24.2	34.6	0.31
Smoking (%)	36.4	18.5	0.07
BMI (kg/m^2)	n = 22 26.6 (23.3 - 29.6)	n = 36 27.0 (22.5 - 32.4)	0.66
NIHSS	12 (8 - 18)	12.5 (8 - 17.3)	0.95

BMI: Body mass index, **HIV**: Human Immunodeficiency Virus, **NIHSS**: National Institutes of Health Stroke Scale

Table 7
Comparison of newly diagnosed and known diabetic patients.

	Newly Diagnosed n = 29 (IQR)	Known Diabetes n = 44 (IQR)	P-value
Age (years)	57 (48 - 65)	61 (55 - 74)	0.02
Male (%)	58.6	52.3	0.59
HPT (%)	79.3	97.7	0.009
Dyslipidaemia (%)	34.5	51.2	0.16
Smoking (%)	34.5	22.7	0.27
BMI (kg/m^2)	n =17 29.9 (24.5 - 38.7)	n = 29 31.7 (28.7 - 35.6)	0.37
HbA1c (%)	n = 28 7.5 (6.9 - 9.8)	n = 43 9.0 (7.2 - 11.0)	0.18
Fasting glucose (mmol/l)	n = 10 8.0 (6.2 – 9.8)	n = 11 10.2 (7.3 – 16.0)	0.10
NIHSS	14 (9 - 16)	11.5 (8 - 17.8)	0.73

BMI: Body mass index, **HbA1c**: Glycated Haemoglobin, **NIHSS**: National Institutes of Health Stroke Scale

recruitment.[32] We acknowledge that it is not possible to screen all individuals for dyslipidaemia in South Africa due to the scarcity of resources and an overburdened public healthcare system. We thus require a more pragmatic, focussed approach to dyslipidaemia screening. A multicentre South African study revealed a prevalence of dyslipidaemia of 76.7 % in 614 patients with HPT and DM.[33] A targeted dyslipidaemia screening strategy beginning with patients already accessing healthcare for the treatment of other RFs is thus likely to detect large numbers of previously undiagnosed dyslipidaemics in a high-risk population.

Our most striking finding was that those with previously undiagnosed dyslipidaemia at the time of stroke had more severe stroke and at a younger age. To our knowledge, this has not been described before. It provides compelling evidence of the detrimental consequences of a poorly screened RF and emphasises the urgent need for intervention. It is unclear why it is only in dyslipidaemia that we noted this phenomenon, and not in HPT, DM or HIV. The 30 patients pre-diagnosed with dyslipidaemia had a median total (4.4mmol/L), HDL (1.1mmol/L) and LDL (2.7mmol/L) cholesterol within the broad targets of the South African Dyslipidaemia Guidelines,[24] suggesting that once diagnosed, the dyslipidaemia management appears to be adequate. All of the patients with known dyslipidaemia were on statin treatment prior to the stroke. Previous studies have described pre-stroke statin therapy being associated with lower stroke severity.[34–36] Whether our described difference in stroke severity and age of stroke is related to the cardiovascular-protective effects of statins cannot be concluded from our data. More important however is our extrapolation that poor community-level screening and diagnosis of dyslipidaemia has catastrophic consequences on stroke morbidity.

In keeping with much preceding literature, the most common RF amongst stroke patients seen in our cohort was HPT.[2,8] However only 20.5 % of our patients with HPT were newly-diagnosed at the time of stroke. In the non-stroke literature, one large multicentre trial found that 47 % were unaware of their diagnosis of HPT.[37] This figure is even higher elsewhere in Sub-Saharan Africa (SSA), where a systematic review revealed a figure up to 70 % in this region.[38] A recent South African study revealed 52 out of 99 (52.5 %) of HPT patients were only diagnosed on presentation with stroke, however the methodology for HPT diagnosis was not clearly described.[13] Our relatively low proportion of newly diagnosed HPT was unexpected. There was no clear methodological limitation or bias which may explain this finding, and our described methods of diagnosing HPT in an acute stroke patient were very unlikely to represent under diagnosis of HPT. It is our hope that this data represents an effective HPT screening program in our urban community. The lack of age difference between our known HPT and newly-diagnosed HPT groups may also be indicative of a screening program which appears to be equally detecting patients of all ages, although the previously noted sex-discrepancy suggests that males may require more targeting. Undiagnosed HPT was found to be associated with higher odds of having an ICH. Even though ICH had a higher median NIHSS than IS, this did not translate to a significantly greater stroke severity in those who were newly diagnosed with HPT compared to those with known HPT. Of concern was our finding that 44.7 % of newly diagnosed hypertensive patients already had other evidence of TOD on presentation with stroke, suggesting a prolonged period of undiagnosed and thus untreated HPT. Our relatively low prevalence of AF (6.9 %) is likely reflective of the young age of our stroke population (median 52 years).

Our high proportion of previously undiagnosed DM (39.7 %) was in keeping with previous non-stroke studies in the South African population.[39,40] This remains a major concern for a common disease such as DM, with an easily accessible, inexpensive, and simple method of screening.

The past 2 decades in South Africa have seen the implementation and rollout of the world's largest antiretroviral therapy (ART) program.[41] Our finding of approximately 40 % of patients with HIV only being diagnosed on presentation with stroke was very concerning. While a recent systematic review of stroke in SSA revealed stroke to be the presenting symptom of HIV in 42 to 57 % of patients,[15] the papers referenced in this review were both from South Africa from the early 2000's, when the ART rollout program had just commenced, and not yet widely implemented.[42,43] The lack of distinct improvement in this figure over the past 15 years, despite the massive ART rollout program, is of great concern and warrants further investigation. As mentioned, the significantly older age of the newly-diagnosed HIV patients, and the higher proportion of undiagnosed HIV in males compared to females may identify particular population groups to target in HIV screening.

To our knowledge this is the first study from South Africa looking 'backwards' at stroke patients' missed RFs, in an attempt to identify gaps in RF screening pathways. A recent study from Zambia reported similarly high proportions of newly-diagnosed traditional RFs (20 % of HPT, 43 % of DM, 91 % of dyslipidaemia) but only 12 % of HIV patients were first diagnosed on presentation with stroke.[44] In 2019, South Africa reported an annual health expenditure of US$ 546 per capita, compared to US$ 69 per capita in Zambia.[45] One would thus expect RF screening in South Africa to be far better, particularly from an urban community in the economic hub of the region, Johannesburg. The identification of characteristic patient profiles which are particularly poorly screened for specific RFs may assist to remedy this.

Our data is surprisingly similar to a recent study from Switzerland, where 69.7 % of 1125 stroke patients with no previous RFs were diagnosed with a new RF, of which dyslipidaemia (61.4 %) was the most frequent.[46] This is despite the vast differences in healthcare resources and access between Switzerland and South Africa. However patients who already had pre-existing RFs (n=3229) had far fewer newly diagnosed RFs than in our cohort (HPT in 8.6 %, DM in 4.1 %), although dyslipidaemia was still newly diagnosed in 37.9 %. This may indicate that patients who are accessing healthcare for a pre-existing RF are

being effectively screened for other RFs, in contrast to our findings. Of note is that the median age of 70 years (IQR 15.2) was almost 20 years older than our cohort. Other studies from Taiwan,[47], Austria[48] and France[49] also indicate that the high proportion of undiagnosed RFs at the time of stroke is indeed a global challenge.

Limitations

A limitation of our study was its hospital-based nature, including only strokes severe enough to warrant presentation to hospital i.e. at the extreme end of the spectrum of target organ damage from cardiovascular RFs. It was not possible to assess stroke patients that were not admitted, but managed at home, and importantly we could not assess the overall community-based RF screening and RF control of the non-stroke "healthy" population. It is also noted that education level and residence in an urban compared to rural setting impacts on knowledge of cardiovascular RFs.[50] Our study was conducted in a large centre in the city of Johannesburg, which may bias patient selection in this regard. However our high rates of undiagnosed RFs despite being in this urban setting likely does not bode well for the efficacy of a similar screening and management program in more isolated, resource-constrained rural healthcare facilities with poorly educated communities. Our use of non-fasting lipograms may have resulted in the over-diagnosis of dyslipidaemia. However, there is evidence to suggest that non-fasting total and LDL cholesterol are equivalent to a fasting sample for cardiovascular risk assessment.[24–27] We elected to use slightly higher total and LDL cholesterol cut-off values than in many other SSA stroke studies as an attempt to mitigate for potential over-diagnosis. We also did not consider a low post-stroke HDL cholesterol to be solely diagnostic for dyslipidaemia, to account for the described transient post-stroke decrease in cholesterol levels.[28–30] Our inability to measure weight and height in patients unable to stand unaided led to missing BMI data in patients with higher stroke severities.

Future directions

Our novel findings on the detrimental effects of poor RF diagnosis, particularly with regards to dyslipidaemia, paves the way for future local research in the form of prospective community-based studies aimed at motivating for policy change on RF screening.

We demonstrated that over 50 % of individuals with pre-existing RFs were diagnosed with a further RF on presentation with stroke. These patients, who are likely already attending healthcare facilities, are the simplest to screen for other RFs and possibly will benefit the most, considering their already elevated cardiovascular risk profile. We recommend a lower threshold for screening such patients for further RFs at a primary healthcare level.

Our findings of a younger age in newly-diagnosed DM and dyslipidaemia, and older age in newly-diagnosed HIV, when compared to with those with previously-diagnosed RFs, suggest that target ages for screening may also need to be revised. Sex differences, with poorer pre-stroke diagnosis of HPT and HIV in males compared to females, may also assist in identifying specific populations to target for screening. Our data points to the need for urgent public health interventions in the screening and diagnosis of RFs in order to best prevent catastrophic cardiovascular outcomes such as stroke.

Conclusions

More than half of our cohort had at least one RF only diagnosed on presentation with stroke, of which dyslipidaemia was the commonest. Newly diagnosed dyslipidaemia was associated with more severe stroke, and at a younger age than those with a pre-existing diagnosis.

CRediT authorship contribution statement

Eitzaz Sadiq: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alexander von Klemperer:** Writing – review & editing, Writing – original draft, Software, Formal analysis. **Angela Woodiwiss:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gavin Norton:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Girish Modi:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2023.107529.

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