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COST ANALYSIS AND COMPARISON OF TWO GLOBAL CARDIOVASCULAR RISK SCORES IN HYPERTENSIVE PATIENTS AT MAFIKENG PROVINCIAL HOSPITAL: A PRELIMINARY EXPLORATORY STUDY

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Research report submitted to the Faculty of Health Science, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Family Medicine



2018

PLAGIARISM DECLARATION

I, Doctor J.P. Mbuilu, hereby declare the following:

I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

I confirm that the work submitted is my own unaided work.

I have followed the required conventions in referencing the thoughts and ideas of others.

I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the sources of the ideas or words in my writing.

Signed at Mafikeng on 28/05/2018



DEDICATION

This work is dedicated to:

- The people of DR Congo, striving for peace and democracy;
- To my wife, Nathaly and my Kids (Jody-Samuel, Jody-Orly, Jody-Sharon and Jody-Narcisse) for their patience and encouragements;
- To my parents Basile and Viviane for their indefectible support.

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Find here my gratitude.

TABLE OF CONTENTS

TITLE PAGE

PLAGIARISM DECLARATION 2

DEDICATION 3

AKNOWLEDGEMENTS 4

TABLE OF CONTENTS 5

CORE RESEARCH REPORT: 6

A. The Submissible article 7

B. Research proposal 30

ANNEXES 67

- Ethic clearance certificate
- MMed research report's submission form
- Turnitin certificate

CORE RESEARCH REPORT:

A. The Submissible article

COST ANALYSIS AND COMPARISON OF TWO GLOBAL CARDIOVASCULAR RISK SCORES IN HYPERTENSIVE PATIENTS AT MAFIKENG PROVINCIAL HOSPITAL: A PRELIMINARY EXPLORATORY STUDY

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Abstract

A preliminary study was done where South African Hypertension guideline risk score was compare with the WHO Cardiovascular risk score (for Southern Africa). At Mafikeng Provincial hospital 130 hypertensive patients were assessed using both scoring algorithms. Ninety (69%) of the 130 patients were high risk. The WHO risk score was able to classify 84 (93%) of the high risk patients by SA risk calculator also as high risk and 36 (90%) of the 40 low risk patients also as low risk. The WHO risk calculator has a sensitivity of 93% and a specificity of 90% with 89% accuracy.

INTRODUCTION

Globally, deaths from non-communicable diseases (NCDs) accounted for two out of every three deaths in 2010.[1] Cardiovascular disease (CVD) has been the leading cause of death from 1990 to 2013.[2] By 2020, CVD will have become the leading cause of death and disability in the world, and the current geographic distribution of the burden caused by CVD is not expected to change.[3] However, 80% of the burden of CVD is borne by low and middle-income countries where resources are scarce.[4] Cardiovascular disease is secondary to atherosclerosis that has evolved over the years, and is the consequence of a complex interaction between many risk factors. Among the major risk factors such as elevated blood pressure, obesity, lipid disorders and tobacco use, hypertension (HT) is the leading condition responsible for deaths due to CVD worldwide.[4] An efficient control of HT and other risk factors is one of the key answers to the CVD pandemic. This response starts with the identification of patients at high risk of developing cardiovascular events like stroke and ischaemic heart disease (IHD), since they represent those who benefit the most from pharmacologic interventions. This discriminative approach of selecting patients on the basis of their potential cardiovascular risk (CVR) is cost-effective and relevant for primary care in low and middle-income countries.[5,6] There are various scoring systems to achieve this cost-effectiveness, but it would be imperative to detect which of these systems are cost-efficient; thus, the need to carry out this study.

The World Health Organization (WHO), the International Hypertension Society (IHS) as well as many other guidelines recommend the use of the absolute or global CVR approach rather than the individual risk approach when treating HT.[7,8,9]The absolute

CVR approach is cheaper and more cost-effective, and saves more lives as compared to the individual risk treatment approach.[10] The global CVR approach is interchangeably referred to as the global risk assessment (GRA).[11] The GRA aims to determine the **global risk score** (**GRS**) by adding, in a mathematical cardiovascular predictive equation or algorithm, values of cardiovascular risk factors (CVRF) present in an individual.[12] From this cardiovascular grading, a specific treatment modality will be initiated as imperative. The cardiovascular grading may be expressed either in cardiovascular level clustering such as low, moderate or high added CVR (South African guideline) or in percentage (Framingham equation).[7,13] The treatment of individual risk factors was used in the past as opposed to the GRA, but the former is no longer supported as it has been demonstrated to be non-cost-effective and clinically irrelevant.[14] With the single risk factor approach, some individuals presenting with isolated risk factors would be treated with unnecessary medication while others with many risk factors would receive only treatment for the recognised risk factors. There is currently a universal agreement on the use the GRA, and this is reflected in different national guidelines. [7,15]

Many CVR scores with specific advantages and limitations have been developed. In Sub-Saharan Africa, the estimation of CVR is performed based on research developed elsewhere. The WHO recommends the use of the modified Framingham equation adapted for each region of the world.[5,16] In South Africa, the guidelines developed by the South African Hypertension Society (SAHS) recommend the use of the risk stratification based on the EHS-ESC guidelines.[7] In South Africa, the GRS is calculated using the chart from the SAHS guideline. This is known as the South

African Hypertension Society Global Risk Score (**SAHS/GRS**) chart. Using the SAHS/GRS, the patient is classified in one of the two CVR clusters: either low/moderate added risk or high/very high added risk. The first group of patients assessed as having low or moderate CVR will undergo three to six months of lifestyle modification without drug treatment. They will be monitored regularly during this period and will at the end of each cycle be reclassified in one of the two clusters of CVR grading, and treated accordingly. The second group labelled as high and very high added CVR leave the health care facility with a plan for lifestyle modification and at least one anti-hypertensive drug. The SAHS/GRS is a laboratory-based score. The current national guideline developed by the SAHS recommends the use of a laboratory-based cardiovascular risk score derived from the EHS-ESC: the **SAHS/GRS.**[7] On the other hand, the WHO recommends the use of a non-laboratory-based GRS (**WHO/GRS**) calculated from the chart specific for the Southern African region: the WHO/IHS Chart AFR E.[5,16]

In a convenient sample, are the Global Risk Scores (GRSs) using the Southern African Hypertension Society chart (**SAHS/GRS**)[7] and the WHO/IHS Chart AFR E[16] (**WHO/GRS**) **equivalent** ? The aim of this study is to compare the cardiovascular risk scores calculated from the SAHS/GRS and the WHO/GRS on hypertensive patients attending the Mafikeng Provincial Hospital (MPH). Cost analysis will be carried out with definitive study.

METHODS

Study design and setting

This is a cross-sectional prospective **preliminary study.** The Mafikeng Provincial Hospital (MPH) serves as a level 1 referral hospital for the Mafikeng Sub-district health facilities (community health centres, primary health clinics and general practices) and as a level 2 hospital for different district hospitals in Ngaka Modiri Molema district. The Mafikeng Provincial Hospital is situated in Mafikeng, the capital of North West Province. The largest part of Mafikeng sub-district is rural. Mafikeng Provincial Hospital has 409 beds, combining level 1 and 2 services.

The Family Medicine Department together with the Gateway clinic constitutes the level one component of Mafikeng Provincial Hospital. The Family Medicine Department consists of 4 units: the accident and emergency unit, the general outpatient department, the wellness clinic and the short stay ward. Hypertensive patients from different primary care facilities within the Mafikeng sub-district are referred to the Mafikeng Provincial Hospital via the General Outpatient Department where a family physician, a registrar and an intern review them initially. The most frequent reason for referral is uncontrolled HT. The General OPD collaborates with specialised “clinics” or OPDs from different level 2 departments like the “HT clinic” in the Medical Outpatient Department where complex clinical situations and patients who need long-term specialised follow-up are seen. Currently 800 hypertensive patients are registered in the Medical OPD and an average of 1,200 hypertensive patients are seen annually in the General OPD.

Study population and sampling

All hypertensive patients referred from primary care facilities in the Mafikeng Sub-district and who were seen initially in the Family Medicine General OPD represent the study population. The recruitment of patients took place in that department. This preliminary study will serve as a reference for a complete investigation including an adequate sample. This study focuses on hypertensive patients from primary care facilities in Mafikeng Sub-district.

The average number of new and follow-up hypertensive patients registered during 2014 was 1,200. This number was included in the Raosoft sample size calculator using a confidence level of 95%, a variability degree of 50% and a margin error of 5%.[17] The calculator generated a minimum number of 292 patients as a representative sample to be studied. However, to allow parametric statistical analysis, this pilot study has conveniently included only 130 patients. Consecutive patients attending the outpatient department at the Mafikeng Provincial Hospital, who agreed to participate in the study were enrolled until the sample size was reached.

Inclusion and exclusion criteria

All hypertensive patients aged18 years and older referred from Mafikeng Sub-district primary care facilities between March 1st and June 30th 2017 who presented in the outpatient department were included in this study, subject to having obtained their informed consent. Patients who needed emergency treatment, those unable to stand or to comply with the anthropometric measurement standards described below, and

patients referred from other hospitals were excluded. Moreover, patients with a history of cardiovascular events such as stroke and IHD were also excluded.

Data collection tool

The WHO stepwise approach to non-communicable disease risk factor surveillance (STEPS) was used for data collection. The WHO STEPS Instrument served as a support for data collection.[18]

Process of data collection

All hypertensive patients were approached individually while in the pre-vitals room. A research team member gave an extensive verbal explanation of this study. Patients willing to participate in the study underwent an informed consent process. At the end of this dialogue all hypertensive patients, irrespective of whether they agreed to participate in this study, received an explanation of how to collect a urine sample. A urine sample bottle was given to each one and they were invited to collect urine and return it to the vital signs room. Patients who agreed to participate in the study were invited to sign a consent form in the presence of a nurse who was not a member of the study team and who acted as a witness. Patients unwilling to participate were given normal care according to hospital standards and current national guidelines. After signing the informed consent form, a special sub-file was included in the hospital record. This sub-file contained the WHO STEPS Instrument designed to assist in data collection.[18] A discriminating colour-coded “orange dot” was glued to the front of the file cover to avoid replication of recruitment. Each patient was invited to the vital signs room where a nurse trained for this study recorded his/her weight,

height, BP, heart rate and urine dipstick results. The patient was then invited to the interview room, where a nurse trained to use the WHO STEPS Instrument approach administered a questionnaire in English or Setswana. After the interview, the patient underwent a clinical consultation including a repeat of the BP measurement and a physical examination. The patient entered the investigation room where a blood sample was drawn and an ECG recorded. The sub-file was then withdrawn from the patient file and kept for data capturing. Before being discharged, the patient received a brief feedback on the entire consultation and was invited for a subsequent visit where definitive management was offered according to the findings and the national guidelines.

Data analysis

Data recorded during the clinical interaction with the patient were recorded onto a Microsoft Excel spreadsheet and then transferred to SPSS 17.0 for summary and analysis. Categorical variables were summarised by their frequency and percentage; continuous variables were summarised by their mean +/- standard deviation (SD). Clusters of CVR categories were compared using a Chi-square test to assess similarity. Tables and charts were used to describe and present different data summaries.

Establishing global cardiovascular risk using the SAHS/GRS

Using Table 4 (Appendix 6), the number of risk factors were plotted in the first column of the table and the level of the systolic BP in the first row. Among the risk factors, the left ventricular hypertrophy was determined using information from the

ECG to populate the cornel score as detailed in the guideline.[21] The intersection of the level of blood pressure against corresponding risk factors determined the level of CVR according to the South African hypertension guideline.

The SAHS/GRS discriminates four groups of CVR namely low, moderate, high and very high added CVR groups. According to this guideline, the first group identified as having low added CVR was followed-up for six to twelve months of lifestyle modification. The second group identified as having moderate added CVR was prescribed a lifestyle modification and followed-up for three to six months. The third group identified as having high added CVR was immediately started on one antihypertensive drug in addition to advice/health education on lifestyle modification. The fourth group classified as having very high CVR was also commenced on one antihypertensive drug in combination with lifestyle modifications.

From a therapeutic perspective, all four CVR groups can be divided into two groups. The first group will start treatment with lifestyle modification and the patients in this group will be reviewed during 3, 6 and 12-month follow-up, with treatment changes depending on the level of risk. The second group will be combining one antihypertensive drug with lifestyle modification from the beginning. For this study, the first group of patients managed with lifestyle modification only will be included in the first category and the second group will include those managed with at least one antihypertensive drug.

Establishing global cardiovascular risk using the WHO/GRS

Using the WHO/GRS for Southern Africa, every patient's clinical data was plotted to determine the percentage of CVR. Patients scoring less than 30% were classified as Category 1. Those scoring equal to or more than 30% were classified as Category 2, since they would be managed with at least one antihypertensive drug from the beginning.

Comparison of the two scores: WHO/GRS vs. SAHS/GRS

All patients were classified into one of the two categories of CVR: low and low to moderate or with a CVR less than 30% (Category 1), or high to very high or with a CVR equal to or more than 30% (Category 2). Using the current SAHS/GRS as reference score ("gold standard"), the sensitivity and specificity of the WHO/GRS to correctly classify patients into one of the two CVR clusters was established. This result will be presented in a 2X2 table. In Table 2, the accuracy or performance of the WHO/GRS to correctly classify the patient in one of the therapeutic group is compared to the SAHS/GRS considered here as a gold standard.

ETHICAL CONSIDERATIONS

During March 2017, a Clearance Certificate (Number M160816) was allocated to this study by the University of Witwatersrand, Johannesburg. Permission from the research site (North West Department of Health: Policy, Planning and Research Directorate and Mafikeng Provincial Hospital) and individual participants informed consent was obtained.

RESULTS

Socio-demographics and Cardiovascular risk profile of participants

Descriptive analysis of 130 study participants of this preliminary study showed that female representation was higher (80 participants [62%]) (Figure1), with 80% coming from surrounding rural settlement and 30% with no formal education.

The overall mean age was (18-84years) 59 ± 13 years with 47% of participants recording age as a non-modifiable risk factor: almost one quarter of male (24%) and female (23%) being older than 55 years and 65 years respectively. A family history of cardiovascular event (CVE_f) like stroke or heart attack reported by the participant accounted for 12% (16/130). Twenty-five participants were diabetics with a mean HbA1c of 10.8 ± 4.8% (7-27) and 35% (46/130) were currently smokers. Participant characteristics are summarised in: Figure 1, Histogram 1, Histogram 2, and Table 1 below. Except for the BMI, there were no statistical differences in continuous variables based on gender except for the serum creatinine level slightly elevated amongst men. The mean age was 59 years ±13 with extremes of 18 and 84 years. Others results are summarised in Table 1.

Comparison of laboratory and non-laboratory based cardiovascular risk scores

Using the SAHS GRS as gold standard (Table 2), 90 (69%) participants were classified as high risk and 40 (31%) as low risk. The WHO GRS performance was able to classify correctly 84 (93% of the 90 classified as high risk with SAHS GRS) participants as high risk and 36 (90% of the 40 classified as low risk with SAHS GRS) as low risk. The WHO sensitivity was calculated as 93%, with a specificity of

90% and an accuracy of 89%. The number of false negative, participants wrongly classified as low risk was 6 (6,7%) bringing the number needed to harm at 15.

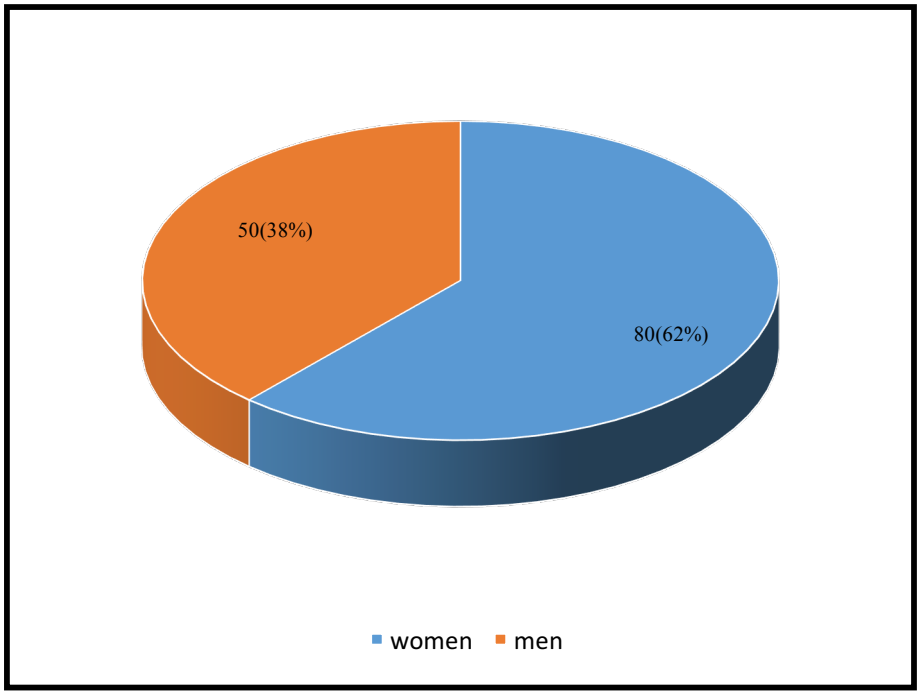
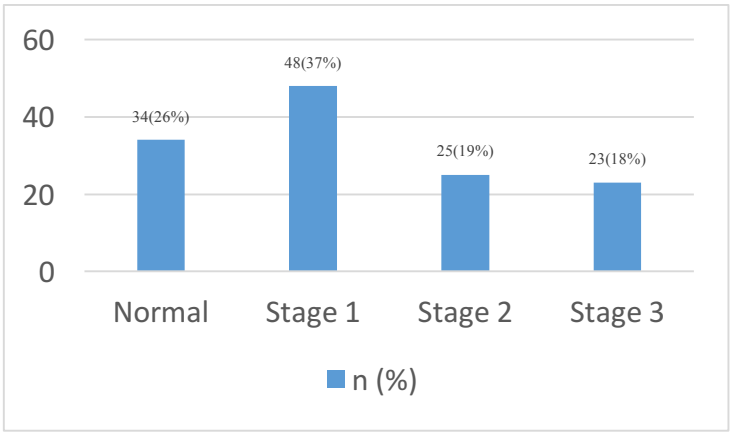


Figure 1: Pie distribution of participants by gender (n=130)



Histogram 1: Blood pressure by Stage
(according to the South African Guideline Classification)

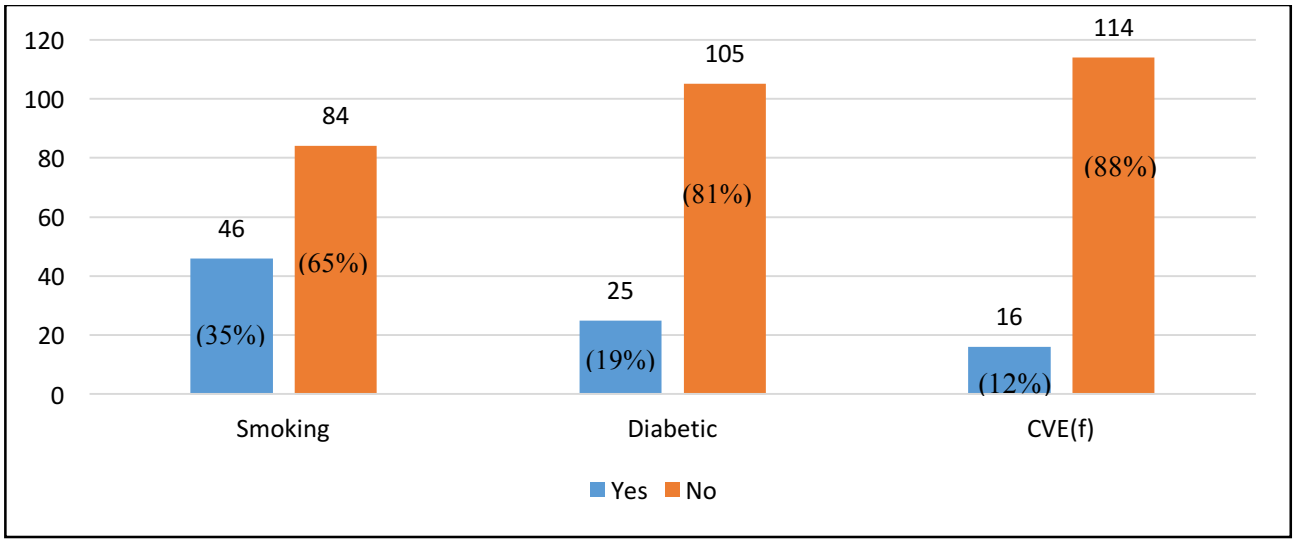


Figure 2: Distribution of smoking, diabetic and cardiovascular event in the family status among study participants (CVE(f): early Cardiovascular event in the family)

Table 1: Participant cardiovascular risk factors summaries

	N	Min	Max	Mean ± Std. Dev.	Male (mean)	Female (mean)	t-student
Age (Years)	130	18	84	59 ± 13	60	59	0.552
BMI (kg/m2)	130	14	52	29 ± 7	26	31	0.515
Waist Circ. (Cm)	130	65	136	97 ± 14	97	98	0.141
SBP (mmHg)	130	101	230	152 ± 23	145	157	0.294
DBP (mmHg)	130	46	141	86 ± 15	83	89	0.152
TChol. (mmol/l)	130	1.7	7.6	4.6 ± 1.1	4.5	4.6	0.972
TG (mmol/l)	130	0.4	5.3	1.9 ± 0.8	1.8	1.9	0.810
LDL (mmol/l)	130	0.5	5.6	2.6 ± 0.9	2.6	2.6	0.898
HDL (mmol/l)	130	0.4	2.4	1.2 ± 0.3	1.2	1.2	0.611
Creatinine. (mg/dl)	130	43	439	91 ± 57	106	81	0.034
Cornell (mm.ms)	130	336	7366	2229 ± 1255	1976	2388	0.286

Waist Circ. = waist circumference in Centimeter, BMI = Body Mass Index in Kg/m^2, age in years, SBP= systolic blood pressure, DBP = diastolic blood pressure, TChol.

= Total Cholesterol in mmol/litter, TG= triglyceride, LDL = low density lipoprotein Cholesterol in mmol/litter, HDL

Table 2: Cross tabulation between participants correctly classify as low or high risk using the SAHS as gold standard

	SAHS GRS high risk	SAHS GRS low risk	Total
WHO GRS high risk	84	4	88 (67%)
WHO GRS low risk	6	36	42 (33%)
Total	90 (69%)	40 (31%)	130

Sensitivity: 93%, Specificity: 90%, Accuracy: 89%,
False negative: 6,7%, NNH:15,
Measure of Agreement kappa: 0.822 ($p<0.0001$)

Discussions

The focus of this research was to compare a non-laboratory cardiovascular risk score (WHO/GRS) with the current score prescribed in the South African guideline for hypertension (SAHS) and to assess its performance. As for comparing two diagnostic tests, the SAHS has been set as the reference test or gold standard and the WHO/GRS as the assessment test; this will constitute the first part of our discussion. Various cardiovascular risk factors collected made the establishment of the cardiovascular risk possible, descriptive analysis of those variables generated information that we will discuss in the second part of this section.

The Kappa agreement of 0.822 between the two scores was very good, reaching a score above 80%. This is the best repeatability result expected when a new test is assessed. In practice, from the 130 patients classified in the two levels of cardiovascular risk in our research, more than 80 percent were correctly classified in the same group by two different tests.

The sensitivity and specificity were respectively 93% and 90% making the WHO/GRS as good as the SAHS/GRS; with an accuracy (89%) close to the reference score recommended by the South African guideline on hypertension.[7] From the above results, the number needed to harm is calculated at 15. In other words, one patient out of every 15 will be misclassified either as low or high risk when the WHO/GRS is used as a replacement for the SAHS/GRS leading to either holding their drug treatment modality or exposing them to drug side effects. With the reserve generally associated with preliminary studies, as developed in the limitation

section below, every patient must have a planned assessment of his cardiovascular risk after benefitting from a speedy classification offered by the WHO/GRS, a non-laboratory based cardiovascular risk score and later on benefitting from a more accurate and recommended classification using the SAHS/GRS.

During this research, many variables were collected. Amongst them, the following cardiovascular risk factors have generated useful information: differing levels of blood pressure, classification according to the South African guideline (as normal or in one of the 3 stages with high readings); the smoking status; the diabetic comorbidity; and the family history of cardiovascular event before 55 years for the father or 65 years for the mother. Alarming results were evident from the percentage of patients seen for hypertension in this clinic. Only 26% presented with a normal blood pressure; all remaining patients (74%) had elevated blood pressure despite being on treatment. This can partially be explained by the fact that as a referral clinic, selected uncontrolled patients are referred.

Tobacco use was prevalent amongst the hypertensive patients studied, with a proportion of 35%. This is a call for further inquiry in this field.

Many studies comparing laboratory and non-laboratory based cardiovascular risk estimation scores have been conducted and published in the literature.[5,12,19,20,21] Amongst them, few were specifically comparing the ESH risk score to the WHO/ISH. As stated earlier in this report, the SAHS risk chart is derived from the ESH chart. Some findings were similar to ours in a few of those studies. In a similar performance

comparison study involving 425 patients, Cuspidi *et al*. found that the WHO/ISH Chart underestimated by more than 15% of patients compared to the risk stratification established using the laboratory based ESH-ESC risk chart. This result is closely similar to ours where 7% of patients were wrongly classified as low risk.[21] The difference in the magnitude of percentage can be understood from the small sample size in our study and the use of a more sensitive detection test in Cuspidi 's study. In fact, the target organ damage assessment did include the use of carotid intima measurement.[21]

In a study conducted on the South African population, comparing the "Gaziano" non-laboratory cardiovascular risk estimation chart with four other commonly used laboratory based cardiovascular risk estimation equations (Framingham, score), correlation findings were in favor of a good performance.[22] More than 92% of participants were correctly classified by the non-laboratory risk estimation chart. This result supports the use of a non-laboratory based cardiovascular estimate. Moreover, this study is particularly important because the study population has been selected in South Africa. However, our preliminary study results are more specific to our local population studied compared with the wide range included in the Gaziano study.

This preliminary study has revealed that a team of five researchers is necessary to carry out a data collection campaigns on 130 participants for a period of two months in our setting. The final cost, not reported here, is close to the prevision established in the current study's proposal.

The average blood pressure control was poor, only 34% of hypertensive participants had their blood pressure within the normal range and the mean HbA1c was high (10,8) amongst diabetics. One third of participants were smokers, raising a concern about tobacco use among this cohort and cardiovascular risk factors control in general. They were no apparent reason accounting for the slight gender difference on the creatinine level observed, further investigation may be needed.

With reserve relating to the underestimation arising from the GRS/WHO due to its loss of accuracy, this score remains cheaper than the GRS/SAHS recommended by the current hypertension guideline in South Africa.

Limitations of this research

This research is only a preliminary study, including a fraction of the required sample size to allow inferences. Although information on feasibility was collected, the results cannot be used to influence future policies. This is mainly due to a high risk of type 2 error, secondary to a small sample size. Ideally patients should have been recruited during the initial diagnosis phase of the disease elimination the bias linked to the effect of the therapy in lowering the global risk estimation. However, in practice the cardiovascular risk estimation is updated continuously on hypertensive patient justifying the current inclusion strategy.

CONCLUSION

This study compared the current South African cardiovascular global risk score estimation chart against the WHO/GRS, which is a non-laboratory based score in a

preliminary study, including 130 hypertensive patients from Ngaka Modiri Molema district in the North-West Province, South Africa. The WHO/GRS was performed at 89% accuracy in identifying patients who qualified for immediate drug therapy in addition to life style modification and a salt free diet recommended for all hypertensive patients. This research confirmed the findings of a more general South African study, but less specific for the Ngaka Modiri Molema district.[12]

Combining our results and Gaziano findings, we recommend the use of WHO/GRS in primary care in our district as a temporary tool to categorize the hypertensive patient, while waiting for a more accurate and robust result based on the current hypertension guideline.[12]

We recommend that a more complete study, including an adequate sample size be conducted in order to confirm our interim results.

We also recommend that the WHO/GRS chart be introduced to our primary care facilities as soon as the completed study validates the performance results. In our district further study is necessary on the profile of cardiovascular risk control and prevention program performance. This will answer questions like:

- How many hypertensive patients are smoking?
- How many patients have been offered smoking cessation counselling?
- How effective is the diabetic patient controlled?

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