HbA1c Control in Type 2 Diabetic Patients with Coronary Artery Disease

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine (Internal Medicine)

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Declaration

Student's contribution to article(s) and agreement of co-author(s) I, Lona Mhlaba, student number 0704643J, declare that this research report is my work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my research report.

Signature of Student: _____ Date: 10 November 2023

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Article Title: HbA1c Control in Type 2 Diabetic Patients with Coronary Artery Disease.

Author	Name	Signature	Date
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Comments by primary supervisor:

Dedication
To my family, thank you for all your support.

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I thank my supervisors, Professor Nqoba Tsabedze and Dr Dineo Mpanya, for their support and guidance. I would also like to extend a word of gratitude to my family for their unwavering love and support.

Author Guidelines: Frontiers in Clinical Diabetes and Healthcare: Diabetes Cardiovascular Complications

Article Title

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Research report

HbA1c Control in Type 2 Diabetic Patients with Coronary Artery Disease

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Abstract

Background: Type 2 diabetes mellitus (T2DM) patients with coronary artery disease (CAD) have an increased risk of recurrent cardiovascular events. These patients require optimal glucose control to prevent the progression of atherosclerotic cardiovascular disease (ASCVD). Current guideline recommendations target an HbA1c ≤7% to mitigate this risk. This study evaluated the level of HbA1c control in T2DM patients with CAD.

Methods: This retrospective study assessed consecutive patients who presented with CAD to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between April 2017 and December 2019. The study included T2DM patients on anti-diabetic medication with angiographically confirmed CAD. HbA1c control was assessed using the HbA1c level measured at the index presentation and during the most recent follow-up visit.

Results: The study population comprised 262 T2DM patients with a mean age was 61.3 ±10.4 years.

Among the T2DM patients, 188 (71.8%) were males. At index presentation, 110 (42.1%) T2DM patients presented with ST-segment elevation myocardial infarction, 69 (26.4%) had non-ST-segment elevation myocardial infarction, 43 (16.5%) had unstable angina, and 39 (14.9%) had stable angina. The baseline median systolic blood pressure was higher in patients with an HbA1c ≤7% [136 mmHg (Interquartile range (IQR): 117-151) vs 124 mmHg (IQR: 112-142), p= 0.0121], compared to those with an HbA1c level above 7%. Furthermore, T2DM with an HbA1c ≤7% also had a higher median diastolic blood pressure [85 mmHg (IQR: 75.5-97) vs 78 mmHg (IQR: 71-88), p=0.0205]. After a median follow-up of 16.5 months (IQR: 7-29), 28.7% of the study participants had an HbA1c ≤7%. On multivariable regression analysis, patients with ST-segment depression on the resting electrocardiogram and index presentation had optimal glycaemic control (Odds ratio: 0.27, CI: 0.12-0.59, p= 0.001).

Conclusion: After a median follow-up duration of 16.5 months, only 28.7% of T2DM patients with CAD had optimal glycaemic control. This finding underscores the substantial unmet need for optimal diabetes control in this very high-risk group.

1 Introduction

Type 2 diabetes mellitus (T2DM) is a global pandemic affecting approximately 537 million adults between the ages of 20-79 in 2021 (1). This figure is expected to rise to 643 million by the year 2030 and to rise even further to 784 million by 2045 (1). In South Africa, 10.1% of individuals above 15 years have diabetes (2). This high prevalence poses significant health and socio-economic consequences (3). Diabetes mellitus leads to many diabetic-related complications, classified as micro and macrovascular. Microvascular complications include retinopathy, nephropathy, and neuropathy. Macrovascular complications include coronary artery disease (CAD), peripheral artery disease, and cerebrovascular disease (4).

Diabetes mellitus is a significant risk factor for CAD, causing accelerated atherosclerosis resulting in severe and diffuse atherosclerotic cardiovascular disease (ASCVD) (5). Intensive glycaemic control may reduce the progression of ASCVD and in particular, reduce the occurrence of myocardial infarction in people living with T2DM (6). Optimal glycaemic control has been found to slow the progression of coronary artery calcification and, therefore, atherosclerosis in asymptomatic patients with diabetes (7).

Multiple cardiovascular outcome trials evaluating the cardiovascular safety of novel anti-diabetic therapy have led to the emergence of new diabetic therapeutic agents with proven cardiovascular benefits. It is now recommended that these agents be used as first-line therapy in T2DM patients with high or very high cardiovascular risk (8). Many T2DM patients in low and middle-income countries (LMICs) cannot access these agents. Yet, most diabetics in these regions fail to achieve adequate glycated haemoglobin (HbA1c) control on traditional agents alone (9). The aim of the study was to evaluate HbA1c control in T2DM patients with CAD and describe the management of these high-risk patients using currently available therapies.

2 Materials and Methods

2.1 Study design and data collection

A retrospective study was conducted on 1000 consecutive patients who presented with CAD in the Division of Cardiology at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between April 2017 and December 2019. The CMJAH is a state-owned tertiary academic centre in

Johannesburg, South Africa. Baseline data was collected from the CMJAH catheterisation laboratory patient registry, which captures demographic data of all patients who undergo angiography, and from the electronic health record system, which stores admission data of patients hospitalised in the cardiac intensive care unit and general cardiology wards.

Patients 18 years of age and older with T2DM and angiographically confirmed CAD were included in the study. Clinical parameters captured included patient demographics, risk factors for CAD, coronary angiography findings, clinical examination findings, laboratory indices, baseline electrocardiogram (ECG) and echocardiogram parameters, medication, and in-hospital all-cause mortality. To evaluate HbA1c control among T2DM patients, we compared the baseline HbA1c collected on the initial or index presentation with the most recent HbA1c available on the National Health Laboratory Service. In our study, good HbA1c control was defined as an HbA1c $\leq$7% and poor glycaemic control was defined as an HbA1c >7%. After excluding patients who did not meet the study inclusion criteria and those without baseline and follow-up HbA1c serum levels, the final cohort consisted of 262 T2DM patients (Figure 1).

2.2 Ethics Approval and Consent to Participate

Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (clearance certificate number: M191191). Patients were not required to provide informed consent as this was a retrospective study.

2.3 Statistical Analysis

Stata (version 17, College Station, Texas) was used for the statistical analysis. Categorical data is

summarised as frequencies and percentages, and Pearson's chi-square test was used to compare categorical variables. Normally distributed continuous data is summarised using the mean and standard deviation (SD), and non-normally distributed continuous data is presented as the median and interquartile range (IQR). The Student t-test was used to compare normally distributed continuous variables, and the Wilcoxon rank sum test was used to compare continuous data with a non-normal distribution. Univariable and multivariable logistic regression analyses were performed to determine clinical variables associated with poor HbA1c control, and the results are presented as odds ratios (OR) with their corresponding 95% confidence intervals (CI). To select candidate variables for inclusion in the univariable logistic regression model, we selected variables with a p-value less than 0.1 after conducting the student t-test, Pearson's chi-square and Wilcoxon rank sum tests. We subsequently included variables in the multivariable logistic regression model with a p-value < 0.05 on the univariable analysis. A p-value of less than 0.05 represented statistical significance.

3 Results

The final study population consisted of 262 T2DM patients, and 148 (75.5%) of these patients had an HbA1c above 7%. The mean age in the entire study population was 61.3 ± 10.4 years. Patients with a baseline HbA1c ≤7% were older than those with poorly controlled HbA1c [63.6 ± 10.1 years (CI: 61.1 – 66.1) vs 60.5 ± 10.4 years (CI: 59.0 – 61.9); p-value= 0.0332]. The median systolic blood pressure was higher in patients with an HbA1c ≤7%, compared to those with an HbA1c above 7% [136 mmHg (IQR: 117-151) vs 124 mmHg (IQR: 112-142), p-value= 0.0121]. The median diastolic blood pressure was also higher in patients with an HbA1c ≤7%, compared to those with an HbA1c

above 7% [85 mmHg (IQR: 75-97) vs 78 mmHg (IQR 71-88), p-value= 0.0205].

Among 262 T2DM patients, 204 (77.9%) presented with Killip 1 symptoms. Of these patients, 45 (68.2%) had an HbA1c ≤7% and 159 (81.1%) had an HbA1c above 7%, p-value= 0.029. Eighty-four patients (32.1%) presented with ST-segment elevation myocardial infarction. Of these patients, 13 (19.7%) had an HbA1c ≤7% and 71 (36.2%) had an HbA1c above 7%, p-value= 0.013. ST-segment depression myocardial infarction was reported in 41 (15.7%) patients, 19 (28.8%) of these patients had an HbA1c ≤7%, while 22 (11.2%) had an HbA1c above 7%, p-value= 0.001. A total of 63 (24.2%) patients presented with triple vessel disease. Of these patients, 12 (18.8%) had an HbA1c ≤7% and 51 (26.0%) had an HbA1c >7%, p-value= 0.497. The rest of the baseline demographics and clinical characteristics are depicted in Table 1.

Metformin was prescribed to 224 (85.5%) patients with T2DM. Among patients with an HbA1c ≤7%, 48 (81.4%) were on metformin monotherapy, while only three (5.1%) patients were on metformin and insulin combination therapy. In patients with an HbA1c above 7%, 92 (55.8%) were on metformin monotherapy, and 38 (23.0%) were on metformin and insulin combination therapy. Table 2 depicts the rest of the medications prescribed to T2DM patients.

The proportion of diabetic patients with a baseline HbA1c ≤7% was 24.4% (95% CI: 18.4%-31.5%), and 75.6% (CI: 68.4%- 81.6%) of T2DM had an HbA1c above 7%. After a median duration between the baseline and follow-up HbA1c measurement of 16.5 months (IQR: 7-29), 28.7% (CI: 22.2%-

36.1%) of T2DM patients had an HbA1c ≤7% and 71.3% (95% CI: 63.9%- 77.8%) of patients had an HbA1c level above 7% (Figure 2).

Logistic regression analyses were conducted to identify clinical variables associated with poor glycaemic control (HbA1c >7%). On univariable logistic regression analysis, T2DM patients with unstable angina had better HbA1c control (OR: 0.40, CI: 0.18-0.89, p= 0.025) (Table 3). Patients on actraphane (neutral protamine Hagedorn (NPH) 70% + short-acting regular human insulin (actrapid) 30%) were at least twice as likely to have an HbA1c above 7% (OR: 2.47, CI: 1.04-5.85, p= 0.040). Furthermore, T2DM patients with ST-segment depression on ECG showed better HbA1c control (OR: 0.32, CI: 0.16-0.65, p= 0.002). On multivariable logistic regression analysis, T2DM patients with ST-segment depression on the baseline ECG were less likely to have an HbA1c above 7% (OR: 0.27, CI: 0.12-0.59, p= 0.001).

4 Discussion

This study found that 35.6% of patients with CAD had concomitant T2DM. The high prevalence of diabetes found in our study population is in keeping with data from the International Diabetes Federation, which predicts a higher increase in the prevalence of diabetes among individuals residing in Africa (1). In our study, the treatment of diabetes involved the use of metformin, sulphonylureas and insulin therapy. However, despite using these traditional anti-diabetic agents, only 28.7% of the participants achieved optimal HbA1c control after a median follow-up of 16.5 months. This finding indicates that diabetic control in our study population is sub-optimal. This is comparable to data

from other LMICs, where studies have shown similar figures indicative of poor glycaemic control (10, 11).

Metformin was the anti-diabetic agent used by 85.5% of T2DM patients included in our study. This is in keeping with current diabetes clinical practice guidelines, which recommend metformin as a first-line treatment in T2DM (12). Metformin monotherapy was prescribed to 55.8% of patients with an HbA1c above 7% in our cohort, and only 23.0% were on metformin and insulin combination therapy. Studies have shown that adding insulin to metformin monotherapy improves glycaemic control (13). Clinical inertia to intensify diabetic therapy is common in LMICs and significantly contributes to poor glycaemic control (14). Therefore, the poor glycaemic control in our study participants may have resulted from a lack of treatment intensification.

Our study findings revealed a substantial unmet need to adequately control HbA1c levels. Novel agents such as sodium-glucose co-transporter 2 inhibitors (SGLT2-I) have demonstrated a reduction in major adverse cardiovascular events in T2DM patients with ASCVD (15-17). Similar results have been shown with some glucagon-like peptide 1(GLP-1) analogues (18-20). The current use of these agents in our setting is limited due to their high cost. However, cost-effectivity analyses investigating the potential impact of SGLT2-I and GLP-1 analogues in preventing ASCVD complications and reducing the overall cost burden on the healthcare systems are still lacking in LMICs (21, 22).

It is well-established that diabetes increases the risk of cardiovascular mortality (23). The risk is even higher in patients who have already had a cardiovascular event (24), such is the case in our study participants. It is therefore important to reduce the risk of recurrent cardiovascular events by

instituting early use of novel anti-diabetic therapy that provides organ protection (25). As noted, most of our cohort was on metformin. 2023 European Society of Cardiology guidelines recommend that in patients with CAD and T2DM, SGLT2-I or GLP-1 analogues should be added to the treatment regimen irrespective of HbA1c control, and in those patients not on metformin, it is recommended that these agents should be instituted as first-line therapy (25).

Glycaemic control in patients with cardiovascular disease should be individualised based on patient age, life expectancy and comorbidities (25). In our study, we did not evaluate HbA1c according to these criteria. It is recommended that in patients with a short life expectancy such as elderly patients with terminal illness and multiple comorbidities, target HbA1c should be ≤8.5%. In individuals with a longer life expectancy, the target HbA1c should be <7% (25).

In our cohort, poor HbA1c control was more common in younger patients. Several reasons could account for this occurrence. Firstly, younger patients are often less likely to adhere to medication and self-management of diabetes practices. Secondly, younger T2DM patients tend to be less informed about their condition and are more likely to have misconceptions about their susceptibility to illness and disease complications because of their younger age (26, 27).

Our study population consisted predominantly of male patients. This is in keeping with international findings, which reveal a higher prevalence of diabetes among men (1). Most of the male patients in our study had an HbA1c >7%. However, studies have shown that poor glycaemic control is more

likely in women than men (28, 29). There are several hypotheses to explain this observation, including differences in glucose metabolism and body mass index, hormonal differences, and psychosocial factors (30).

Type 2 diabetes mellitus is associated with the development of hypertension due to various pathophysiological mechanisms (31, 32). Studies have shown a positive correlation between HbA1c levels and hypertension (33). High HbA1c levels are associated with high blood pressure (34). In our study, patients with optimal glycaemic control had higher systolic and diastolic blood pressure. A possible explanation is that poorly controlled diabetes is associated with more severe coronary artery disease (35). We hypothesise that clinicians managing T2DM patients with CAD likely scheduled more frequent outpatient visits for these patients and also uptitrated the anti-diabetic medication more efficiently.

Diabetes mellitus is often associated with more complex CAD with multi-vessel involvement. Increased HbA1c levels result in extensive coronary artery involvement (35). In our study, 24.2% of the patients had triple vessel disease, most of whom had an HbA1c above 7%. These patients generally require surgical revascularisation, translating to higher healthcare costs (36). This further underscores the need to optimise HbA1c control, thereby decreasing the prevalence of complex CAD and the need for surgical interventions, ultimately leading to decreased total healthcare costs.

In our study, among T2DM patients with poor glycaemic control and concomitant CAD, 36.2%

presented with ST-segment elevation myocardial infarction, and 11.2% had ST-segment depression myocardial infarction. T2DM patients with poor glycaemic control likely have more severe atherosclerotic disease characterised by vulnerable plaques. Therefore, these patients are more likely to have acute plaque rupture and present with ST-segment elevation myocardial infarction (35, 37). Our study found that ST-segment depression on ECG was independently associated with optimal HbA1c control, likely because patients with better-controlled diabetes have less atherosclerotic burden and more stable plaques than those with poor glycaemic control (38).

Given the poor HbA1c control found in our study population, other strategies, in addition to the novel anti-diabetic agents, need to be implemented. T2DM patients should be educated about critical aspects of self-management of their condition. These aspects include adherence to medication, dietary advice, physical activity, and self-monitoring of glucose levels. Self-management of diabetes is inadequate in most individuals residing in sub-Saharan Africa (39). Other strategies to optimise control include frequent follow-up of patients, decentralisation of care and implementation of nurse practitioner or community health care worker home-based visits.

Multiple landmark trials have demonstrated that intensive glycaemic control results in a reduction in the occurrence of microvascular complications both in type 1 and type 2 diabetic patients (40, 41). However, strict glycaemic control did not yield a similar reduction in the occurrence of macrovascular complications. There is some evidence that exists that demonstrates that initial tight glycaemic control reduces macrovascular complications in the long term (40, 42). These results are most likely attributed

to the legacy effect or metabolic memory of tight glycaemic control (43).

However, it has also been noted that tight glycaemic control may have adverse effects. The ACCORD trial evaluated tight glycaemic control in T2DM patients with established CVD, with patients assigned either to intensive treatment with a target HbA1c of <6% versus standard treatment with target HbA1c of 7-7.9%. The average HbA1c achieved in the intensive therapy group was 6.4% and this was associated with increased rates of mortality, hypoglycaemia, and weight gain (44). Similarly, the UKPDS trial evaluated tight glycaemic control in newly diagnosed T2DM patients and demonstrated similar adverse results (41). These effects are deleterious and may increase the risk of cardiovascular events and mortality (45, 46). It is therefore, a first-line recommendation to avoid hypoglycaemia, especially in patients with cardiovascular disease to prevent the risk of subsequent events (25).

Our study had several limitations. Patient data was reviewed retrospectively, and we excluded many T2DM patients whose laboratory biochemical results could not be retrieved. This significantly reduced the study sample size. Furthermore, this was a single-centre study. Therefore, the generalisability of the findings may not apply to other centres. However, most patients seen in our hospital were referred from primary and secondary-level hospitals to our centre for further specialist-driven management. Also, our study did not consider psychosocial factors and duration of disease, which may have played a role in the glycaemic control of our study participants. We also attempted to evaluate patient compliance to anti-diabetic therapy. However, such information was rarely documented in patient files. Despite these limitations, this data provides real-world insights into

the standard of diabetic control in a South African state-owned tertiary hospital for this very high-risk population with established ASCVD.

5 Conclusion

In our study, only 28.7% of T2DM patients with CAD achieved an HbA1c ≤7% after a median follow-up of 16.5 months. The small proportion of T2DM with optimal glycaemic control highlights the urgent need for better management strategies to improve HbA1c control in this very high-risk group of patients.

6 Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest. However, NT has received consulting and speaker fees from Acino Health Care Group, Boehringer-Ingelheim, Boston Scientific, Eli Lilly, Merck, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Phillips, Servier, and Takeda. NT has also received educational grants from Biotronik, Boston Scientific, Medtronic, and Vertice Health Care Group. DM and LM have no declarations.

7 Author Contributions

NT and LM conceptualised the study. LM wrote the first draft of the manuscript. NT and DM reviewed and edited the manuscript and supervised the research project. DM contributed to the statistical analysis and validation of results. All authors read and approved the final version of the

manuscript.

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11. Supplementary material

None

12. Data availability statement

The dataset analysed for this study is available from the authors upon reasonable request.

Appendices
13. Tables

a. Table 1 Baseline characteristics of patients with Type 2 Diabetes Mellitus and coronary artery disease

	ALL T2DM Patients n= 262	**HbA1c ≤ 7% n= 66 (25.2%)**	**HbA1c > 7% n= 196 (74.8%)**	**p-value**
Age (years)	61.3 ± 10.4	63.6 ± 10.1	60.5 ± 10.4	0.0332
Male, *n* (%)	188 (71.8)	40 (60.6)	148 (75.5)	0.020
Ethnicity				
Black, *n* (%)	56 (21.4)	14 (21.2)	42 (21.4)	0.970
White, *n* (%)	84 (32.1)	25 (37.9)	59 (30.1)	0.242
Indian/ Asian, *n* (%)	102 (39.0)	22 (33.3)	80 (40.8)	0.281
Mixed ancestry, *n* (%)	20 (7.6)	5 (7.6)	15 (7.7)	0.984
Risk Factors For CAD				
Previous CAD/CVA, *n* (%)	94 (36.6)	24 (37.5)	70 (36.3)	0.859
Hypertension, *n* (%)	198 (75.6)	52 (78.8)	146 (74.5)	0.482
Dyslipidaemia, *n* (%)	173 (66.0)	43 (65.2)	130 (66.3)	0.862
Chronic kidney disease, *n* (%)	40 (15.3)	13 (19.7)	27 (13.8)	0.247
Peripheral vascular disease, *n* (%)	11 (4.2)	5 (7.6)	6 (3.1)	0.114
Family history of CAD, *n* (%)	94 (35.9)	24 (36.4)	70 (35.1)	0.924
Smoker/ ex-smoker, *n* (%)	150 (57.3)	37 (56.1)	113 (57.7)	0.821
Vital Signs				
Heart rate* (bpm)	75 (64-90)	74 (66-89)	78 (69-96)	0.1628
Systolic blood pressure* (mmHg)	124 (112-142)	136 (117-151)	124 (112-142)	0.0121
Diastolic blood pressure* (mmHg)	80 (70-92)	85 (75.5-97)	78 (71-88)	0.0205
NYHA Functional Class				
NYHA 1, *n* (%)	132 (65.4)	33 (63.5)	99 (66.0)	0.740
NYHA 2, *n* (%)	61 (30.2)	13 (25.0)	48 (32.0)	0.343
NYHA 3, *n* (%)	6 (3.0)	4 (7.7)	2 (1.3)	0.020
NYHA 4, *n* (%)	3 (1.5)	2 (3.9)	1 (0.7)	0.102
Killip Class				
Killip 1, *n* (%)	204 (77.9)	45 (68.2)	159 (81.1)	0.029
Killip 2, *n* (%)	28 (10.7)	8 (12.1)	20 (10.2)	0.663
Killip 3, *n* (%)	9 (3.4)	3 (4.6)	6 (3.1)	0.567
Killip 4, *n* (%)	6 (2.3)	3 (4.6)	3 (1.5)	0.157
Biochemistry				
Troponin (ng/L)	1558 (204-5175)	1253 (28-4674)	1153 (158-3947)	0.8128
Estimated GFR (mL/min/1.73m²)	73.4 ± 27.5	67.5 ± 25.8	75.3 ± 27.9	0.0480
LDL cholesterol (mmol/L)	3.0 (2.3-3.8)	2.6 (2.0-3.4)	2.9 (2.1-3.6)	0.4844
ECG Parameters				
ST segment normal, *n* (%)	87 (33.2)	28 (42.4)	59 (30.1)	0.066
ST elevation, *n* (%)	84 (32.1)	13 (19.7)	71 (36.2)	0.013
ST depression, *n* (%)	41 (15.7)	19 (28.8)	22 (11.2)	0.001
Q waves, *n* (%)	76 (29.0)	13 (19.7)	63 (32.1)	0.054

T wave inversion, *n* (%)	33 (12.6)	9 (13.6)	24 (12.2)	0.768
Echocardiogram				
LVEF (%)	50 ± 14.1	51.1 ± 14.4	50.0 ± 14.0	0.6207
LVIDd (mm)	49.9 ± 8.9	50.6 ± 9.6	49.7 ± 8.7	0.5404
LVIDs (mm)	35.8 ± 9.5	37.7 ± 10.0	36.8 ± 9.5	0.5889

DM: Diabetes mellitus, CAD: Coronary artery disease, CVA: Cerebrovascular accident, bpm: Beats per minute, NYHA: New York heart association, GFR: Glomerular filtration rate, HbA1c: Glycated haemoglobin, LDL: Low-density lipoprotein, ECG: Electrocardiogram, LVEF: Left ventricular ejection fraction, LVIDD: Left ventricular internal diameter at end-diastole, LVIDS: Left ventricular internal diameter at end-systole. T2DM: Type 2 Diabetes Mellitus. *Heart rate and blood pressure measurements were captured during patient admission.

b. Table 2 Diabetic medication prescribed to patients with Type 2 Diabetes Mellitus

	All T2DM Patients n= 262	**HbA1c ≤7% n=66 (25.2%)**	**HbA1c >7% n= 196 (74.8%)**	**p-value**
Metformin, *n* (%)	224 (85.5)	59 (89.4)	165 (84.2)	0.298
Glimepiride, *n* (%)	38 (14.5)	5 (7.6)	33 (16.8)	0.065
Gliclazide, *n* (%)	7 (2.7)	3 (4.6)	4 (2.0)	0.275
Glibenclamide, *n* (%)	3 (1.2)	0 (0.0)	3 (1.5)	0.312
Actrapid, *n* (%)	7 (2.7)	0 (0.0)	7 (3.6)	0.120
Protaphane, *n* (%)	23 (8.8)	2 (3.0)	21 (10.7)	0.056
Actraphane, *n* (%)	51 (19.5)	7 (10.6)	44 (22.5)	0.036
Metformin monotherapy, *n* (%)	140 (62.5)	48 (81.4)	92 (55.8)	0.000
Metformin and Sulphonylurea, *n* (%)	40 (17.9)	8 (13.6)	32 (19.4)	0.315
Metformin and Insulin, *n* (%)	41 (18.3)	3 (5.1)	38 (23.0)	0.002

HbA1c: Glycated haemoglobin, T2DM: Type 2 diabetes mellitus, Actrapid: Short-acting regular human insulin, Protaphane: Neutral protamine Hagedorn (NPH), Actraphane: NPH 70% + short-acting regular human insulin 30%.

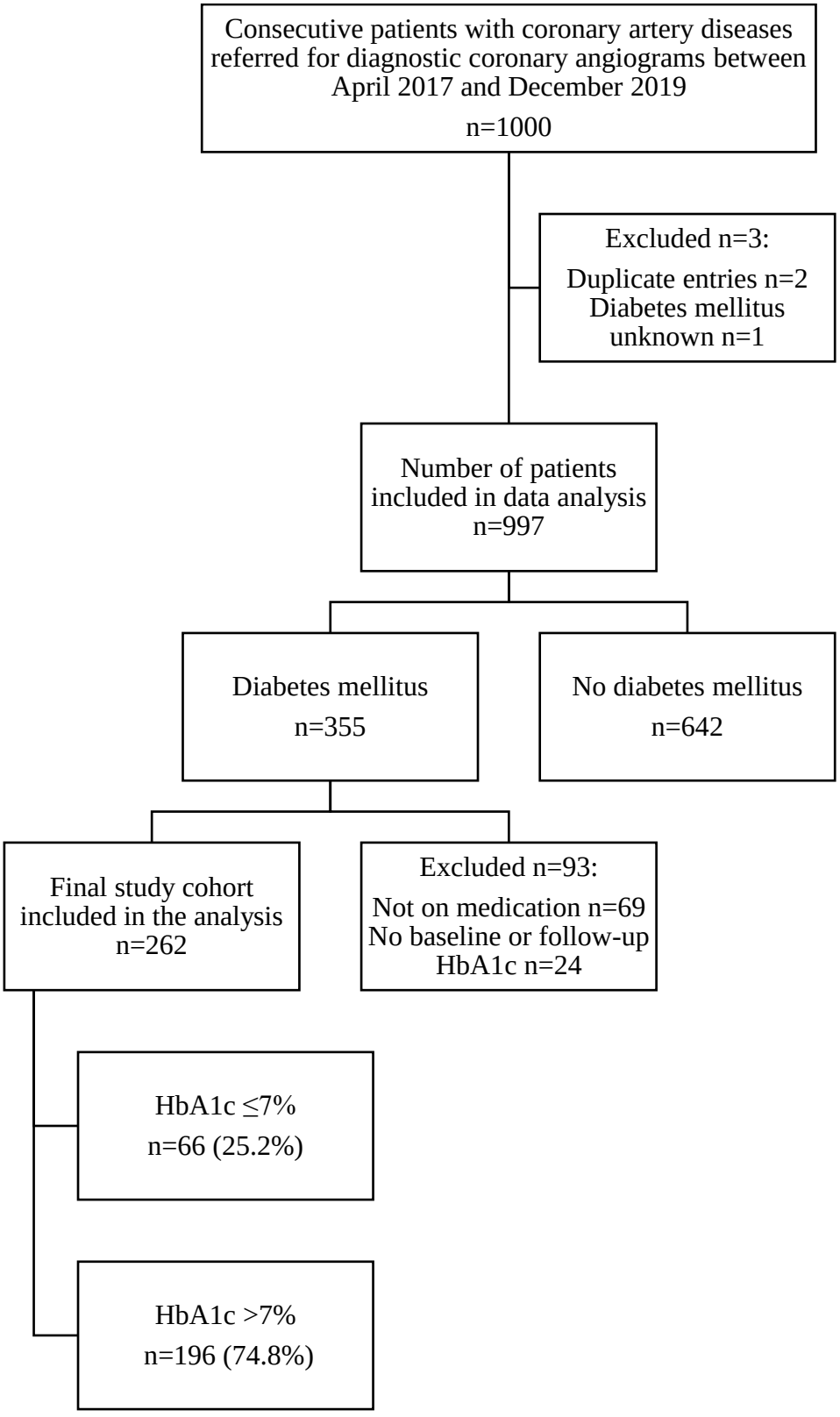
c. Table 3 Univariable and multivariable logistic regression analysis evaluating factors associated with poor glycaemic control (HbA1c above 7%)

	Univariable regression			**Multivariable regression**		
	OR	**p-value**	**CI**	**OR**	**p-value**	**CI**
NSTEMI	0.72	0.378	0.35-1.49	1.63	0.392	0.53-5.02
Unstable angina	0.40	0.025	0.18-0.89	0.63	0.417	0.20-1.94
Stable angina	0.91	0.830	0.37-2.23	1.18	0.796	0.34-4.04
ST depression	0.32	0.002	0.16-0.65	0.27	0.001	0.12-0.59
ST elevation	2.01	0.047	1.00-4.03	2.82	0.073	0.91-8.76
Actraphane	2.47	0.040	1.04-5.85	2.09	0.131	0.80-5.47

HbA1c: Glycated haemoglobin, NSTEMI: Non-ST-Elevation myocardial infarction, OR: odds ratio, CI: confidence intervals.

13 Figure Legends

d. Figure1: Flow chart outlining patient selection.



e. Figure 2: Baseline versus follow-up HbA1c in diabetic patients.

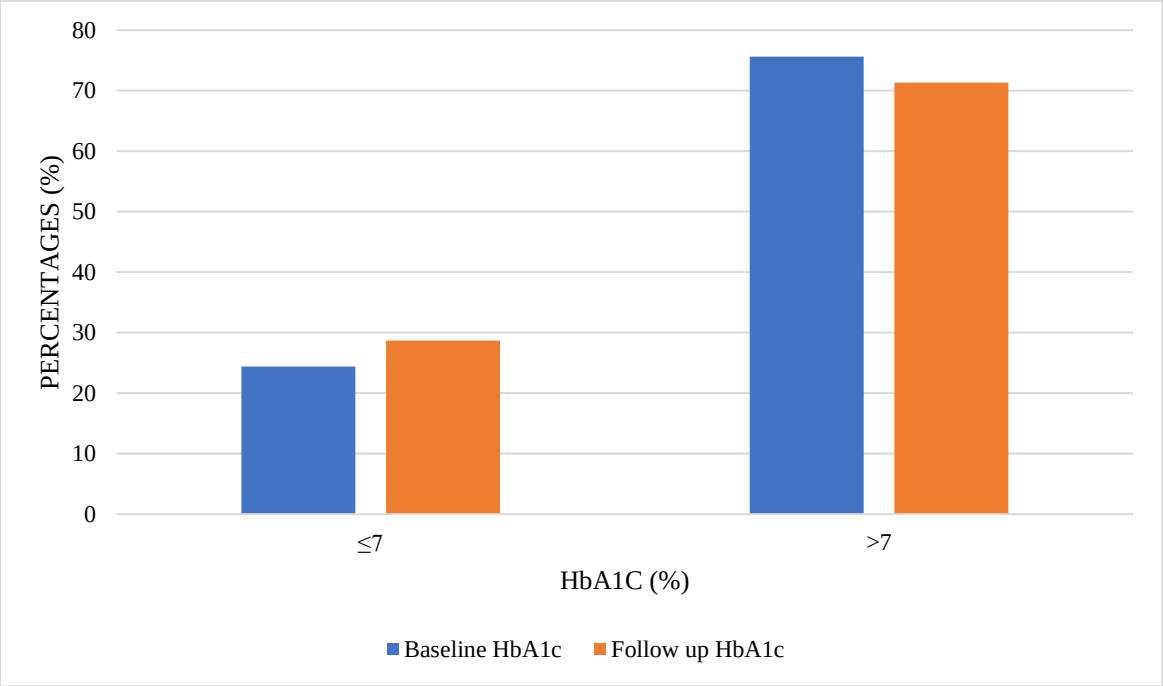


Figure 2: Graph showing baseline versus follow-up HbA1c in diabetic patients categorized as controlled diabetes mellitus (HbA1c ≤7) and non-controlled diabetes mellitus (HbA1c >7%).

f. Protocol.

HBA1C CONTROL IN TYPE 2 DIABETIC PATIENTS WITH CORONARY HEART DISEASE

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterised by hyperglycaemia and disturbances in carbohydrate, fat and protein metabolism (1). It is caused by several inherited or acquired conditions which result in defects in either insulin secretion, action or both (1). This metabolic dysregulation can lead to pathophysiological changes in multiple organ systems (1).

Background and Significance

Diabetes mellitus is a global pandemic affecting people of all socio-economic standing. According to the International Diabetes Federation, in 2017, approximately 425 million people worldwide were living with diabetes, half of whom were undiagnosed (2). It is estimated that the number will rise to approximately 642 million by the year 2046 (2). In 2017, it was estimated that there were over 2 million South Africans aged between the ages of 20-79 living with diabetes (2).

Diabetes mellitus causes both microvascular and macrovascular complications (3). Cardiovascular disease is the main comorbid condition and is noted to be one of the primary contributors to mortality (4). The risk of cardiovascular disease in patients with type 2 diabetes is increased by up to two-fold in men and up to four-fold in women when compared to the non-diabetic population (5). Hyperglycaemia, not meeting diagnostic criteria for diabetes is also a risk factor for cardiovascular disease (6).

Cardiovascular disease is a major cause of morbidity and mortality in diabetic patients (4). Patients living with diabetes have accelerated development of atherosclerosis, which further increases the risk of cardiovascular disease (7). Often patients with type 2 diabetes have other comorbidities such as hypertension, dyslipidaemia and obesity, which are commonly referred to as the metabolic syndrome, which further increases the risk of cardiovascular diseases (8). The importance of good glycaemic control for the prevention of microvascular complications and cardiovascular disease in type 1 diabetes is well established, but is not as clear in type 2 diabetes (9). The most effective measures for the prevention of cardiovascular

disease are multifactorial. These include glycaemic control, smoking cessation, diet, physical activity, blood pressure control and treatment of dyslipidaemia (8). The purpose of good glycaemic control is not only to relieve symptoms of hyperglycaemia, but also to prevent the complications associated with diabetes (9). It should be noted however that extremely well-controlled diabetes leading to hypoglycaemia is in itself a risk factor for cardiovascular disease. The Veterans Affairs Diabetes randomised controlled Trial (VADT trial), found that intensive treatment leading to severe hypoglycaemia increased the risk of cardiovascular events and mortality (10).

Diabetes and coronary artery disease

Atherosclerosis is a major mechanism for the development of coronary artery disease (7). The pathogenesis of atherosclerosis is initiated by noxious stimuli, such as hyperglycaemia, which cause endothelial dysfunction. This is followed by migration of mononuclear cells, such as monocytes and T-lymphocytes, into the subendothelial space. The monocytes mature into macrophages which engulf lipid and become foam cells. Smooth muscle cells then migrate to the surface to form a fibrous layer over the lipid core. The lipid-laden macrophages release matrix metalloproteinases, which cause rupture of the plaque resulting in obstruction of the vessel and lead to acute coronary syndromes (7).

Coronary artery calcification is an indicator of subclinical atherosclerosis (11). There is an established link which exists between hyperglycaemia and coronary artery calcification (11). Coronary artery calcification is more evident in people with dysglycaemia, even in those people without diabetes mellitus (11).

There is an increased risk of atherosclerotic coronary artery disease in diabetic patients with higher HbA1c levels (12). On a ten year follow up of patients who received intensive glycaemic control immediately after the diagnosis of diabetes, HbA1c levels of less than 6.5% were associated with less microvascular and macrovascular complications (12). Diabetic patients with an HbA1c of more than 7% had a greater risk of mortality from both microvascular and macrovascular complications (12).

Coronary artery disease in diabetes mellitus is associated with more complex coronary artery lesions with multivessel involvement (13). This increases the risk of morbidity and mortality (13). Elevated HbA1c levels are associated with higher syntax II scores, therefore indicating that poor glycaemic control results in more severe coronary artery disease (13). Studies have demonstrated that type 2 diabetes mellitus further exacerbates coronary artery disease by causing impairment in the formation of collateral coronary vessels in patients with chronic total occlusions (14). The greater the extent of coronary artery disease, the higher the risk for developing acute coronary syndromes (15).

The legacy effect or metabolic memory refers to the reduction in microvascular as well as cardiovascular events observed years after initial intensive glycaemic control (12). Studies initially demonstrated that intensive glycaemic control did not significantly reduce cardiovascular events when compared to standard therapy and only had a positive effect on microvascular outcomes (12). Follow up of the cohort of patients included in these studies, years after initiation of the trial, revealed that intensive glycaemic control after diagnosis also resulted in decreased cardiovascular outcomes, therefore demonstrating the legacy effect (12).

New hypoglycaemic agents

Glycated haemoglobin (HbA1C) has been used as the standard method for monitoring long term glucose control, the efficacy of diabetic treatments and as the primary predictor of long term complications of diabetes (16). In addition to HbA1C control, it is now mandated by the Food and Drug Administration (FDA) and other regulatory agencies that all new anti-diabetic drugs demonstrate cardiovascular safety (17). This has now resulted in several cardiovascular outcome trials to demonstrate the cardiovascular safety of newer hypoglycaemic agents before their FDA approval. This came about because of the increased risk of adverse cardiovascular events that were associated with the use of anti-diabetic drugs, such as the thiazolidinediones, which were noted to increase risk of heart failure and myocardial infarction in diabetic patients (17). These trials have led to the emergence of novel hypoglycaemic agents which demonstrate cardiovascular safety.

Sodium-glucose linked transporter 2 inhibitors

Sodium-glucose linked transporter 2 is a sodium and glucose transporter located in the proximal tubule of the nephron. It is responsible for reabsorbing approximately 90% of glucose filtered on a daily basis and the remaining 10% is reabsorbed by the sodium-glucose linked transporter 1 (18). In people with type 2 diabetes, this reabsorption of glucose is increased by 20-40%, which further exacerbates hyperglycaemia (19). Inhibition of this transporter results in a decrease in glucose reabsorption of approximately 30-50%, which then leads to glycosuria (19). This inhibition results in three net effects. Firstly improvement of hyperglycaemia, secondly osmotic diuresis resulting in blood pressure control and calorie reductions of 200-300 kcal/day resulting in weight loss (19).

The EMPA-REG OUTCOME trial was a trial which compared the effects of empagliflozin, a sodium-glucose linked transporter-2 inhibitor (SGLT-2-I), with placebo in type 2 diabetic patients with high cardiovascular risk. High cardiovascular risk patients included those with at least one of the following; myocardial infarction, unstable angina or stroke more than two months prior to the trial, patients with single or multi-vessel coronary disease and patients with peripheral arterial disease. The trial results revealed that patients on empagliflozin had significantly lower rates of adverse cardiovascular outcomes and of note, the risk reductions occurred early in the trial and continued throughout the study (20). The patients assigned to the empagliflozin group showed lower rates of death from cardiovascular causes (95% CI, 0.49 to 0.77; $P<0.001$) lower rates of hospitalisation for heart failure (95% CI, 0.50 to 0.85; $P = 0.002$) and lower rates of all-cause mortality (95% CI, 0.57 to 0.82, $P<0.001$) (20).

The CANVAS trial also achieved similar results which were consistent with those of the EMPA-REG OUTCOME trial. Canagliflozin, an SGLT-2-I, was shown to be better than placebo in reducing the primary combined outcome of cardiovascular death, myocardial infarction and stroke with lower rates of 26.9% versus 31.5%, $P=0.02$ (21).

The sodium-glucose linked transporter inhibitors show similar results with regards to cardiovascular outcomes. These trials have demonstrated that treatment with SGLT-2 inhibitors is associated with lower risks of hospitalisations for heart failure and death when

compared to other hypoglycaemic agents. This suggests that the benefits observed with empagliflozin in the EMPA-REG OUTCOME trial are a class effect (22).

Glucagon-like peptide-1 analogues

Glucose homeostasis is dependent on the interplay of several hormones, including a group known as incretins (23). Incretins are hormones released from the gastrointestinal tract in response to ingested nutrients, resulting in augmentation of insulin secretion. Examples of such hormones include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) (23). These hormones are responsible for what is known as the incretin effect. The incretin effect is when oral glucose has a greater stimulatory effect on insulin secretion than intravenous glucose (24).

Glucagon-like peptide-1 analogues are a group of drugs which mimic endogenous glucagon-like peptide-1 (23). They are structurally homologous to GLP-1 but are resistant to enzymatic breakdown by dipeptidyl peptidase-4, an enzyme which breaks down endogenous GLP-1 (23). This results in an increased therapeutic half-life and therefore increased duration of action (23). The net effect is increased insulin secretion, decreased glucagon release, enhanced satiety, a delay in gastric emptying and modest weight loss (23).

The LEADER trial which assessed cardiovascular outcomes in type 2 diabetic patients who were at high risk for cardiovascular events concluded that patients who were on liraglutide, a GLP-1 analogue, had lower rates of cardiovascular events and death from any cause when compared to placebo (25). Fewer patients died from cardiovascular causes in the liraglutide group as compared to placebo (95% CI, 0.66 to 0.93; P = 0.007). The rate of death from any cause was lower in the liraglutide group than in the placebo group (95% CI, 0.74 to 0.97; P = 0.02) (25).

The SUSTAIN-6 trial, which assessed cardiovascular outcomes in type 2 diabetic patients with high cardiovascular risk, also showed beneficial results. The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (including silent), or nonfatal stroke. The primary outcome occurred less in the semaglutide group when compared to placebo (95% CI, 0.58 to 0.95; P<0.001) (26). In this trial it was noted that the beneficial effects of semaglutide may have resulted from the modified progression of atherosclerosis (26).

The ELIXA trial, which evaluated the use of lixisenatide, a GLP-1 analogue, in acute coronary syndromes, did not show any cardiovascular benefits in patients with type 2 diabetes who had recently had an acute coronary syndrome. The results in this study were more neutral for cardiovascular outcomes when compared with the above studies (27). However, the drug was safe. It did not increase cardiovascular outcomes.

There are a few reasons that have been proposed to explain why the ELIXA trial had a neutral effect on cardiovascular outcomes. Firstly, the study included patients with recent myocardial infarction or patients hospitalised for unstable angina within 180 days of screening, which was unlike the other trials (27). It has also been noted that favourable outcomes with reduced rates of cardiovascular events required longer duration of follow up and longer exposure to the treatment (27). Lixisenatide is based on a structure with only 50 percent homology to GLP-1, compared to liraglutide and semaglutide which are almost similar to endogenous GLP-1 (28). This difference in structure could have also contributed to the neutral results achieved.

The rationale for the study

In South Africa, approximately 73% of patients with self-reported diabetes have an associated cardiovascular disease as a comorbidity (29). The above illustrates the extent of association of these diseases in our setting and therefore demonstrates the importance of adequate treatment for both.

Given the above results from various cardiovascular outcome trials, it is reasonable to conclude that type 2 diabetic patients with a high risk of cardiovascular events would benefit from these newer agents.

Study objectives

Primary objective:

1. To determine HbA1c control in type 2 diabetic patients with angiographically proven coronary artery disease.

Secondary objectives:

1. To describe other cardiovascular risk factors present in these patients.
2. To describe the anti-diabetic agents used in these patients.
3. To determine the proportion of patients who have achieved HbA1c target on the currently available anti-diabetic medication.
4. Motivate for the clinical need of the new anti-diabetic medication currently not available in the state sector.

Methods

Inclusion criteria

1. Type 2 diabetes treated with one or more oral anti-diabetic drugs or treated with insulin or a combination of both.
2. Coronary artery disease as evidenced by coronary angiogram
3. Prior coronary artery revascularisation

Exclusion criteria

1. Type 1 diabetes
2. Acute decompensation of glycaemic control.
3. Acute coronary event within 14 days of data collection

Study design

This study will be a retrospective study with data collected from Charlotte Maxeke Johannesburg Academic Hospital cardiology clinic. I will collect the data of one hundred type 2 diabetic patients following up at the cardiology clinic who have angiographically proven coronary artery disease. Data on the treatment taken by patients as well as baseline and follow-up HbA1c results obtained at the time of the adverse cardiovascular event will also be collected to assess the control of diabetes mellitus.

Data analysis

All data will be captured using Redcap software hosted at the University of the Witwatersrand. The statistical analysis will be done using STATA (version 15, College Station, Texas). Demographic data will be presented using frequency tables and a chi-square test will be used for categorical variables. Normally distributed data will be presented as mean and standard deviation (SD) and skewed data will be presented as median and interquartile range. For normally distributed data, continuous variables will be analysed using student t-test. A p- value of less than 0.05 will indicate statistical significance.

Limitations

The limitation is the retrospective nature of the study. We are unable to control the collection of information specific to our study and therefore are relying on adequate record-keeping within the cardiology department. We are also unable to assess patient compliance to

medication as well as adherence to a strict diabetic diet as these factors will also influence glycaemic control.

Ethics

This proposal will be submitted to the University of the Witwatersrand Health Sciences Research Ethics Committee for assessment and approval. The data collected from this study will be kept confidential and no patient identifying details will be published.

Timing

	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
Literature Review											
Preparing protocol											
Protocol assessment											
Ethics application											
Data collection											
Data analysis											
Final write up											

Funding

As this is a retrospective study, there will be no funding required.

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g. Data collection spreadsheet.

Demographics

Record ID	_____
Hospital number	_____
what is the age of the patient	_____
What is the patient's date of birth?	_____
please indicate the race of the patient	◯ Caucasian ◯ Asian/Indian ◯ African ethnicity ◯ Coloured ◯ Other
please indicate the gender of the patient	◯ Male ◯ Female
which area does the patient come from	◯ City of Jhb Metropolitan municipality ◯ Ekurhuleni Metropolitan municipality ◯ City of Tshwane ◯ Sedibeng District ◯ West Rand District ◯ Other

Risk Factors

Does the patient have hypertension?	○ Yes ○ No
Does the patient have diabetes mellitus?	○ Yes ○ No
Does the patient have dyslipidaemia?	○ Yes ○ No
Does the patient have chronic kidney disease?	○ Yes ○ No
Does the patient have peripheral vascular disease?	○ Yes ○ No
Does the patient have a family history of coronary artery disease?	○ Yes ○ No
Does the patient smoke?	○ Yes ○ No
Does the patient have any stressors?	○ Yes ○ No
Does the patient have any other risk factors?	_____

Baseline Characteristics

please indicate which type of acute coronary syndrome the patient presented with	○ STEMI ○ NSTEMI ○ Unstable Angina
where was the patient admitted	○ CCU ○ General ward
what was the Heart rate on admission	_____
please indicate what the systolic blood pressure was on admission	_____
Please indicate the diastolic blood pressure	_____
weight	_____
height	_____
BMI (kg/m^2)	_____
NYHA functional class	○ I ○ II ○ II ○ IV
What was the killip score	☐ I No congestion ☐ II S3 gallop, basal rales ☐ III Acute pulmonary oedema ☐ IV Cardiogenic shock
was a thrombolytic agent given	○ Yes ○ No
what was the time to thrombolysis	_____

	Metalyse	Alteplase	Streptokinase
Which thrombolytic agent was used	○	○	○

Baseline Rythm	_____
What was the baseline interval on presentation	_____

ST Segment changes	☐ Normal ☐ Elevation ☐ Depression ☐ Anterior ☐ Inferior ☐ lateral
ECHOCARDIOGRAM Findings	☐ LV ☐ LV wall motion ☐ Diastolic function ☐ Valves ☐ Right Ventricle ☐ pericardial effusion
LVEF	_____
LA size	_____
LVIDd	_____
LVIDs	_____
LV wall motion	☐ Akinesia ☐ dyskinesia ☐ hypokinesia ☐ global hypokinesia
Findings on Cardiac catheterization	☐ RCA ☐ Left main ☐ LAD ☐ D1 ☐ Circumflex ☐ OM/Ramus ☐ LV ☐ PCI ☐ Other
Distribution of disease on angiography	○ Single vessel ○ Double vessel ○ Triple vessel
vessel condition	☐ Normal ☐ Stenosis ☐ Proximal ☐ Mid ☐ Distal ☐ < 50% ☐ 50-70% ☐ >70% ☐ Occlusion
Left Ventricular function on cardiac catheterization	○ Normal ○ Abnormal
Type of Percutaneous intervention done	☐ PTCA ☐ Drug-eluting stent ☐ Bare metal stent ☐ LAD ☐ Cx ☐ RCA

Medications

Was the patient on oral hypoglycaemic agents?	☐ Glucophage (metformin) ☐ Glibenclamide ☐ Gliclazide (diamicron) ☐ Glimepiride (amaryl) ☐ No oral hypoglycaemic agents

	5mg PO dly	7.5mg PO DLY	10mg PO dly	12.5mg PO dly	15mg PO dly
What dose of glibeclamide was the patient taking	○	○	○	○	○

	40mg PO dly	80mg PO dly	120mg PO dly	160mg POdly	200mg PO dly	240mg PO dly	280mg PO DLY	320mg PO dly
please indicate how much the patient was on?	○	○	○	○	○	○	○	○

	1mg pPO dly	2mg PO dly	3mg PO dly	4mg PO dly
what dosage was the patient on?	○	○	○	○

	500mg PO dly	500mg PO bd	850mg po dly	850mg po bd	850mg po tds	1g po bd
what dose was the patient on?	○	○	○	○	○	○

was the patient on insulin therapy?	☐ Actrapid ☐ Protaphane ☐ Actraphane ☐ Other ☐ No insulin therapy
what dose of insulin was the patient on?	_____
Was the patient on antihypertensive therapy?	☐ Hydrochlorothiazide (ridaq) ☐ Indapamide ☐ Furosemide (lasix) ☐ Spironolactone (aldactone) ☐ Propanolol ☐ Atenolol ☐ Bisoprolol ☐ Carvedilol ☐ Amlodipine (norvasc) ☐ Nifedipine ☐ Verapamil ☐ Diltiazem ☐ Enalipril (pharmapress) ☐ Perindopril (coversyl) ☐ Losartan ☐ Methyldopa ☐ Doxazosin (cardura) ☐ Hydralazine ☐ Minoxidil ☐ No antihypertensive therapy
what dose of Ridaq/HCTZ was the patient on ?	○ 12.5mg PO dly ○ 25mg PO dly
What dose of spironolactone was the patient taking?	○ 12.5mg ○ 25mg ○ 50mg ○ 75mg ○ 100mg

what dosage of Indapamide was the patient on ?	◯ 1.25mg PO dly ◯ 2.5 mg PO dly ◯ 3.75mg PO dly ◯ 5mg PO dly
What dose of propanolol was the patient taking?	◯ 10mg ◯ 20mg ◯ 30mg ◯ 40mg ◯ 60mg
what dosage of furosemide was the patient on?	◯ 20mg PO dly ◯ 40mg PO dly ◯ 60mg PO dly ◯ 80mg PO dly ◯ 100mg PO dly ◯ 120mg PO dly ◯ 160mg PO dly ◯ 180mg PO dly ◯ 200mg PO dly
what dose of atenolol was the patient on?	◯ 25mg PO dly ◯ 50mg Po dly ◯ 75mg PO dly ◯ 100mg PO dly
what dose of Bisoprilol was the patient on?	◯ 2.5 mg PO dly ◯ 5mg PO dly ◯ 7.5mg PO dly ◯ 10mg PO dly
What dose of carvedilol was the patient taking?	◯ 6.25 mg ◯ 12.5mg ◯ 25mg ◯ 50mg
what dosage of amlodopine was the patient on?	◯ 5mg Po dly ◯ 10mg PO dly
What dose of nifedipine was the patient taking?	◯ 30mg ◯ 60mg ◯ 90mg
what dose of Verapamil CR was the patient on ?	◯ 100mg PO dly ◯ 120mg PO dly ◯ 180mg POdly ◯ 200mg PO dly ◯ 240mg PO dly ◯ 300mg PO dly ◯ 360mg PO dly ◯ 480mg P) dly
What dose of diltiazem was the patient taking?	◯ 60mg ◯ 90mg ◯ 120mg ◯ 180mg ◯ 240mg
What dose of enalipril was the patient taking?	◯ 5mg ◯ 10mg ◯ 20mg ◯ 40mg
What dose of perindopril was the patient taking?	◯ 4mg ◯ 8mg
What dose of losartan is the patient taking?	◯ 25mg ◯ 50mg ◯ 75mg ◯ 100mg
What dose of doxazocin was the patient taking?	◯ 1mg ◯ 2mg ◯ 4mg ◯ 8mg
What dose of hydralazine was the patient taking?	◯ 25mg ◯ 50mg ◯ 75mg ◯ 100mg ◯ 150mg ◯ 200mg
what dose of minoxidil was the patient taking?	◯ 2.5mg ◯ 5mg ◯ 10mg
what dose of simvastatin was the patient on?	◯ 5mg PO nocte ◯ 10mg PO nocte ◯ 20mg PO nocte ◯ 40mg PO nocte ◯ 80mg PO nocte

what dosage of atorvastatin was the patient on?	◯ 10mg PO dly, ◯ 20mg PO dly ◯ 40mg PO dly ◯ 80mg PO dly
Is the patient compliant to medication and dietary advise?	◯ Yes ◯ No ◯ not documented

Biochemical parameters

Provide the value of the troponin I result	_____
Please indicate the patient's HIV status	☐ Positive ☐ Negative
Please provide the patient's haemoglobin result	_____
Please provide the patient's sodium result	_____
Please provide the patient's potassium result	_____
Please provide the patient's creatinine result	_____
Estimated GFR (eGFR) in ml/min	_____
Please provide the patient's INR (International normalised ratio) result	_____
Please provide the patient's total cholesterol result	_____
Please provide the patient's LDL cholesterol result	_____
Please provide the patient's HDL cholesterol result	_____
Please provide the patient's triglyceride result	_____
Please provide the patient's random glucose result	_____
Please provide the patient's most recent HbA1c (glycated haemoglobin) result	_____
Please provide the patient's BNP (brain natriuretic peptide) result	_____
Please provide the TSH (thyroid stimulating hormone) result	_____
Please provide the patient's FT4 (thyroxine) result	_____

Patient outcomes

Mortality?	☐ Yes ☐ No ☐ Unknown

h. Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Drs L Mhlaba and D Mpanya

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M191191

NAME: (Principal Investigator)	Drs L Mhlaba and D Mpanya
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	HBA1c (glycated haemoglobin) control in Type 2 diabetic patients with coronary heart disease
DATE CONSIDERED:	2019/11/29
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr N Tsabedze
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/01/31

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

10 February 2020
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

i. Turnitin similarity report

HbA1c Control in Type 2 Diabetic Patients with Coronary Heart Disease (3).docx

by Lona Mhlaba

Submission date: 23-May-2023 06:14PM (UTC+0200)
Submission ID: 2100168900
File name: HbA1c_Control_in_Type_2_Diabetic_Patients_with_Coronary_Heart_Disease_283_29.docx (77.3K)
Word count: 3607
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Abstract

Background: Type 2 diabetes mellitus (T2DM) patients with coronary artery disease (CAD) have an increased risk of recurrent cardiovascular events. These patients require optimal glucose control to prevent the progression of atherosclerotic cardiovascular disease (ASCVD). Current guideline recommendations target an HbA1c ≤7% to mitigate this risk. This study evaluated the level of HbA1c control in T2DM patients with CAD.

Methods: This retrospective study assessed 1000 consecutive patients who presented with acute coronary syndromes (ACS) to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between April 2017- December 2019. The study included T2DM patients over the age of 18 with CAD. Participant HbA1c at index presentation and the most recent follow-up visit were assessed. The patients were classified into two groups: HbA1c ≤7% and HbA1c >7%.

Results: 262 patients met the inclusion criteria, and 188 (71.8%) were male. The mean age was 61.3 (SD ±10.4) years. After a median follow-up of 16.5 months (Interquartile range (IQR) 7-29), 28.7% of the study participants had an HbA1c ≤7%. The median systolic blood pressure was 136 mmHg (IQR 117-151) in patients with an HbA1c ≤7% and 124 mmHg (IQR 112-142) in patients with an Hba1c >7%, p= 0.0121. The median diastolic blood pressure was 85 mmHg (IQR 75.5-97) in patients with an HbA1c ≤7% and 78 mmHg (IQR 71-88) in patients with an HbA1c >7%, p=0.0205. Metformin was prescribed in 224 (85.5%) patients. Metformin monotherapy was prescribed in 140 (62.5%), 41 (18.3%) were on Metformin and Insulin combination therapy, and 40 (17.9%) were on Metformin and Sulphonylurea combination therapy. On multivariate regression analysis, better HbA1c control was associated with ST-segment depression on the resting electrocardiogram (Odds ratio: 0.27, CI: 0.12-0.59, p= 0.001).

Conclusion: After a median follow-up duration of 16.5 months, only 28.7% of T2DM patients with CAD had an HbA1c ≤7%. This finding underscores the substantial unmet need for optimal diabetes control in this very high-risk group. Adequately powered prospective multicentre studies from low and middle-income countries are required to determine the cost-effectivity and total health systems impact of making novel anti-diabetic agents with proven cardiovascular benefits accessible to patients with high ASCVD risk.

Keywords: South Africa, Type 2 diabetes-mellitus, HbA1c control, coronary artery disease.

Background

Type 2 diabetes mellitus (T2DM) is a worldwide pandemic affecting approximately 537 million adults between the ages of 20-79 in 2021 (1). This figure is expected to rise to 643 million by the year 2030 and to rise even further to 784 million by 2045 (1). Africa is projected to have the largest percentage increase between 2021 and 2045. In South Africa, 10.1% of people above 15 years have diabetes (2). This high prevalence poses significant health and socio-economic consequences (3).

Diabetes mellitus leads to many diabetic-related complications, classified as micro- and macrovascular. Microvascular complications include retinopathy, nephropathy, and neuropathy. Macrovascular complications include coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease (4). Diabetes mellitus is a significant risk factor for CAD. It causes accelerated atherosclerosis resulting in more severe and diffuse atherosclerotic cardiovascular disease (ASCVD) (5).

Multiple cardiovascular outcome trials evaluating the cardiovascular safety of novel anti-diabetic therapy have led to the emergence of new diabetic therapeutic agents with proven cardiovascular benefits. It is now recommended that these agents be used as first-line therapy in T2DM patients with high or very high cardiovascular risk (6). Unfortunately, many T2DM patients in low and middle-income countries (LMIC) cannot access these agents. Yet, most diabetics in these regions fail to achieve adequate HbA1c control on traditional agents alone (7). This study evaluated HbA1c control in T2DM patients with CAD to determine how well these very high-risk patients are managed using currently available therapies.

Methods

This retrospective study evaluated 1000 consecutive patients who presented with acute coronary syndromes (ACS) to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between the period of April 2017 to December 2019. Data was collected from the CMJAH catheterisation laboratory patient registry, which captures demographic data of all patients who undergo angiography and from the CMJAH Division of Cardiology medical record database, which includes clinical admission data of patients hospitalised in the cardiology wards.

Patients with angiographically confirmed CAD were included in the study. Clinical parameters captured included patient demographics, risk factors for CAD, type of ACS on presentation, coronary angiographic findings, clinical examination findings, blood biochemistry, electrocardiogram (ECG), echocardiogram, patient medication, and in-hospital patient outcomes,

including mortality. This data was collected on the initial presentation, and only the most recent HbA1c was reviewed at follow-up. After exclusions, the final cohort consisted of 262 patients assessed for HbA1c control, comparing baseline HbA1c at the time of presentation with ACS and HbA1c at the most recent follow-up visit (Figure 1).

Data analysis

Stata (version 17, College Station, Texas) was utilised for the statistical analysis. Demographic data is summarised as absolute numbers and percentages, and Pearson's chi-square test was used to compare categorical variables. Normally distributed data is summarised using the mean and standard deviation (SD), and the non-normally distributed data is presented as the median and interquartile range (IQR). The Student t-test was used for normally distributed continuous variables, and the Wilcoxon rank sum test was used to compare continuous data with a skewed distribution. Logistic regression analysis was performed to determine factors associated with poor HbA1c control, and the results are presented as odds ratios (OR) with their corresponding 95% confidence intervals (CI). A p-value of less than 0.05 was set as a statistical significance threshold.

Results

Our final study cohort consisted of 262 T2DM patients. The mean age was 61.3 (SD ± 10.4) years. Patients with an HbA1c ≤7%, had a mean age of 63.6 (SD ± 10.1) years, CI: 61.1 – 66.1, while patients with an HbA1c >7%, had a mean age was 60.5 (SD ± 10.4) years, CI: 59.0 – 61.9; p-value= 0.0332. The study cohort consisted of 188 (71.8%) males; and 148 (75.5%) study participants had an HbA1c > 7%.

Patients with an HbA1c ≤7% had a median systolic blood pressure of 136 mmHg (IQR 117-151), and patients with an HbA1c >7% had a median systolic blood pressure of 124 mmHg (IQR 112-142), p-value= 0.0121. Patients with an HbA1c ≤7% had a median diastolic blood pressure of 85 mmHg (IQR 75.5-97), and patients with an HbA1c >7% had a median diastolic blood pressure of 78 mmHg (IQR 71-88), p-value= 0.0205. A total of 204 (77.9%) patients presented with Killip 1 symptoms. Of these patients, 45 (68.2%) had an HbA1c ≤7% and 159 (81.1%) had an HbA1c >7%, p-value= 0.029.

ST-segment elevation myocardial infarction was reported in 84 (32.1%) patients. Of these patients, 13 (19.7%) had an HbA1c ≤7% and 71 (36.2%) had an HbA1c >7%, p-value= 0.013. ST-segment depression myocardial infarction was reported in 41 (15.7%) patients, 19 (28.8%) had an HbA1c

≤7% and 22 (11.2%) had an HbA1c >7%, p-value= 0.001. The rest of the baseline demographics and clinical characteristics are reported in Table 1.

Metformin was prescribed in 224 (85.5%) diabetic patients. In patients with an HbA1c ≤7%, 48 (81.4%) were on Metformin monotherapy, and 3 (5.1%) were on Metformin and Insulin combination therapy. In patients with an HbA1c >7%, 92 (55.8%) were on Metformin monotherapy, and 38 (23.0%) were on Metformin and Insulin combination therapy. Table 2 depicts the rest of the medications utilised by the study cohort.

The median duration between baseline and follow-up HbA1c was 16.5 months (IQR 7-29). At the study baseline, the proportion of diabetic patients with an HbA1c of ≤7% was 24.4% (CI: 18.4%-31.5%), and the proportion of patients with an HbA1c of >7% was 75.6% (CI: 68.4%- 81.6%). At the recent study follow-up, the proportion of patients with an HbA1c of ≤7% was 28.7% (CI: 22.2%- 36.1%), and the proportion of patients with an HbA1c of >7% was 71.3% (CI: 63.9%-77.8%) (Figure 2).

Regression analyses were conducted to identify factors which predispose patients with diabetes to inadequate control, i.e., HbA1c >7% (Table 3). On univariate analysis, unstable angina was associated with better HbA1c control (OR: 0.40, CI: 0.18-0.89, p= 0.025). Patients on Actraphane were at least twice as likely to have an HbA1c >7% (OR: 2.47, CI: 1.04-5.85, p= 0.040). ST-segment depression on ECG was associated with better HbA1c control (OR: 0.32, CI: 0.16-0.65, p= 0.002). On multivariate analysis, only patients with ST-segment depression on the baseline electrocardiogram were less likely to have an HbA1c >7% (OR: 0.27, CI: 0.12-0.59, p= 0.001).

Discussion

This study found that 35.6% of patients with CAD had concomitant T2DM. This high prevalence of diabetes found in our cohort is in keeping with data from the International Diabetes Federation, which predicts the highest increase in diabetes prevalence in Africa (1). In our study, the treatment of diabetes involved the use of Metformin, Sulphonylureas and Insulin therapy. However, despite using these traditional anti-diabetic agents, only 28.7% of the participants achieved HbA1c control after a median follow-up of 16.5 (IQR 7-29) months. This finding indicates that diabetic control in our cohort is sub-optimal. This is comparable to data from other LMICs where studies have shown similar figures of poor glycaemic control (8, 9).

Metformin was the anti-diabetic agent used by most patients in our cohort. This is in keeping with current diabetes clinical practice guidelines, which recommend that for the treatment of T2DM,

Metformin be utilised as a first-line treatment (10). Metformin monotherapy was utilised by 55.8% of patients with an HbA1c >7% in our cohort, and only 23.0% were on Metformin and Insulin combination therapy. Studies have shown that adding insulin to Metformin monotherapy improves glycaemic control (11). Clinical inertia to intensify diabetic therapy has been found to be very common in LMICs and significantly contributes to poor glycaemic control (12). Therefore, the poor glycaemic control in our study participants may have resulted from a lack of treatment intensification.

In our cohort, where most patients failed to attain an HbA1c ≤ 7%, we found a substantial unmet need to control the HbA1c better and provide additional cardiovascular benefits. Novel agents such as specific sodium-glucose co-transporter 2 inhibitors (SGLT2-I) have demonstrated a reduction in major adverse cardiovascular events in type 2 diabetic patients with ASCVD (13-15). Similar results have been shown with some glucagon-like peptide 1(GLP-1) analogues (16-18). The current use of these agents in our setting is limited due to the high cost. However, there are few cost-effectivity analysis studies done in LMICs investigating the potential impact these agents may have in preventing ASCVD complications of diabetes and reducing the overall cost burden on the healthcare systems.

In our cohort, poor HbA1c control was more common in younger patients. This occurrence could be explained by a number of reasons, such as that younger patients are often less likely to adhere to medication and self-management of diabetes practices, may often be less informed about their condition and are more likely to have misconceptions about their susceptibility to illness and complications of disease because of their younger age (19, 20).

Our cohort consisted predominantly of male patients. This is in keeping with international statistics, which reveal a higher prevalence of diabetes among men (1). Most of the male patients in our cohort had an HbA1c >7%. However, studies have shown that poor glycaemic control is more likely to occur in women than men (21, 22). There are several hypotheses to explain this observation, including differences in glucose metabolism and body mass index, hormonal differences, and psychosocial factors, to name a few (23).

T2DM is associated with the development of hypertension due to multiple pathophysiological mechanisms (24, 25). Studies have shown a positive correlation between HbA1c levels and hypertension (26). High HbA1c levels are associated with high blood pressure (27). In our cohort, it was noted that patients with poor glycaemic control had lower blood pressure, and patients with good glycaemic control had higher blood pressure. A possible explanation for this is that poorly controlled diabetes is associated with more severe coronary artery disease (28). It is therefore likely

that this will result in acute coronary syndromes with more extensive myocardial injury leading to a worse clinical picture manifested by lower blood pressure. More local prospective studies are required to investigate this relationship better.

Diabetes mellitus is often associated with more complex CAD with multi-vessel involvement. Increased HbA1c levels result in greater coronary artery involvement (28). In our cohort, 24.2% of the patients had triple vessel disease, most of whom had an HbA1c >7%. These patients generally require surgical revascularisation, translating to higher healthcare costs (29). This further underscores the need to optimise HbA1c control, thereby decreasing the prevalence of complex CAD and the need for surgical interventions, ultimately leading to decreased total healthcare costs.

More patients with poor glycaemic control presented with ST-segment elevation myocardial infarction compared to ST-segment depression myocardial infarction, 36.2% and 11.2%, respectively. This association is likely because poorly controlled patients have more severe atherosclerotic disease characterised by vulnerable plaques. Therefore, these patients are more likely to have acute plaque rupture and present with ST-segment elevation myocardial infarction (28, 30). Our study found that ST-segment depression on ECG was independently associated with good HbA1c control. This is likely because patients with better-controlled diabetes have less atherosclerotic burden and more stable plaques than those with poor glycaemic control (31). Therefore, it is likely that these patients will present with ST-segment depression on ECG.

Given the poor HbA1c control found in our cohort, other strategies, in addition to the novel anti-diabetic agents, need to be implemented. T2DM patients should be educated regarding key aspects of self-management of their condition. These aspects include adherence to medication, dietary advice, physical activity, and patients' monitoring of their own glucose levels, to name a few. Self-management of diabetes has been found to be inadequate in sub-Saharan African countries, including South Africa (32). Other strategies to optimise control include closer follow-up of patients, decentralisation of care and implementation of nurse practitioner or community health care worker home-based visits.

This study had several limitations. Data from the Division of Cardiology medical records database were reviewed retrospectively, and not all data was captured, resulting in patient exclusion. This was a single-centre study; therefore, the generalisability of the findings may not apply to other centres. Another limitation is that our study did not consider psycho-social factors, which may have played a role in the glycaemic control of our study participants. Despite these limitations, this data provides real-world insights into the standard of diabetic control in a South African public sector tertiary hospital for this very high-risk population with established ASCVD.

Conclusion

This study found that only 28.7% of T2DM patients with CAD achieved an HbA1c ≤7% after a median follow-up of 16.5 months. This highlights the urgent need for better management strategies to improve HbA1c control in this very high-risk group of patients. Furthermore, prospective multicentre studies from LMICs focused on determining the cost-effectivity and total health systems impact of making novel anti-diabetic agents with proven cardiovascular benefits accessible to high and very-high-risk diabetic patients with ASCVD are required.

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