Cardiovascular Topics

Comprehensive ABC (HbA_{1c}, blood pressure, LDL-C) control and cardiovascular disease risk in patients with type 2 diabetes mellitus and major depressive disorder in a South African managed healthcare organisation

Lovina A Naidoo, Neil Butkow, Paula Barnard-Ashton, Elena Libhaber

Abstract

Aim: Patients with type 2 diabetes mellitus (T2DM) who have suboptimal control of the triad of glucose (A), blood pressure (B) and lipid profile (C) have an increased risk of cardiovascular disease (CVD). Additionally, the presence of major depressive disorder (MDD) can lead to poor outcomes. Therefore, the aim of this study was to assess the role of MDD with ABC control in patients with T2DM in a South African private healthcare setting.

Methods: Healthcare medical claims and electronic health records of 1 211 adult patients with T2DM and/or MDD were analysed for 2019.

Results: Only 24% of the T2DM +/– MDD patients reached a low-density lipoprotein cholesterol (LDL-C) target < 1.8 mmol/l, and only 13% of the T2DM + MDD and 7.1% of T2DM – MDD patients achieved simultaneous ABC targets. The proportion of patients admitted due to macrovascular complications was higher in the T2DM + MDD group (22.8%) compared to the T2DM – MDD (13.1%) and MDD group (9.9%) (p = 0.012). Multivariate logistic regression analysis showed that older patients with T2DM + MDD achieved better glycated haemoglobin and LDL-C control. Significantly more patients with T2DM + MDD (12%) had repeat macrovascular admissions in 2019 compared to the T2DM – MDD patients (2.9%) (p = 0.005).

Conclusion: Despite a managed-care environment, the comprehensive ABC control among patients with T2DM was suboptimal, particularly in those with MDD, placing them at greater risk for CVD events.

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Type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD) are highly prevalent diseases in South Africa (SA),[1,2] with co-morbid MDD presenting in 17% of patients with T2DM in a privately managed healthcare organisation.[3] Claims data showed that more patients with T2DM and co-morbid MDD (T2DM + MDD) (73%) experienced hyperlipidaemia than those with T2DM (61%) alone (T2DM – MDD).[3] T2DM is considered a cardiovascular (CV) risk equivalent.[4]

The ABC practice guidelines[5] (glycated haemoglobin, blood pressure, low-density lipoprotein cholesterol) for atherosclerotic CV risk management indicate the evidence-based levels required to determine control of blood glucose, systolic blood pressure (SBP) and serum lipid levels to reduce the risk of atherosclerotic cardiovascular events.[6-8] The ABC goals of T2DM were defined by South African diabetes guidelines[6] as meeting glycated haemoglobin (HbA_{1c}) levels < 7%, SBP < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg, and low-density lipoprotein cholesterol (LDL-C) levels < 1.8 mmol/l. ABC is an abbreviation put together by the American Diabetes Association[9] and the American College of Cardiology[5] to bring awareness to the public.

Poor ABC management in patients with T2DM results in a significant increase in the risk of cardiovascular disease (CVD) events such as myocardial infarctions, strokes and cardiac failure and mortality.[10,11] The control of blood glucose is a fundamental goal in T2DM, with HbA_{1c} level being the best marker of glucose levels and microvascular (nephropathy, retinopathy and neuropathy) outcomes.[6] However, chronic hyperglycaemia is also an added risk factor for atherosclerosis in patients with T2DM.

Atherosclerosis is often accelerated and severe in T2DM.[6] Complex manifestation of atherogenic dyslipidaemia[12] and significant alteration of circulating LDL-C level, a major determinant of atherosclerotic CV risk predisposed to coronary artery disease (CAD), occurs in T2DM over time.[13] Hypertension,

another vascular disease, affects people with T2DM during the course of their disease. They are then at a greater risk of developing target-organ damage than non-diabetics.[14]

The importance of achieving individual and composite three-part (ABC) risk-factor control has been reported from the National Health and Nutrition Examination Survey (NHANES) with yearly clinical reminders for diabetes care and enhanced patient education.[7] The simultaneous control of ABC risk factors has been projected to prevent 38% of CAD events over 10 years.[15]

Depression related to long-term control of HbA_{1c} and LDL-C levels and SBP in patients with T2DM has been well studied in the USA. Heckbert *et al*.[16] reported that MDD was associated with slightly higher average HbA_{1c} levels, and no difference in average SBP or LDL-C levels during follow up in patients with T2DM. However, the study by Katon *et al*.[17] showed patients with T2DM and MDD, with or without evidence of heart disease, had a higher number of CVD risk factors. A recent study in Ghana conducted in a tertiary public healthcare facility reported no independent association of MDD with poor glycaemic control in the T2DM + MDD patients.[18]

In SA, the national prevalence of adults with T2DM is 12.7%[19] and with MDD is 9.7%.[2] However, the national co-prevalence of MDD in patients with T2DM is yet to be enumerated. Private managed healthcare individuals in SA have a high incidence of T2DM with all the CV sequelae, in addition to having MDD overlapping as a most frequent co-morbidity.[3] T2DM is a significant contributor to disease burden and together with MDD may have a negative effect on the CV outcomes of T2DM;[20] hence this study examined the ABC control achieved in individuals with T2DM + MDD.

Emerging evidence demonstrates shared mechanisms between non-communicable diseases (NCD) such as MDD and T2DM and between MDD and atherosclerotic cardiovascular disease (ASCVD) are attributed predominantly due to the immunometabolic pathways.[21-24] MDD has been attributed to high levels of pro-inflammatory cytokines,[25,26] which over a length of time can lead to elevated BP and blood glucose levels, abdominal obesity and dyslipidaemia,[27] known as traditional risk factors for T2DM, ASCVD and other related disorders.[28]

Statins [3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors] have been demonstrated to be effective in both primary and secondary prevention of ASCVD.[11] This effect is largely dependent on the extent to which LDL-C level is lowered and not by the type of statin used.[11,29,30] The main cause of death in MDD remains ASCVD,[31] where statins have proven to have therapeutic benefits.[32] The combination of a selective serotonin reuptake inhibitor (SSRI) and a statin has been associated with lower risk for psychiatric hospitalisations due to depression, compared to the use of SSRI alone.[33]

This study aimed to assess the CVD risk and the attainment of control of the triad ABC guideline in individuals with T2DM with and without co-morbid MDD in a South African privately managed healthcare environment.

Methods

This cross-sectional, retrospective, descriptive study was conducted in a private managed healthcare organisation in SA. We utilised an integrated database of electronic health records (EHR), laboratory data, and the medical, hospital and pharmacy administrative claims data of members with T2DM and MDD of a South African managed healthcare organisation in the year 2019. The EHR of study members registered with the medical scheme was linked to the administrative claims system, which together provided processed data of membership, healthcare and claims. The database included patient-level demographics and clinical characteristics such as illnesses, hospital events, diagnosis and follow-up BP readings, HbA_{1c} levels and lipogram reports. Medications claimed by the study subjects were extracted from the administrative system claims database.

The data set included patients enrolled as members of a health insurance scheme. Of the 47 380 registered beneficiaries on the scheme in 2019, 879 adults (18 years and older) with a registered diagnosis of T2DM were included if: (1) their latest HbA_{1c} value was recorded on the healthcare system in 2019, and (2) they had a pharmacy claim of oral and/or injectable hypoglycaemic agents, or insulin claimed sequentially for over six months.

The diagnosis of T2DM was identified according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD10).[34] Diagnosis codes E11.0 (T2DM with hyperosmolarity), E11.1 (T2DM with ketoacidosis), E11.2 (T2DM with renal complications), E11.3 (T2DM with ophthalmic complications), E11.4 (T2DM with neurological complications), E11.5 (T2DM with peripheral circulatory complications), E11.6 (T2DM with other specified complications), E11.7 (T2DM with multiple complications), E11.8 (T2DM with unspecified complications) to E11.9 (T2DM without complications) were used to classify patients having T2DM as stated by the practitioner.

From these 879 patients with T2DM, two groups were identified: T2DM + MDD: those registered with a diagnosis of MDD and claiming antidepressants over six months (n = 223), and T2DM – MDD: those without a diagnosis of MDD or claiming for antidepressants (n = 656). The third group, the MDD control group (n = 332), was selected from the beneficiaries as being diagnosed with MDD and claiming antidepressant usage without any history of T2DM.

The diagnosis of MDD was identified with ICD10 codes F32.2 (MDD, single episode, severe without psychotic features) to F33.9 (MDD, recurrent, unspecified). The ICD10 codes were obtained from the Council of Medical Schemes Prescribed Minimum Benefit ICD10 coded list.[35] Patients with no available clinical data for HbA_{1c} and LDL-C level, and SBP were excluded from this study. Glycaemic, BP and lipid level indices were defined and characterised with reference to the 2017 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines.[6]

Using medical record review, the schemes hospitalisation management database, ICD10 diagnostic code and current procedural terminology, 4th edition (CPT-4) procedure code data, physician-diagnosed, documented major macrovascular hospitalisations were identified. Major macrovascular hospitalisations were identified as the presence of a diagnosis or an event of a CAD (unstable angina, angiogram, angina pectoris, atherosclerotic heart disease), congestive heart failure, atrial fibrillation, stroke, transient cerebral ischaemic attack, embolism and thrombosis of arteries or other specified veins, and peripheral vascular disease; or procedures such as coronary revascularisation (acute transmural myocardial infarction percutaneous procedures, coronary artery bypass, angioplasty,

percutaneous transluminal coronary angioplasty, bare metal or balloon or drug-eluting, pacemaker insertion and cardioversion).

Using the administrative medicines claims data that were categorised according to anatomical therapeutic chemical (ATC) classification,[36] individuals claiming hypoglycaemic agents were identified as using A10B (blood glucose-lowering drugs excluding insulins), which are the older oral agents (metformin, glibenclamide, gliclazide, glimepiride, repaglinide, pioglitazone), the newer agents (vildagliptin, dapagliflozin, liraglutide, empagliflozin, sitagliptin, exenatide, saxagliptin) and who were on insulin as A10A (insulin and analogues).

Those on antihypertensive therapy were identified according to ATC C02 (antihypertensives), C03 (diuretics), C07 (beta-blocking agents), C09 (agents acting on the renin–angiotensin system), C08 (calcium channel blockers) and G04CA03 (alpha-adrenoreceptor antagonist). The choice of selecting antihypertensive medication is based mainly on the patient's glycaemic and lipid profiles. Patients claiming treatment for dyslipidaemia ATC C10 [lipid-modifying therapy, which are statins (98% claim rate), fibrates, ezetimibe and bile acid sequestrants] were identified.

Patients claiming antidepressant ATC (N06A) were characterised according to those on SSRIs (Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram, Fluvoxamine) versus those not on SSRIs, such as, patients on serotonin norepinephrine reuptake inhibitors (Venlafaxine, Desvenlafaxine, Duloxetine), noradrenergic and specific serotonergic antidepressants (Mirtazapine; Mianserin), serotonin receptor antagonists and reuptake inhibitors (Trazodone), norepinephrine dopamine reuptake inhibitor (Bupropion), serotonergic antidepressant (Vortioxetine) or melatonergic agonist (Agomelatine). The class of SSRI was characterised separately as data show that in combination with a statin, it had a larger effect on depressive symptoms than either drug alone.[37]

Confidentiality was maintained throughout the analysis by using the patients' unique scheme membership number and dependent code to align patient-level records. The University of the Witwatersrand, Johannesburg, Faculty of Health Sciences Human Ethics Committee (M140326; M1911196) approved the study. Approval was granted by the principal officer of the scheme for the scheme data to be used in the study and by the human resources manager to gather data from the scheme administrative database for the research.

Statistical analysis

Data extracted from the database were exported to Microsoft Excel 2016 and statistical analysis was performed with Statistica 13.3 (StatSoft Inc, Tulsa, OK) and SAS 9.4. Study patients were those with a total cholesterol level < 4.5 mmol/l; those below target LDL-C < 1.8 mmol/l; those above target high-density lipoprotein cholesterol > 1.0 mmol/l in men and > 1.2 mmol/l in women; those below triglyceride target level < 1.7 mmol/l; and BP in patients with SBP < 140 mmHg.

HbA_{1c} and lipid levels are given as median (IQR). Categorical variables such as gender, number of claims for medicines and disease control measures are summarised as frequencies and percentages and were compared using Chi-square or Fisher-exact tests. Multiple comparisons were analysed using Bonferroni correction among the three groups and the level of significance was set at $p < 0.0166$.

Stepwise univariate and multivariate logistic regression analyses were performed to determine factors predicting HbA_{1c} and LDL-C control in the study groups of patients with T2DM and MDD only. A sensitivity analysis was performed on patients claiming different classes of antidepressants. Claims were compared between those on SSRIs with those not on SSRIs and equated to their HbA_{1c} targets attained. The significance level was set at $p < 0.05$.

Results

Table 1 shows the characteristics of the patients in the T2DM + MDD and T2DM – MDD groups compared to the control (MDD) group. More females and older patients were among the T2DM + MDD ($p < 0.001$) and MDD groups ($p < 0.0001$) compared to the T2DM – MDD group. The T2DM groups showed similar claiming patterns for lipid-lowering medications. Over 70% of those with T2DM with or without MDD were on lipid-lowering treatment with statins, and among those, < 7% were on combined therapies such as statin + ezetimibe (2.7, 3.2%) or statin + fibrate (3.6, 3.9%). However, a higher proportion of patients among the T2DM + MDD group versus the T2DM – MDD group claimed antihypertensives (79 vs 68%) ($p = 0.0010$). A small number (12.5, 10.8%) ($p = 0.601$) claimed sodium-glucose transport protein 2 inhibitors (SGLT2i).

Table 2 depicts the CV indices of glycaemic, BP and lipid profiles of the patients attaining targets. The median (IQR) HbA_{1c} level in patients with T2DM + MDD was higher compared to the T2DM – MDD group [7.4% (6.0–8.2) vs 7.2% (6.2–8.5), $p < 0.05$]. A higher proportion of patients in the T2DM + MDD group achieved HbA_{1c} levels of < 7% compared to the T2DM – MDD group ($p < 0.05$). The LDL-C median (IQR) was similar in the T2DM + MDD [2.4 mmol/l (1.8–3.1)] and T2DM – MDD [2.4 mmol/l (1.8–3.1)] groups, but significantly lower when compared to the MDD group [3.0 mmol/l (2.4–3.8),

Table 1. Characteristics of patients with T2DM + MDD, T2DM – MDD and MDD

Characteristics	*T2DM + MDD (n = 223) (25%)*	*T2DM – MDD (n = 656) (75%)*	p-*value*	*MDD control (n = 332)*	p-*value*
Age (years) (mean ± SD)	61 ± 13	57 ± 14	0.01	50 ± 17	< 0.0001
Female, *n* (%)	121 (54)	245 (37)	< 0.001	213/332 (64)	< 0.0001
Therapy claimed, *n* (%)					
Antihypertensives	177/223 (79)	447/656 (68)	0.001	121/332 (36)	< 0.0001
Lipid-lowering therapy	173/223 (78)	471/656 (72)	0.092	117/332 (35)	< 0.0001
Antidepressant therapy	223/223 (100)	–	–	262/332 (79)	< 0.001
Selective serotonin reuptake inhibitors	108/223 (48)	–	–	168/332 (51)	0.478

MDD, major depressive disorder; T2DM, type 2 diabetes mellitus.

Table 2. Clinical profile of patients with T2DM + MDD, T2DM – MDD and MDD achieving targets

Clinical characteristics	*T2DM+MDD*	*T2DM–MDD*	*MDD control*
HbA_{1c} (%)	*n* = 223	*n* = 656	*n* = 332
HbA_{1c}, median (IQR)	7.4 (6.0–8.2)	7.2 (6.2-8.5)#	5.4 (5.2-5.8)**
HbA_{1c} < 7%, *n* (%)	125/223 (56)#	295/656 (45)	–
HbA_{1c} < 7%, median (IQR)	6.1 (5.7–6.6)	6.2 (5.8–6.5)	–
TC (mmol/l)	*n* = 217	*n* = 520	*n* = 278
TC, median (IQR)	4.4 (3.6–5.3)	4.3 (3.6–5.1)	5.1 (4.3–5.8)**
TC < 4.5 mmol/l, *n* (%)	118/217 (54)	298/520 (57)	83/278 (30)**
LDL-C (mmol/l)	*n* = 220	*n* = 519	*n* = 268
LDL-C, median (IQR)	2.4 (1.8–3.1)	2.4 (1.8–3.1)	3.0 (2.4–3.8)**
LDL-C < 1.8 mmol/l, *n* (%)	52/220 (24)	125/519 (24)	–
LDL-C < 1.8 mmol/l, median (IQR)	1.4 (1.1–1.6)	1.5 (1.2–1.6)	–
HDL-C (mmol/l)	*n* = 215	*n* = 507	*n* = 139
HDL-C, median (IQR)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.3 (1.1–1.6)**
HDL-C ≥ 1 mmol/l (male); ≥ 1.2 mmol/l (female), *n* (%)	129/215 (60)	328/507 (65)	118/139 (85)**
Triglycerides (mmol/l)	*n* = 216	*n* = 508	*n* = 266
Triglycerides, median (IQR)	1.70 (1.3–2.3)	1.7 (1.2–2.6)	1.3 (0.9–1.9)**
Triglycerides < 1.7 mmol/l, *n* (%)	99/216 (46)	255/508 (50)	177/266 (67)**
BP (mmHg)	*n* = 181	*n*= 451	*n* = 107
SBP, mean ± SD	132 ± 17	134 ± 17	135 ± 17
DBP, mean ± SD	79 ± 12#	82 ± 12	83 ± 12
SBP ≤ 140 mmHg, *n* (%)	135/181 (75)	340/451 (75)	78/107 (73)

BP, blood pressure; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol; T2DM, type 2 diabetes mellitus.
*p < 0.01 and **p < 0.001 between the three groups; #p < 0.05 between T2DM with and without MDD groups.

Table 3. Stepwise multivariate logistic regression of HbA_{1c} control in T2DM + MDD and T2DM – MDD groups

Variables	*OR**	*95% CI*	p-*value*
Age	1.02	1.01–1.04	0.002
Statins claimed	2.09	1.41–3.11	< 0.0001
Metformin claimed	0.51	0.27–0.97	0.040
Newer hypoglycaemic agents claimed	0.45	0.21–0.99	0.048
MDD diagnosis	2.30	1.47–3.61	< 0.0001

*Adjusted for claims for antihypertensive agents, gender and the interaction factor of newer hypoglycaemic agents and metformin.

p < 0.001]. Only 24% of patients in the T2DM groups achieved target LDL-C levels of < 1.8 mmol/l. The SBP of patients in the T2DM + MDD, T2DM – MDD and MDD groups was similar and on target.

Fig. 1 shows that only 13% of the T2DM + MDD and 7.1% of T2DM – MDD groups achieved simultaneous ABC targets.

Table 3 depicts a stepwise multivariate logistic regression analysis, which identified predictors of HbA_{1c} control of the T2DM study groups. The HbA_{1c} control was independently associated with older (p = 0.002) patients, claims for statins, and being diagnosed with MDD (p < 0.0001).

In Table 4, a stepwise multivariate logistic regression analysis identified predictors of LDL-C control of the T2DM + MDD versus T2DM – MDD groups. Significant contributing factors to LDL-C control between the two groups were being older (p < 0.0001) and claiming statins (p = 0.001).

Fig. 2 exhibits the percentage of patients with T2DM + MDD on SSRIs reaching HbA_{1c} levels of < 7%. There was no statistically significant difference in the proportion of patients achieving HbA_{1c} target regardless of the nature of their antidepressant therapy. After performing a multiple logistic regression in patients with T2DM + MDD, SSRIs (p = 0.19) and metformin (p = 0.27) were not independently associated with HbA_{1c} control when adjusted for age and gender.

There was a significant difference in the macrovascular

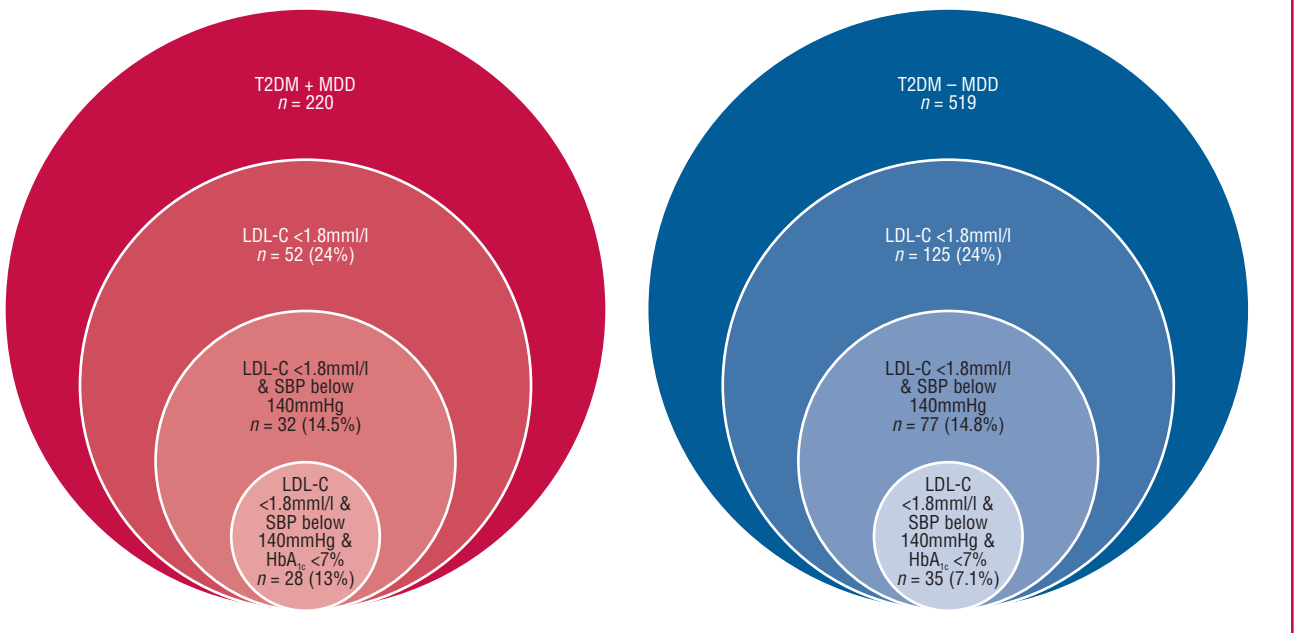

Fig. 1. Percentage of patients with T2DM with and without MDD achieving ABC (HbA_{1c}, SBP and LDL-C) goal. HbA_{1c}, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure.

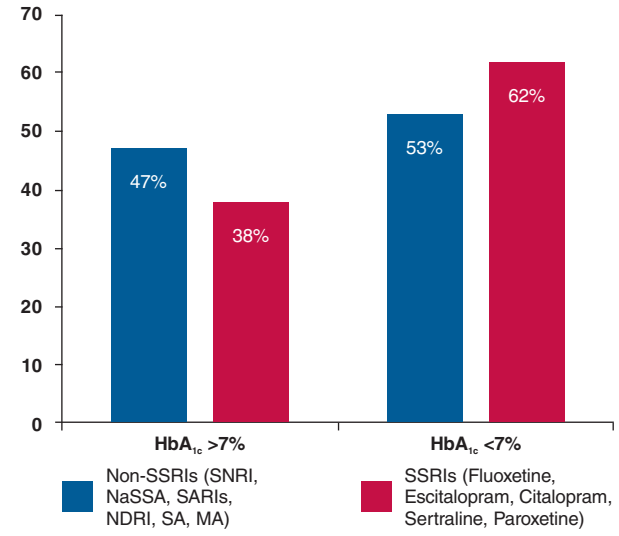

Fig. 2. Percentage of patients with T2DM + MDD on antidepressants (SSRIs vs non-SSRIs) achieving HbA_{1c} target. HbA_{1c}, glycated haemoglobin; MDD, major depressive disorder; MA, melatonergic agonist; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine dopamine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor; SARIs, serotonin receptor antagonists and reuptake inhibitors; SA, serotonergic antidepressant); T2DM, type 2 diabetes mellitus.

hospitalisations between the T2DM + MDD and T2DM – MDD groups (Table 5). A higher proportion of patients in the T2DM + MDD group were admitted for macrovascular events (22.8%, $p = 0.012$). Fewer patients with T2DM + MDD (3.3%) were admitted for depressive episodes compared to the patients from the MDD control group (15.5%, $p = 0.003$). More patients with T2DM + MDD (12%) had repeated macrovascular admissions versus those with T2DM – MDD (2.9%, $p = 0.005$).

Discussion

While over 70% of patients in all three groups achieved the target SBP of ≤ 140 mmHg, the findings indicated inadequate glycaemic and lipid control among the T2DM patients managed in a private healthcare organisation, despite the high rate of claims for hypoglycaemic and lipid-lowering medications. Both study groups had a median target HbA_{1c} closer to 7%, although the group with a diagnosis of co-morbid MDD had a higher HbA_{1c} of 7.4% compared with the T2DM – MDD group. Findings of this study are similar to studies by Akpalu *et al.*[18] and Kaulgud *et al.*[38] that reported no association between poor glycaemic control and MDD.

The successful management of diabetes care is reduction of CV risk biomarkers HbA_{1c}, BP and LDL-C. Each individual biomarker goal achieved has proven to be associated with a reduction in micro- and macrovascular complications.[15,39,40] The composite attainment of the three goals simultaneously is known as the ABCs of diabetes,[9] which are considered individually in the clinical management of patients with T2DM, evidenced in

Table 4. Stepwise multivariate logistic regression of LDL-C control in T2DM + MDD and T2DM – MDD groups

Variables	*OR**	*95% CI*	p-*value*
Age	1.03	1.01–1.04	< 0.0001
Statins claimed	2.51	1.50–4.21	0.001

*Adjusted for claims for antihypertensive agents, metformin and gender.

Table 5. Hospitalisations of patients with T2DM + MDD, T2DM – MDD and MDD

Characteristics	*T2DM+MDD (n = 223)* n *(%)*	*T2DM–MDD (n = 656)* n *(%)*	*MDD control (n = 332)* n *(%)*	p-*value*
Total number of hospital admissions	200/223 (89.7)	493/656 (75.2)	290/332 (87.3)	< 0.0001
Total number of patients admitted	92/223 (41.3)	236/656 (36)	161/332 (48.5)	0.0007
Admissions per patient	200/92 (2.2)	493/236 (2.1)	290/161 (1.8)	–
Patients admitted for macrovascular events	21/92 (22.8)	31/236 (13.1)	16/161 (9.9)	0.012
Patients admitted for repeated macrovascular admissions	11/92 (12)	7/236 (2.9)	8/161 (5.6)	0.005
Patients admitted for depressive episodes	3/92 (3.3)	–	25/161 (15.5)	0.003

MDD, major depressive disorder; T2DM, type 2 diabetes mellitus.

South African studies whereby separate measures are reported as opposed to the combined triad of ABC control.

In this study, the participants' glucose control in isolation showed better rates of glycaemic control [T2DM + MDD (56%) and T2DM – MDD (45%)], in comparison with the 22% seen across three public healthcare centres in rural Africa.[41] The privately managed healthcare environment is well resourced and the study population may be more aware of their diabetes status and have access to newer hypoglycaemic agents and health technology assessment devices, including diabetes management programmes via a capitated risk-sharing model to improve patient outcomes and reduce healthcare costs.[42] Therefore, one would expect better clinical (glycaemic, lipid control and macrovascular complications) outcomes of patients with T2DM.

SGLT2i, a newer class of hypoglycaemic agents, had just been introduced to the healthcare system and a small number of patients with T2DM in both groups claimed SGLT2i during this period of analysis. SGLT2i, in addition to lowering blood glucose levels, has been shown to reduce BP with an average reduction of 3.6/1.7 mmHg (systolic/diastolic) in 24-hour ambulatory BP,[43] and may have influenced those patients claiming SGL2i in achieving BP goals. As the number of patients were too small to analyse, future studies will look at the CV risk reduction of SGLT2i in this sub-group when there is a much higher utilisation of this class of drugs.

Of concern, only 24% of patients in the T2DM groups in this study achieved LDL-C control of < 1.8 mmol/l. The number of patients with T2DM achieving LDL-C targets would have been far fewer if the latest 2023 European Society of Cardiology (ESC) guideline-recommended LDL-C target of < 1.4 mmol/l was used[44] [T2DM + MDD group (10.5%), T2DM – MDD (10.2%), compared to 24% achieved in both groups]. In contrast, Boekholdt *et al.*[45] found that approximately 40% of patients failed to adequately lower their LDL-C levels on high-potency statin therapy, due to inter-individual variation of

statin response and possible non-adherence to medication. Dose-related adverse events, inadequate patient education, incorrect statin doses prescribed, and mood issues such as depression are some important factors as to why patients are non-compliant with their medications.[46,47]

The South African International Cholesterol Management Practice Study[48] reported that the low rates of LDL-C goal achievement among private health-insured participants were due to inadequate statin doses prescribed, use of low-potency statins and non-compliance. The American Heart Association guidelines recommend utilising an appropriate statin dose for percentage reduction of LDL-C rather than treatment goals, as well as altering clinicians' behaviour concerning the treatment of hyperlipidaemia.[49]

The increased risk of CV events among this group of patients suggests possible medication adjustments, such as switching medication to a different class or dose to achieve guideline-recommended target LDL-C levels.[11] Some patients may even require combination therapy with other classes of lipid-lowering therapies (ezetimibe, fibrates, bile acid sequestrants or niacin)[49] to sufficiently lower LDL-C levels. The magnitude of the change in LDL-C level in the T2DM groups indicated a level of LDL-C that was 1.2 ± 0.8 mmol/l away from target levels. This clearly indicates that LDL-C targets remain a distinct reminder that a large proportion of the CV risk has not been adequately addressed within the confines of a managed care organisation.

Individuals with T2DM must attain glycaemic control, maintain a healthy lifestyle, and manage co-morbid hypertension and hyperlipidaemia. The simultaneous control of all three ABC parameters is seldom achieved in most adults with T2DM.[50-52] Only 13% of patients with T2DM + MDD and 7.1% of patients with T2DM – MDD attained comprehensive glycaemic, SBP and LDL-C control (ABC levels) in this study.

The composite ABC targets achieved in an Iranian population with T2DM (42%)[53] and in the NHANES 2007–2012 was 23.7%.[54] Another study conducted in Japan[55] showed patients achieved a 28.0% triple ABC goal. In the NHANES survey, patients with T2DM and severe depression were associated with lower rates of ABC goal attainment compared to those with no depression (5.0 vs 25.4%).[54] The lower rates of simultaneous control of all three parameters in this study compared to the previous studies may be attributed to the differences in the demographics, the medication regimen, and diabetes management, patient education and depression severity.

Regarding the discrete $HbA_{1c,}$ BP and lipid targets[56] within a South African tertiary public hospital, the percentage of T2DM patients reaching BP and HbA_{1c} targets were 49.4 and 16.5%, respectively,[56] which were lower than in the T2DM + MDD and T2DM – MDD groups in the private sector of our study. However, the lipid targets attained were higher (46.9%)[56] compared to the private sector patients in this study (24%). The LDL-C levels attained by patients in the tertiary hospital were lower and can be attributed to better compliance enforced by positive clinical inertia displayed by the clinical staff in the hospital setting.[56] Factors affecting BP control were perhaps due to the increasing age, hyperglycaemia and its pathogenic effects on vascular function,[57] and the use of angiotensin-converting enzyme inhibitors.

On the other hand, in T2DM patients from 20 countries, including Europe and the USA, a pooled target achievement rate of 42.8% (95% CI: 38.1–47.5%) for glycaemic control, 29% (95% CI: 22.9–35.9%) for BP and 49.2% (95% CI: 39.0–59.4%) for LDL-C was reported in a meta-analysis.[58] Conversely the present study reflects a better glycaemic (56, 49%) and BP control (75, 75%), and worse LDL-C control (24, 24%) in people with T2DM, with and without MDD, respectively.

A major finding in this study was patients in the T2DM + MDD group achieved better ABC control compared to the T2DM – MDD group, yet a higher number of patients in the T2DM + MDD group were admitted for repeated macrovascular events. This may possibly be explained by the presence of a significant residual CV risk not accounted for by lipid-lowering therapies. There could be some residual inflammatory risk in patients with low LDL-C levels or pro-inflammatory pathways[59,60] that may not be modulated by statins, or even high-potency statins or combined lipid-lowering therapies.[61]

Furthermore, the present study shows a beneficial link between treatment modalities claimed (statins, metformin and newer hypoglycaemic agents) and HbA_{1c} and LDL-C levels in older patients with T2DM and MDD. Medication claims appeared to be better in older patients, possibly because the elderly are more vigilant of their cardiometabolic indices, as these indices need to be stringently self-managed. The elderly are more aware of their trajectory of a healthier lifestyle and try to reduce their risks and better manage their glycaemic and lipid levels. These findings were supported in middle-aged and older USA adults[62] among health maintenance organisation members in the USA[63] and Asia.[64]

Patients with MDD being treated in this managed-care setting showed better compliance and HbA_{1c} control. Screening and treatment of depression in patients with CAD were found to improve the outcomes of CVD,[65] alongside the benefits of mood elevation. Similarly, the recognition and monitoring of depression in T2DM are of relevance due to their association with hyperglycaemia, diabetic complications and poor quality of life.[66]

Patient care in T2DM has an emphasis on blood glucose levels and hence, intake of hypoglycaemic agents to achieve the targeted glycaemic control may be enforced during their medical reviews. Additionally, over the past decade, health technology in T2DM and antidiabetic agents have received much attention, allowing diabetics a range of hypoglycaemic agents to lower blood glucose levels.[67-70] This may account for more patients reaching the glycaemic control target. However, the LDL-C targets were not met as patients may not have been aware of the detrimental effects of not complying with their lipid-lowering therapy and the limited choices of lipid-lowering therapy.

Elevated serum levels of LDL-C are perhaps the strongest contributor to atherosclerosis in CAD and thromboembolic stroke.[71,72] Reduction of LDL-C levels, usually with statins, confers protection. Therefore, a reduction in LDL-C level of 1 mmol/l usually lowers the CV risk by approximately 20%.[21] Patients within the managed-care setting of this study needed to be educated on the importance of compliance with lipid-lowering therapies in conjunction with their hypoglycaemic, BP and/or antidepressant medications. Association of depressive symptoms with increased risk of macrovascular complications has been reported in several cohort studies.[73-75]

Active surveillance of MDD in patients without T2DM, but with established CVD, demonstrated a greater severity of depressive symptoms than those without a CVD event.[65]

The aggressive amelioration of treatment of these depressive symptoms has shown a reduction in CVD events of up to 43%.[76] Numerous interventional studies with statins have shown a reduction of coronary events, all cardiovascular events and mortality of between 10 and 30% for every mmol/l reduction in LDL-C level, even if the baseline LDL-C level was in the normal range[32] in individuals with established CAD.[77-79]

Besides their lipid-lowering properties, large studies report that statin use was associated with a reduced risk of depression.[80] This intrinsic property of statins is beneficial in patients post heart attack and in individuals experiencing excess inflammation due to physical diseases such as stroke, which are highly co-morbid with MDD.[81] Lipophilic statins (simvastatin and atorvastatin) showed greater potential to decrease depressive symptoms than hydrophilic statins (rosuvastatin and pravastatin) as these statins can cross the blood–brain barrier.[82]

In T2DM patients with co-morbid MDD, certain antidepressants such as an SSRI (Fluoxetine) and norepinephrine dopamine reuptake inhibitor (Bupropion) have been associated with improvement in HbA_{1c} control in patients with T2DM + MDD.[83,84] In the T2DM + MDD group in this study, 62% of those on SSRIs were at the HbA_{1c} level of < 7%, while 53% of those not on SSRIs achieved the same target, suggesting glycaemic control among patients with T2DM diagnosed and treated for MDD fared well with their diabetes. Future research should be implemented on the CV risk profile of patients with MDD using the Framingham risk score[85] to identify individuals at increased risk for future CVD, and depressive outcomes of the interaction of statins and SSRIs in this group.

The present study suggests the need for holistic management of T2DM and associated co-morbidities such as MDD and CVD. Glycaemic and lipid targets attained as per guideline recommendations were suboptimal when treatment and management of NCDs are in silos as seen in this study. Bringing in more awareness on LDL-C control to patients with T2DM and MDD, and to their treating physicians and service providers, through collaborative care for patients with T2DM and co-morbidities in this setting, is a gap that has to be addressed. Early intervention may be needed to assist younger individuals with T2DM and early onset T2DM with MDD, to achieve better glycaemic control.

Limitations

Firstly, the onset of T2DM and MDD was not recorded in this sample, which is a key feature in the risk stratification of individuals with diabetes for a CVD event. Secondly, the medication compliance of the patients was not recorded. Data on other risk factors such as obesity, smoking and physical exercise, which contribute to the risk of a premature CVD event was not available, as very few members or practitioners forwarded this data to the healthcare organisation. Lastly, this analysis referenced the target LDL-C control for very high-risk patients with T2DM and CVD risk factors at < 1.8 mmol/l. The result would have been even less if the latest ESC guideline-recommended LDL-C target of < 1.4 mmol/l was used.[44] Discrete variables of patients claiming insulin only [12/223 (5.4%) in the T2DM + MDD group and 15/656 (2.3%) in the T2DM – MDD group] were excluded from the multivariate regression analysis as very few were claiming for insulin only.

Conclusion

In a private managed healthcare setting in SA, this study shows poor ABC goal attainment in both the T2DM – MDD and T2DM + MDD patients. Older patients with T2DM + MDD showed better HbA_{1c} and LDL-C control, highlighting the need to assist younger adults who show poor adherence to medication to achieve ABC control. A significantly higher rate of repeated macrovascular hospitalisations for 2019 in patients with T2DM + MDD may reflect the effect of MDD in the increased risk of CV events. The majority of patients with T2DM with and without MDD showed very poor achievement of the LDL-C target level recommended by the South African Heart Association and Lipid and Atherosclerosis Society of Southern Africa. Currently, the triad of LDL-C, BP and HbA_{1c} are reported independently in the interpretation of patient clinical presentation, however, there is a need to consider all three measures within the context of the ABC target levels in patients with T2DM. A change in clinical case management would potentially reduce the risk of CV events.

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References

1. International Diabetes Federation. *IDF Diabetes Atlas*, 10th edn. https://www.idf.org/e-library/epidemiology-research/diabetes-atlas.html [Accessed on July 22, 2022]
2. Tomlinson M, Grimsrud AT, Stein DJ, Williams DR, Myer L. The epidemiology of major depression in South Africa: results from the South African stress and health study. *S Afr Med J* 2009; **99**(5): 368–373.
3. Naidoo L, Butkow N, Barnard-Ashton P, Libhaber E. Hospitalisation of type 2 diabetes mellitus patients with and without major depressive disorder in a private managed healthcare organisation. *J Endocrinol Metab Diabetes S Afr* 2019; **24**(3): 70–76.
4. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, *et al*. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**(9733): 2215–2222.
5. ABC goals in patients with Type 2 diabetes. https://pro.aace.com/disease-state-resources/diabetes/depth-information/type-2-diabetes-glucose-management-goals [Accessed on April 3, 2022]
6. Amod A. The society for endocrinology, metabolism and diabetes of South Africa type 2 diabetes guidelines expert committee. The 2017 SEMDSA guideline for the management of type 2 diabetes guideline committee. *J Endocrinol Metab Diabetes S Afr* 2017; **22**(1): S1–S196.
7. Vouri SM, Shaw RF, Waterbury NV, Egge JA, Alexander B. Prevalence of achievement of A1c, blood pressure, and cholesterol (ABC) goal in veterans with diabetes. *J Managed Care Pharm* 2011; **17**(4): 304–312.
8. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. *Diabetes Care* 2013; **36**(8): 2271–2279.
9. American Diabetes Association. Standards of medical care in diabetes – 2010. *Diabetes Care* 2010; **33**(Suppl 1): S11–61.
10. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, *et al*. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **129**(25 Suppl 2): S1–45.

11. Klug E. South African Heart Association (SA Heart); Lipid and Atherosclerosis Society of Southern Africa (LASSA). South African Dyslipidaemia Guideline Consensus Statement. *S Afr Med J* 2012; **102**(3).
12. Yahagi K, Kolodgie FD, Lutter C, Mori H, Romero ME, Finn AV, *et al*. Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2017; **37**(2): 191–204.
13. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, *et al*. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008; **371**(9607): 117–125.
14. Vargas-Uricoechea H, Cáceres-Acosta MF. Control of blood pressure and cardiovascular outcomes in type 2 diabetes. *Open Med* 2018; **13**: 304–323.
15. Wong ND, Patao C, Malik S, Iloeje U. Preventable coronary heart disease events from control of cardiovascular risk factors in US adults with diabetes (projections from utilizing the UKPDS risk engine). *Am J Cardiol* 2014; **113**(8): 1356–1361.
16. Heckbert SR, Rutter CM, Oliver M, Williams LH, Ciechanowski P, Lin EH, *et al*. Depression in relation to long-term control of glycemia, blood pressure, and lipids in patients with diabetes. *J Gen Intern Med* 2010; **25**(6): 524–529.
17. Katon WJ, Lin EH, Russo J, Von Korff M, Ciechanowski P, Simon G, *et al.* Cardiac risk factors in patients with diabetes mellitus and major depression. *J Gen Intern Med* 2004; **19**(12): 1192–1199.
18. Akpalu J, Yorke E, Ainuson-Quampah J, Balogun W, Yeboah K. Depression and glycaemic control among type 2 diabetes patients: a cross-sectional study in a tertiary healthcare facility in Ghana. *BMC Psychiatry* 2018; **18**(1): 1–7.
19. International Diabetes Federation. *IDF Diabetes Atlas*, 9th edn. Brussels, Belgium: Int Diabetes Fed. 2019. www.diabetesatlas.org 2019 [Accessed on May 19, 2021]
20. Nowakowska M, Zghebi SS, Ashcroft DM, Buchan I, Chew-Graham C, Holt T, *et al*. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. *BMC Med* 2019; **17**(1): 145.
21. Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *Lancet Diabetes Endocrinol* 2015; **3**(6): 461–471.
22. Hackett RA, Steptoe A. Type 2 diabetes mellitus and psychological stress – a modifiable risk factor. *Nature Rev Endocrinol* 2017; **13**(9): 547–560.
23. Do Prado-Lima PS. Medical comorbidities and functioning in depression: a clinical perspective. *Medicographia* 2014; **36**(4): 464–469.
24. Kim SW, Kang HJ, Jhon M, Kim JW, Lee JY, Walker AJ, *et al*. Statins and inflammation: new therapeutic opportunities in psychiatry. *Frontiers Psychiatry* 2019; **10**: 103.
25. Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, *et al*. Regulation of the hypothalamic–pituitary–adrenocortical stress response. *Comprehens Physiol* 2016; **6**(2): 603–621.
26. Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, *et al*. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience* 2015; **300**: 141–154.
27. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med* 2013; **11**: 129.
28. Nikkheslat N, Zunszain PA, Horowitz MA, Barbosa IG, Parker JA, Myint AM, *et al*. Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain Behav Immun* 2015; **48**: 8–18.
29. Reiner Ž, Catapano AL, De Backer G, Graham I, Taskinen M-R, Wiklund O, *et al*. ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011; **32**(14): 1769–1818.
30. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; **376**(9753): 1670–1681.
31. Subramaniapillai M, Chen VC, McIntyre RS, Yang YH, Chen YL. Added burden of major depressive disorder on cardiovascular morbidity and mortality among patients with cardiovascular disease and the modifying effects of antidepressants: A national retrospective cohort study. *J Affect Disord* 2021; 2**94**: 580–585.
32. Heart Protection Study Collaborative G. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet* 2011; **378**(9808): 2013–2020.
33. Köhler O, Gasse C, Petersen L, Ingstrup KG, Nierenberg AA, Mors O, *et al*. The effect of concomitant treatment with SSRIs and statins: a population-based study. *Am J Psychiatry* 2016; **173**(8): 807–815.
34. International Statistical Classification of Diseases and Related Health Problems, 10th Revision. ICD-10 Version:2019. www.icd.who.int/browse10/2019/en. [Accessed on August 30, 2020]
35. Prescribed Minimum Benefits (PMB) Council for Medical Schemes. CMS PMB ICD-10 CODED LIST 2013 www.medicalschemes.com. [Accessed on May 19, 2021]
36. Anatomical Therapeutic Chemical (ATC) classification https://www.whocc.no/atc/structure_and_principles/ [Accessed on March 18, 2022]
37. Kim SW, Bae KY, Kim JM, Shin IS, Hong YJ, Ahn Y, *et al.* The use of statins for the treatment of depression in patients with acute coronary syndrome. *Translat Psychiatry* 2015; **5**(8): e620.
38. Kaulgud R, Nekar M, Sumanth K, Joshi R, Vijayalakshmi P, Desai S, *et al*. Study of depression in patients with diabetes compared to non-diabetics among elderly population and its association with blood sugar, HbA_{1c} values. *Int J Biomed Res* 2013; **4**: 55–61.
39. Group UPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998; **317**(7160): 703.
40. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *New Engl J Med* 2008; **359**(15): 1577–1589.
41. Masilela C, Pearce B, Ongole JJ, Adeniyi OV, Benjeddou M. Factors associated with glycemic control among South African adult residents of Mkhondo municipality living with diabetes mellitus. *Medicine* 2020; **99**(48): e23467.
42. Naidoo LA, Butkow N, Barnard-Ashton P, Miot J, Libhaber E. Is the risk really shared? A retrospective analysis of healthcare costs of patients with type 2 diabetes mellitus on a capitation model. *Value Health Region Issues* 2022; **28**: 29–37.
43. Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, *et al*. Twenty-four-hour blood pressure-lowering effect of a sodium-glucose cotransporter 2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. *Circulation* 2019; **139**(18): 2089–2097.
44. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, *et al.* 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes: Developed by the task force on the management of cardiovascular disease in patients with diabetes of

the European Society of Cardiology (ESC). *Eur Heart J* 2023; **44**(39): 4043–4140.
45. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, *et al*. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* 2014; **64**(5): 485–494.
46. McGinnis B, Olson KL, Magid D, Bayliss E, Korner EJ, Brand DW, *et al*. Factors related to adherence to statin therapy. *Ann Pharmacother* 2007; **41**(11): 1805–1811.
47. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000; **160**(14): 2101–2107.
48. Blom DJ, Raal F, Amod A, Naidoo P, Lai YE. Management of low-density lipoprotein cholesterol levels in South Africa: the International ChoLesterol management Practice Study (ICLPS). *Cardiovasc J Afr* 2019; **30**(1): 15–23.
49. Okerson T, Patel J, DiMario S, Burton T, Seare J, Harrison DJ. Effect of 2013 ACC/AHA blood cholesterol guidelines on statin treatment patterns and low-density lipoprotein cholesterol in atherosclerotic cardiovascular disease patients. *J Am Heart Assoc* 2017; **6**(3): e004909.
50. Holland AT, Zhao B, Wong EC, Choi SE, Wong ND, Palaniappan LP. Racial/ethnic differences in control of cardiovascular risk factors among type 2 diabetes patients in an insured, ambulatory care population. *J Diabetes Complicat* 2013; **27**(1): 34–40.
51. Bertoni AG, Clark JM, Feeney P, Yanovski SZ, Bantle J, Montgomery B, *et al.* Suboptimal control of glycemia, blood pressure, and LDL cholesterol in overweight adults with diabetes: the Look AHEAD Study. *J Diabetes Complicat* 2008; **22**(1): 1–9.
52. Elis A, Rosenmann L, Chodick G, Heymann AD, Kokia E, Shalev V. The association between glycemic, lipids and blood pressure control among Israeli diabetic patients. *Q J Med* 2008; **101**(4): 275–280.
53. Larry M, Alizadeh S, Naderi S, Salekani B, Mansournia MA, Rabizadeh S, *et al*. Inadequate achievement of ABC goals (HbA_{1c}, blood pressure, LDL-C) among patients with type 2 diabetes in an Iranian population, 2012–2017. *Diabetes Metabolic Syndr* 2020; **14**(4): 619–625.
54. Shah BM, Mezzio DJ, Ho J, Ip EJ. Association of ABC (HbA_{1c}, blood pressure, LDL-cholesterol) goal attainment with depression and health-related quality of life among adults with type 2 diabetes. *J Diabetes Complicat* 2015; **29**(6): 794–800.
55. Kitaoka K, Takenouchi A, Minato-Inokawa S, Takeuchi M, Tsuboi A, Kurata M, *et al.* Association of ABC (HbA_{1c}, blood pressure and LDL-cholesterol) goal achievement with visit-to-visit ABC variability and postprandial dysmetabolism in type 2 diabetic patients. *Asia Pacific J Clin Nutr* 2020; **29**(3): 476–482.
56. Pinchevsky Y, Shukla VJ, Butkow N, Chirwa T, Raal F. Multi-ethnic differences in HbA1c, blood pressure, and low-density-lipid cholesterol control among South Africans living with type 2 diabetes, after a 4-year follow-up. *Int J Gen Med* 2016; **9**: 419.
57. Stern N, Marcus Y. Hypertension in diabetes: the role of the vasculature. *Curr Hypertens Rep* 2004; **6**(2): 90–97.
58. Khunti K, Ceriello A, Cos X, De Block C. Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: A meta-analysis. *Diabetes Res Clin Pract* 2018; **137**: 137–148.
59. Henein MY, Vancheri S, Longo G, Vancheri F. The role of inflammation in cardiovascular disease. *Int J Molec Sci* 2022; **23**(21).
60. Guedeney P, Claessen BE, Kalkman DN, Aquino M, Sorrentino S, Giustino G, *et al.* Residual inflammatory risk in patients with low LDL cholesterol levels undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2019; **73**(19): 2401–2409.
61. Ridker PM. How common is residual inflammatory risk? *Cir Res* 2017; **120**(4): 617–619.
62. Chiu CJ, Wray LA. Factors predicting glycemic control in middle-aged and older adults with type 2 diabetes. *Prevent Chronic Dis* 2010; **7**(1): A08.
63. Nichols GA, Hillier TA, Javor K, Brown JB. Predictors of glycemic control in insulin-using adults with type 2 diabetes. *Diabetes Care* 2000; **23**(3): 273–277.
64. Chuang LM, Soegondo S, Soewondo P, Young-Seol K, Mohamed M, Dalisay E, *et al*. Comparisons of the outcomes on control, type of management and complications status in early onset and late onset type 2 diabetes in Asia. *Diabetes Res Clin Pract* 2006; **71**(2): 146–155.
65. Lichtman JH, Bigger JT, Jr., Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance F, *et al*. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation* 2008; **118**(17): 1768–1775.
66. De Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. *Psychosomat Med* 2001; **63**(4): 619–630.
67. Ismail R, Csóka I. Novel strategies in the oral delivery of antidiabetic peptide drugs – Insulin, GLP 1 and its analogs. *Euro J Pharmaceut Biopharmaceut* 2017; **115**: 257–267.
68. Wieczorek-Surdacka E, Surdacki A, Świerszcz J, Chyrchel B. Novel antidiabetic drugs in diabetic kidney disease accompanying type 2 diabetes – a minireview. *Folia Medica Cracoviensia* 2020; **60**(4): 97–101.
69. Masson W, Lavalle-Cobo A, Lobo M, Masson G, Molinero G. Novel antidiabetic drugs and risk of cardiovascular events in patients without baseline metformin use: a meta-analysis. *Eur J Prevent Cardiol* 2021; **28**(1): 69–75.
70. Blum A. Freestyle Libre glucose monitoring system. *Clin Diabetes* 2018; **36**(2): 203–204.
71. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; **139**(25): e1082–e1143.
72. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *Br Med J* 2003; **326**(7404): 1423.
73. Lin EH, Rutter CM, Katon W, Heckbert SR, Ciechanowski P, Oliver MM, *et al.* Depression and advanced complications of diabetes: a prospective cohort study. *Diabetes Care* 2010; **33**(2): 264–269.
74. Scherrer JF, Garfield LD, Chrusciel T, Hauptman PJ, Carney RM, Freedland KE, *et al.* Increased risk of myocardial infarction in depressed patients with type 2 diabetes. *Diabetes Care* 2011; **34**(8): 1729–1734.
75. Ismail K, Moulton CD, Winkley K, Pickup JC, Thomas SM, Sherwood RA, *et al*. The association of depressive symptoms and diabetes distress with glycaemic control and diabetes complications over 2 years in newly diagnosed type 2 diabetes: a prospective cohort study. *Diabetologia.* 2017; **60**(10): 2092–2102.
76. Taylor CB, Youngblood ME, Catellier D, Veith RC, Carney RM, Burg MM, *et al*. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry* 2005; **62**(7): 792–798.

77. Athyros VG, Katsiki N, Tziomalos K, Gossios TD, Theocharidou E, Gkaliagkousi E, *et al.* Statins and cardiovascular outcomes in elderly and younger patients with coronary artery disease: a *post hoc* analysis of the GREACE study. *Arch Med Sci* 2013; **9**(3): 418–426.
78. Sever PS, Poulter NR, Dahlöf B, Wedel H. Different time course for prevention of coronary and stroke events by atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA). *Am J Cardiol* 2005; **96**(5a): 39f–44f.
79. Kones R. Rosuvastatin, inflammation, C-reactive protein, JUPITER, and primary prevention of cardiovascular disease – a perspective. *Drug Design Develop Ther* 2010; **4**: 383–413.
80. Redlich C, Berk M, Williams LJ, Sundquist J, Sundquist K, Li X. Statin use and risk of depression: a Swedish national cohort study. *BMC Psychiatry* 2014; **14**: 348.
81. Kim JM, Stewart R, Kang HJ, Bae KY, Kim SW, Shin IS, *et al*. A prospective study of statin use and poststroke depression. *J Clin Psychopharmacol* 2014; **34**(1): 72–79.
82. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundament Clin Pharmacol* 2005; **19**(1): 117–125.
83. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care* 2000; **23**(5): 618–623.
84. Lustman PJ, Williams MM, Sayuk GS, Nix BD, Clouse RE. Factors influencing glycemic control in type 2 diabetes during acute- and maintenance-phase treatment of major depressive disorder with bupropion. *Diabetes Care* 2007; **30**(3): 459–466.
85. Lloyd-Jones DM, Wilson PW, Larson MG, Beiser A, Leip EP, D'Agostino RB, *et al*. Framingham risk score and prediction of lifetime risk for coronary heart disease. *Am J Cardiol* 2004; **94**(1): 20–24.