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Metabolic control and incidence of hypoglycaemia, hospitalisation and complications among Saudi patients with type 2 diabetes initiating second-line therapy: an analysis of the Saudi Arabia data from the DISCOVER Observational Study programme

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ABSTRACT

Objectives The aim of the global DISCOVERing Treatment Reality of Type 2 Diabetes in Real World Settings (DISCOVER) Study was to provide a comprehensive real world assessment of the treatment pattern changes for patients with type 2 diabetes. The aim of this analysis was to assess the metabolic control and the annual incidence of hypoglycaemia, hospitalisation and complications among Saudi patients with type 2 diabetes initiating second-line therapy.

Design This study is part of the observational, longitudinal, prospective multinational DISCOVER Study.

Setting Governmental and private health sectors from different regions within Saudi Arabia.

Participants The study recruited 519 patients with type 2 diabetes aged ≥18 years who were switching to second-line therapy. Patients who were already using insulin/injectable agents, patients with type 1 diabetes, pregnant women, and patients undergoing dialysis or with a history of renal transplantation were excluded.

Primary and secondary outcome measures Metabolic control among patients with type 2 diabetes mellitus; fear of hypoglycaemia; quality of life; and the incidence of complications, hypoglycaemic events and/or hospitalisations. Data were analysed using descriptive statistics.

Results A total of 519 patients were recruited with a mean age of 52.4±11 years. Of these participants, 54.7% were male and 45.3% were female. The incidence of hypoglycaemia was 56.72/1000 patient-years. The Hypoglycemia Fear Survey II showed a significant increase in patient worry related to hypoglycaemia from 6.4±11.9 at baseline to (p=0.0446) at the 36-month follow-up. The incidence of hospitalisation was 30.81/1000 patient-years. There was a moderate improvement in glycaemic control, represented as an HbA1c reduction from 8.8% at baseline to 8.2% at the 36-month follow-up. The incidence of macroangiopathy was 24.51/1000 patient-years and the incidence of microvascular complications such as retinopathy and albuminuria was 47.00/1000 patient-years and 221.71/1000 patient-years, respectively. The mean score of fear of hypoglycaemia showed an increase with 13.0±21.5 at baseline to 16.1±22.2 at the 36-month follow-up. When assessing the patients' quality of life, there was an improvement in the mental component score from 47.4±9.1 at baseline to 53.0±6.7 at the 36-month follow-up.

Conclusions Treatment intensification decisions should be made individually, weighing the benefit of good glycaemic control against the risk of hypoglycaemia.

Trial registration number NCT02322762 and NCT02226822.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Strengths include the study's low dropout rate of 8.1%, which was achieved by being part of an international multicentre study based on observational prospective longitudinal data from hospitals around the world.
⇒ The study results could be generalised.
⇒ The data collected through the medical file review could have resulted in missing data such as HbA1c levels, incidence of microalbuminuria, neuropathy test results and fundus examination results.
⇒ Another limitation was the potential for recall bias by the patients for events that occurred during the follow-up period.
⇒ A third limitation was the assumption of patients' adherence to their medications.

INTRODUCTION

The management of patients with type 2 diabetes is a complex process that must be individualised and patient-centred. The management usually follows clinical guidelines with consideration of the patient's personal and

clinical characteristics. Age, time since diabetes diagnosis, presence of comorbidities, risk of hypoglycaemia, physician experience and existing national guidelines are key factors in the selection of a management pathway.[1] Type 2 diabetes is an established risk factor for cardiovascular disease, especially when associated with hypertension, obesity and dyslipidaemia, and contributes to the observed increase in mortality rate.[2 3] The need for early achievement of good glycaemic control to reduce the risk of microvascular and macrovascular complications among patients with type 2 diabetes was well established by the UK Prospective Diabetes Study.[4]

In the last three decades, new classes of glucose-lowering agents for the treatment of type 2 diabetes have become commercially available globally. Despite the availability of these new therapeutic classes, there continues to be high risk of hospitalisation, heart failure, myocardial infarction and stroke.[5] One explanation for such increased rates of complications is the clinical inertia for treatment intensification among patients with diabetes, since it is reported to be associated with an increased incidence of hypoglycaemia.[6] Additionally, fear of hypoglycaemia may also limit physicians from intensifying the treatment, as the patient's quality of life may be negatively affected by fear of hypoglycaemia even if effective glycaemic control is achieved.[7]

Real world data analysis is useful for healthcare providers and insurance companies to identify treatment patterns and unmet needs among patients with type 2 diabetes. This consequently facilitates improvements in the actual diabetes management workflow and establish further management plans that target the reduction of morbidity and mortality that eventually reduce both direct and indirect costs. Such data would also highlight the best approach to achieving good glycaemic control without negatively affecting the patient's quality of life or increasing the risk of hypoglycaemia.

As a part of the international multicentre DISCOVERing Treatment Reality of Type 2 Diabetes in Real World Settings (DISCOVER) Study,[8] which looks at patients with type 2 diabetes initiating second-line therapy, the objective of this study is to assess physicians and the healthcare system's observed practice towards patients failing first-line management, based on data collected from centres in Saudi Arabia. The study also aims to assess the rate of hypoglycaemia and hospitalisation due to chronic diabetes complications. In addition, quality of life was assessed at baseline and throughout follow-up. This is not to mention that reporting such real world data for the reality of management of type 2 diabetes at the level of the country will enable informed healthcare decisions in the context of the country's healthcare system and resources.

METHODS

Study design and participants

The multinational DISCOVER Study was an observational, longitudinal, prospective study conducted in 37 countries, including the Kingdom of Saudi Arabia.[8] The study was conducted at nine hospitals across four of the five provinces in the Kingdom of Saudi Arabia. A total of 519 Saudi patients with type 2 diabetes who were non-insulin users, aged ≥18 years and switching to second-line therapy were studied. The eligible patients were recruited between 31 December 2014 and 30 June 2016, to start a 36-month follow-up period. Eligible patients starting second-line therapy, either as an add-on or when transitioning from first-line oral monotherapy, dual therapy or triple therapy, were enrolled in the study. Patients using an injectable agent, namely insulin or a GLP-1-receptor agonist, were excluded due to disease severity. Other exclusion criteria included patients with type 1 diabetes, pregnant women, patients using herbal remedies or natural medicines alone, and patients undergoing dialysis or with a history of renal transplantation.

Data collection

Data were collected from eligible patients using an electronic case report form (eCRF). Clinical evaluations, including selected laboratory investigations at baseline and follow-ups at 6 months, 12 months, 24 months and 36 months, were also performed. Data were captured at 6 months, 12 months, 24 months and 36 months within a 4-month window (±2 months) as shown in online supplemental appendix 1. The study staff ensured that all eCRFs were complete before saving the forms in a centralised database.

During each visit, demographic and socioeconomic characteristics as well as physiological parameters, including blood pressure, pulse rate, weight, height, body mass index and waist circumference were collected by the treating physician and trained research team. Any changes in glucose-lowering therapy reflected by HbA1c levels or fasting, random or postprandial blood glucose levels were reported. Other laboratory parameters, including lipid parameters (total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides), renal function test values (serum creatinine and albumin/creatinine ratio) and uric acid levels were also collected from the patient's medical file. Liver function biomarkers, including serum albumin, aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transpeptidase were measured at each visit. The complete blood count parameters tested included leucocytes, haemoglobin, haematocrit and platelets. Based on the chart review and patient's report, the investigators reported major and minor hypoglycaemic events and comorbidities that involved microvascular and macrovascular complications. Microvascular complications were classified into nephropathy (chronic kidney disease and/or albuminuria), retinopathy (non-proliferative retinopathy (NPDR), proliferative retinopathy or having received retinal laser photocoagulation) and neuropathy (autonomic neuropathy, peripheral neuropathy and/or erectile dysfunction). Macrovascular complications were coronary artery disease (angina, myocardial infarction,

percutaneous coronary intervention and coronary artery bypass grafting), heart failure and implantable cardioverter defibrillator use. Cerebrovascular disease was reported in the form of stroke, transient ischaemic attack, carotid artery stenting or carotid endarterectomy. Peripheral artery diseases (PADs), namely revascularisation procedures, diabetic foot and amputation, were also reported. Hypoglycaemic data were obtained on an anamnestic, retrospective basis (within the last 12 months prior to the baseline visit) and during follow-up visits based on the patient's self-recall and/or medical records. Major hypoglycaemic events were defined as those that required an emergency room visit, hospital admission, visit to a physician or other healthcare professional, or external help from a caregiver or family member. Minor hypoglycaemic events were defined as those that did not require external help or meet the major hypoglycaemia definition.[9]

Changes in HbA1c levels, body weight, blood pressure and lipid profile were recorded during each follow-up visit. During the follow-up period, the incidence of microvascular complications, namely nephropathy, neuropathy and retinopathy, was reported. The incidence of macrovascular complications was reported if the patient manifested heart failure, myocardial infarction, stroke or diabetes-related revascularisation. Quality of life was assessed for all patients using the self-reporting 36-item Short Form Health Survey version 2 (SF-36v2) Questionnaire, and the fear of hypoglycaemic events was assessed using the self-reporting Hypoglycemia Fear Survey II (HFS-II), which assesses the level of fear related to hypoglycaemia and consists of two subscales: behaviour and worry.[10] Data on the incidence and reasons for hospitalisations or emergency room visits were also collected during the follow-up period.

Statistical analysis

Descriptive analysis was used to describe demographic variables, patient characteristics, changes in HbA1c levels, blood glucose levels, lipid profile, body weight, body mass index and blood pressure. Mean values are presented with ±SDs and medians with IQRs. One-way analysis of variance was used for continuous variables and the χ^2 test for categorical variables. All parameters were analysed during the follow-up period using $p<0.05$ to define statistical significance. The incidence of diabetes-related or unrelated complications and hypoglycaemia episodes per 1000 patient-years was determined using 1428 patient-years. Frequency analyses were used to report clinical and demographic data for all participants and subcategories. The categorical data are presented as numbers and percentages. Data from each domain of the HFS-II were analysed for descriptive statistics using the mean (±SD) and the median (IQR). Multiple imputations were used to account for unreported data and missing values. Imputation was carried out using IVEware (University of Michigan). Since the data were entered using eCRFs, any outliers were reported back to the principal investigator of each site for revision and correction before the final database lock. All statistical analyses were performed using the SAS v.9.4 statistical software system (SAS Institute, Cary, North Carolina, USA).

Patient and public involvement

None.

RESULTS

A total of 519 patients were recruited with a mean age of 52.4±11 years; 54.7% of participants were male and 45.3% were female. Patients' baseline characteristics are shown in online supplemental appendix 2. A total of 477 patients (91.9%) completed the 36-month follow-up visits and had clinical and biochemical assessments. Even though the mean waist circumference increased significantly from 107.2±10.3 cm at baseline to 107.2±10.3 cm at the 36-month follow-up; it may be negligible due to the non-significant mean body weight change from the baseline.

Primary outcome measures

There was a significant reduction in all glycaemic and lipid parameters in addition to diastolic blood pressure, indicating better medical care. The mean value of HbA1c dropped from 8.8% at baseline to 8.2% at the end of the follow-up period (36 months), indicating moderate control of diabetes. Serum creatinine levels and the albumin/creatinine ratio demonstrated a significant increase, supporting the noted increase in the incidence of albuminuria of 22.71/1000 patient-years and projecting the increase in the incidence of diabetic nephropathy, as shown in online supplemental appendices 3 and 4.

Incidence of mild hypoglycaemia that did not warrant admission was 56.72/1000 patient-years, while the incidence of major hypoglycaemic events was 0.70/1000 patient-years, as shown in table 1. A total of 30.81 admissions per 1000 patient-years were recorded. The incidence rates of cardiovascular events (8.40/1000 patient-years), major infections (2.10/1000 patient-years) and cancer (1.40/1000 patient-years) were all higher than the incidence rates of all other causes combined.

Secondary outcome measures

The incidence of emergency room visits was 81.23/1000 patient-years, mainly single visits, as shown in table 2. Emergency room visits were mainly related to cardiovascular disease and occurred at an incidence of 10.50/1000 patient-years; 7/1000 patient-years were due to myocardial infarctions and 4.20/1000 patient-years were related to Class II heart failure as defined by the New York Heart Association.

The incidence of retinopathy was 47.0/1000 patient-years, mainly in the form of NPDR. The incidence of neuropathy was higher, at a rate of 61.62/1000 patient-years, presenting mainly as erectile dysfunction. Hypertension and hyperlipidaemia occurred at an incidence of

Table 1 Incidence and annual frequency of major and minor hypoglycaemia during the 3-year follow-up

Clinical condition		Follow-up period 6 months, n=470 Number (%)	12 months, n=478 Number (%)	24 months, n=473 Number (%)	36 months, n=477 Number (%)	Incidence (/1000 patient-years)(95%CI)
Major hypoglycaemic event		1 (0.2)	0	0	0	1 (0.70) (0.01 to 3.90)
Minor hypoglycaemic event		21 (4.8)	15 (3.2)	19 (4.0)	26 (5.5)	81 (56.72) (45.05 to 70.50)
Number of minor hypoglycaemic attacks in the previous 4 weeks	1	5 (1.1)	6 (1.3)	8 (1.7)	11 (2.3)	30 (21.01) (14.17 to 29.99)
	2	7 (1.5)	4 (0.8)	8 (1.7)	7 (1.5)	24 (16.81) (10.77 to 25.01)
	3	7 (1.5)	1 (0.2)	3 (0.6)	2 (0.4)	13 (9.10) (4.84 to 15.56)
	4	1 (0.2)	3 (0.6)	0	1 (0.2)	5 (3.50) (1.13 to 8.17)
	≥5	1 (0.2)	1 (0.2)	0	4 (0.8)	6 (4.20) (1.54 to 9.14)

51.82/1000 patient-years and 79.83/1000 patient-years, respectively. Thyroid disorder events occurred at an incidence rate of 67.23/1000 patient-years, where 94% of events were hypothyroidism. The incidence of cancer was 4.20/1000 patient-years, mainly colorectal and breast cancer. The most commonly reported infection was urinary tract infection with an incidence of 21.01/1000 patient-years. Depression was reported at an incidence of 7.70/1000 patient-years, as shown in table 3 and online supplemental appendix 5. The rates of macrovascular and microvascular complications at baseline are reported in online supplemental appendix 1.

The Hypoglycemia Fear Survey-II (HFS-II for the total cohort demonstrated a significant increase in the mean and median scores for both behaviour and worries throughout the 3 years of follow-up. The mean score for

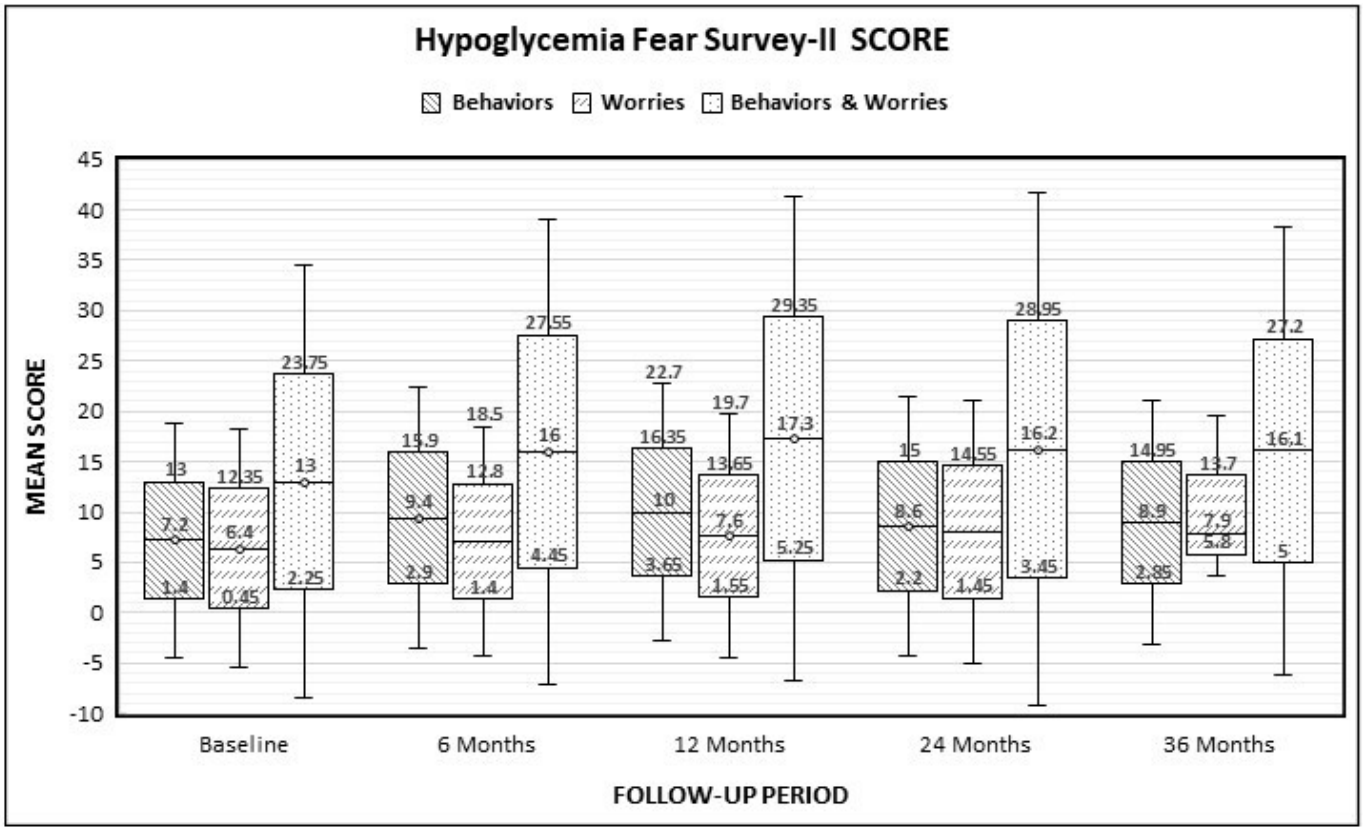
Table 2 The crude prevalence and calculated incidence of hospitalisations and emergency visits during the follow-up period for the studied cohort

Medical care event	Follow-up period 6 months, n=470 Number (%)	12 months, n=478 Number (%)	24 months, n=473 Number (%)	36 months, n=477 Number (%)	Incidence (/1000 patient-years) (95% CI)
Hospitalisations since the last follow-up	8 (1.7)	8 (1.7)	12 (2.5)	16 (3.4)	44 (30.81) (22.67 to 41.89)
Number of hospitalisations since the last follow-up					
1	7 (1.5)	7 (1.5)	11 (2.3)	15 (3.1)	40 (28.01) (20.27 to 38.63)
2	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	4 (2.80) (0.77 to 7.26)
Reason for hospitalisation					
Other reason	3 (0.6)	5 (1.0)	10 (2.1)	9 (1.9)	27 (18.91) (12.62 to 27.86)
Cardiovascular event	4 (0.9)	2 (0.4)	1 (0.2)	5 (1.0)	12 (8.40) (4.39 to 14.86)
Serious infections	0	1 (0.2)	1 (0.2)	1 (0.2)	3 (2.10) (0.43 to 6.21)
Cancer	1 (0.2)	0	0	1 (0.2)	2 (1.40) (0.17 to 5.12)
Renal failure	0	0	0	1 (0.2)	1 (0.70) (0.01 to 3.90)
Emergency room visits since the last follow-up	19 (4.0)	13 (2.7)	42 (8.9)	42 (8.8)	116 (81.23) (67.12 to 97.43)
Number of emergency room visits					
1	15 (3.2)	9 (1.9)	35 (7.4)	32 (6.7)	91 (63.73) (51.31 to 78.24)
2	3 (0.6)	3 (0.6)	5 (1.1)	8 (1.7)	19 (13.31) (8.01 to 20.78)
≥3	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)	5 (3.50) (1.13 to 8.17)
Reason for emergency room visits					
Cardiac related complication	2 (0.4)	2 (0.4)	5 (1.1)	6 (1.3)	15 (10.50) (5.88 to 17.33)
Diabetes-related complication	1 (0.2)	2 (0.4)	2 (0.4)	2 (0.4)	7 (4.90) (1.97 to 10.10)
Neurological disorders	1 (0.2)	0	0	0	1 (0.70) (0.01 to 3.90)
Peripheral arterial disease related complication	0	0	0	1 (0.2)	1 (0.70) (0.01 to 3.90)

Table 3 The crude prevalence and calculated incidence of microangiopathy and macroangiopathy for the studied cohort since the previous follow-up visit

Clinical condition	Follow-up period				Incidence (/1000 patient-years)
	6 months, n=470 Number (%)	12 months, n=478 Number (%)	24 months, n=473 Number (%)	36 months, n=477 Number (%)	
Cardiovascular event	10 (2.3)	11 (2.6)	9 (2.1)	5 (1.2)	35 (24.51) (17.07 to 34.09)
Events					
Myocardial infarction	4 (0.9)	2 (0.4)	3 (0.7)	1 (0.2)	10 (7.00) (3.35 to 12.87)
Single vessel disease	4 (0.9)	2 (0.4)	0	0	6 (4.20) (1.54 to 9.14)
Multiple vessels disease	0	0	3 (0.7)	1 (0.2)	4 (2.80) (0.76 to 7.17)
PCI	2 (0.5)	3 (0.7)	4 (0.9)	2 (0.5)	11 (7.70) (3.84 to 13.78)
PCI stent	2 (0.5)	3 (0.7)	3 (0.7)	2 (0.5)	10 (7.00) (3.35 to 12.87)
Other cardiac conditions					
Atrial fibrillation event	0	0	1 (0.2)	2 (0.5)	3 (2.10) (0.43 to 6.14)
Severe valve event	0	1 (0.2)	1 (0.2)	0	2 (1.40) (0.17 to 5.05)
Outpatient cardiac test	14 (3.3)	8 (1.9)	4 (0.9)	5 (1.2)	31 (22.71) (14.75 to 30.81)
Events					
Heart failure according to NYHA class	0	0	4 (0.9)	2 (0.5)	6 (4.20) (1.54 to 9.14)
I	0	0	1 (0.2)	0	1 (0.70) (0.017 to 3.90)
II	0	0	2 (0.4)	2 (0.4)	4 (2.80) (0.76 to 7.17)
III	0	0	1 (0.2)	0	1 (0.70) (0.017 to 3.90)
Events					
Peripheral vascular disease	0	0	0	2 (0.5)	2 (1.40) (0.17 to 5.05)
PAD procedure	1 (0.2)	0	0	0	1 (0.70) (0.017 to 3.90)
DM foot event	1 (0.2)	1 (0.2)	0	0	2 (1.40) (0.17 to 5.05)
Event					
Chronic kidney disease	1 (0.2)	1 (0.2)	1 (0.2)	4 (0.9)	7 (4.90) (1.97 to 10.00)
Stage 2 and 3 eGFR>30 mL/min/1.73m^2	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.4)	5 (3.50) (1.13 to 8.17)
Stage 4 and 5 eGFR=5–29 mL/min/1.73m^2	0	0	0	2 (0.4)	2 (1.40) (0.17 to 5.05)
Albuminuria	10 (2.7)	8 (2.2)	2 (0.5)	11 (3.2)	31 (22.71) (14.75 to 30.81)
Events					
Retinopathy	14 (4.9)	15 (4.9)	18 (6.0)	21 (6.5)	68 (47.00) (36.98 to 60.37)
Maculopathy	0	1 (0.2)	2 (0.5)	3 (0.6)	6 (4.20) (1.54 to 9.14)
Non-proliferative	13 (2.8)	14 (2.9)	12 (2.5)	17 (3.6)	56 (39.22) (29.62 to 50.92)
Proliferative	1 (0.2)	0	4 (0.9)	1 (0.2)	6 (4.20) (1.54 to 9.14)
Events					
Peripheral neuropathy	42 (9.2)	46 (10.0)	56 (12.2)	54 (11.7)	88 (61.62) (49.42 to 75.92)
Autonomic neuropathy	2 (0.5)	3 (0.7)	6 (1.4)	7 (1.6)	18 (12.61) (7.47 to 19.92)
Erectile dysfunction	10 (4.2)	13 (5.1)	17 (7.0)	17 (7.1)	57 (39.92) (30.23 to 51.72)
Outpatient neuropathy test	2 (0.5)	4 (0.9)	1 (0.2)	6 (1.4)	13 (9.10) (4.84 to 15.86)
Hypertension since the last follow-up	70 (15.2)	68 (14.5)	109 (23.2)	144 (30.3)	74 (51.82) (40.69 to 65.06)

DM, Diabetes Mellitus; eGFR, Estimated glomerular filtration rate; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, Percutaneous Coronary Intervention.



Hypoglycemia Fear Survey-II (HFS II)	Baseline Number (519)	6 months Number (470)	12 months Number (478)	24 months Number (473)	36 months Number (477)
Behaviours: mean (±SD)	7.2±11.6	9.4±13.0	10.0±12.7	8.6±12.8	8.9±12.1
P value related to baseline	1.0000	0.0050	0.0003	0.0710	0.0238
Behaviors: median (IQR)	0.0 (0.0, 11.0)	2.0 (0.0, 17.0)	4.0 (0.0, 17.0)	0.0 (0.0, 15.0)	2.0 (0.0, 18.0)
Worries: mean (±SD)	6.4±11.9	7.1±11.4	7.6±12.1	8.0±13.1	7.9±11.6
P value related to baseline	1.0000	0.3462	0.1149	0.0441	0.0446
Worries: median (IQR)	0.0 (0.0, 7.0)	0.0 (0.0, 12.0)	0.0 (0.0, 10.0)	0.0 (0.0, 12.0)	0.0 (0.0, 14.0)
Behaviors and worry: mean (±SD)	13.0±21.5	16.0±23.1	17.3±24.1	16.2±25.5	16.1±22.2
P value related to baseline	1.0000	0.0347	0.0030	0.0324	0.0254
Behaviors and worry: median (IQR)	0.0 (0.0, 17.0)	3.0 (0.0, 25.0)	4.5 (0.0, 27.0)	0.0 (0.0, 19.0)	2.0 (0.0, 33.0)

Figure 1 Hypoglycemia Fear Survey II (HFS-II) Scores at baseline and during the follow-up period.

behaviour alone increased from 7.2±11.6 at baseline to 8.2±12.1 at 36 months follow-up with a value of p=0.0238, while the mean score for worries alone increased from 6.4±11.9 at baseline to 7.9±11.6 at 36 months follow-up with a value of p=0.0446, as shown in figure 1.

Table 4 demonstrates the physical and mental component scores for the quality of life throughout the follow-up period. The mental component scores were significantly higher at each follow-up visit compared with baseline (p<0.0001), with the highest mean score=53.8±7.1 at the

Table 4 The mean physical and mental component scores of the 36-item Short Form Health Survey version 2 (SF-36v2) from baseline to 36-month follow-up

	Follow-up period				
SF36v2 measures	**Baseline (n=519)**	**6 months (n=470)**	**12 months (n=478)**	**24 months (n=473)**	**36 months (n=477)**
SF-36v2 Physical Component Score	51.0±7.0	49.0±7.0	49.2±6.2	50.4±5.7	49.8±5.3
SF-36v2 Physical Component Score (Median (IQR))	51.9 (47.0 to 56.0)	50.4 (43.2 to 54.2)	49.3 (44.2 to 54.2)	51.0 (46.0 to 54.9)	50.6 (45.9 to 54.1)
SF-36v2 Mental Component Score	47.4±9.1	51.4±8.0	52.8±8.4	53.8±7.1	53.0±6.7
SF-36v2 Mental Component Score (Median (IQR))	48.6 (40.9 to 54.4)	52.5 (47.3 to 57.4)	53.7 (48.5 to 59.4)	54.8 (49.5 to 58.5)	53.7 (49.1 to 57.1)

24-month visit. The score differences from baseline were 4.0, 6.40 and 5.6, respectively. However, the mean physical component score did not change significantly during the 36-month follow-up period.

DISCUSSION

In the current study, the incidence rate of major hypoglycaemia was 0.7 per 1000 patient-years, which is low when compared with data from Korean patients with type 2 diabetes, at an incidence of 4.43 per 1000 patient-years.[11] The low incidence rate of hypoglycaemia among the current study cohort may have resulted from the early stage of diabetes, where patients had recently transitioned to second-line therapy. On the other hand, the current study reported an incidence rate of 56.72 per 1000 patient-years for minor hypoglycaemia. Both rates were within the range reported by a recent meta-analysis, where the incidence rate of hypoglycaemia among patients with type 2 diabetes ranged from 0.072 to 16 360 episodes per 1000-patient years.[12]

Additionally, as per the findings of the current study, second-line management significantly improved the metabolic control of diabetes in the form of a reduction in HbA1c levels during the 36-month follow-up period. These real world findings were consistent with a recent meta-analysis in which all investigated drug classes lowered HbA1c levels to a similar extent.[13] The second-line treatments chosen for glycaemic control by the treating physicians were not associated with the risk of weight gain or significant severe hypoglycaemia as observed in other studies.[13] This could be due to the fact that the most commonly prescribed hypoglycaemic medications as a second-line therapy among this cohort, as reported in a previous publication,[14] were dipeptidyl peptidase 4 inhibitors, which are known for their weight neutrality and low risk of hypoglycaemia.[15]

The delay in the introduction of second-line therapy, mainly insulin, observed in this study could be described as clinical inertia. Such practice may have affected the degree of glycaemic control which did not reach the targeted level. This practice was reported in similar studies across different societies[16] as well as in the IMPROVE (GLP-1:glucagon-like peptide-1, HbA1c:hemoglobin A1c) Study, which was conducted in eight countries, involved over 50 000 patients, and highlighted the concern that initiation of second-line therapy, particularly insulin, is commonly delayed in clinical practice.[17]

The improvement in glycaemic parameters with the initiation of second-line therapy was reflected in the lipid parameters, with a significant decrease in the total cholesterol, LDL, and triglycerides and an increase in HDL. There was a reduction in the crude prevalence of cardiovascular disease during the follow-up period, especially in the first 6 months of follow-up (2.3%). This observation was more pronounced in the Western countries but occurred less often in the south-east Asian countries.[18] The reduction in the crude prevalence of cardiovascular disease in this study may have resulted from both mild improvements in glycaemic control and the lower mean age of this cohort. This highlights the importance of age as a risk factor for cardiovascular disease, which may even be stronger than poor glycaemic control in this community. A similar finding was also reported among patients in this population who experienced ischaemic stroke.[19] This observation was made in patients with PAD characterised by foot ischaemia at an incidence rate of 0.2%, which was lower than the value reported by the same study in Europe, at a rate of 1.2%,[18] which could be a reflection of the younger age of our study group as well as the effect of ethnicity. This cohort also demonstrated an increase in the crude prevalence of microvascular complications, namely neuropathy, retinopathy and nephropathy. Each year, 61 patients with type 2 diabetes will develop neuropathy, 47 will develop retinopathy and 4 will develop chronic kidney disease. This rise in crude prevalence may be explained by the moderate reduction in HbA1c that did not match the prescribed targets and the legacy effect in the early phases of diabetes management,[20] which necessitates a greater treatment intensity and earlier intervention.[21] The all-cause hospitalisation rate was 10 times higher than the value reported in the General Practice Research Database linked to the Hospital Episode Statistics data in England for diabetes type and mean age.[22] This could have been explained by the limited access to inpatient admission due to long waiting lists. The second reason behind such a low hospitalisation rate could have been the low incidence of severe complications warranting admission. In addition, along with the optimisation of diabetes management in the study cohort, hypoglycaemia was mainly limited to minor events with a low recurrence rate that did not warrant hospitalisation or emergency room visit.

The main reason for hospital admission in this cohort was cardiovascular disease, which is in accordance with results from the global DISCOVER data.[18] Cardiovascular disease was also the most frequent reason for emergency room visits, as expected in such patients.[23] This study confirmed that patients with diabetes are more prone to associated diseases like thyroid disease, osteoarthritis, and urinary and chest infections. Such findings support the fact that diabetes mellitus is associated with increased direct and indirect costs due to complications and associated diseases which put pressure on health services and the economy.[24]

The fear of hypoglycaemia restricts patients' likelihood of achieving and maintaining glycaemic control and negatively affects their quality of life.[25] The HFS-II Worry Score was associated with the use of first-line insulin secretagogues and the glycaemic response to second-line agents or insulin use in the studied cohort. The score for behaviour, worries or both significantly increased with more interventions or loss of glycaemic control, in concordance with findings reported from the same study at an international level by Wang *et al*.[26] This finding emphasises the importance of assessing

patients' fear of hypoglycaemia prior to treatment intensification, especially if comorbidities are present. On the other hand, treatment intensification and the addition of second-line therapy were associated with improved Quality of life (QOL) in terms of the Mental Component Score. The difference between the mean Quality of life (QoL) scores at baseline and at any follow-up visit exceeded the minimal clinically important difference for the SF-36v2 Score, which is over 3 points.[27] There was a greater improvement in the mental QoL than the physical QoL with tight glycaemic control, which is in line with findings from Lau *et al*.[28] A possible explanation of such a finding is that the increased regimen complexity required to achieve better glycaemic control and the increased risk of hypoglycaemia may negatively impact the patient's perception of physical QoL. On the other hand, an increased sense of empowerment associated with improved glycaemic control positively impacted the mental component of QoL.[29] The improvement in quality of life despite the increased fear of hypoglycaemia indicates that the patient's quality of life is affected more by the improvement of their glycaemic control than with hypoglycaemic fear management.

This study has the strength of being a prospective longitudinal hospital-based study and being part of an international multicentre study with a low dropout rate of 8.1%. The study sample is a representative of both governmental and private sectors across different regions in Saudi Arabia. Study limitations are related to data collection from the medical file which may have had missing data such as HbA1c levels, presence of microalbuminuria, neuropathy test results and fundus examination data. Another limitation is the potential for recall bias by the patients for events that occurred during the follow-up period. However, since all the patients were recruited through their primary treating physician for diabetes, all the patients were advised to document events such as hospitalisation, emergency room visits, and hypoglycaemic and hyperglycaemic events. A third limitation is the assumption of patients' adherence to their medications.

In conclusion, early initiation of second-line management would improve glycaemic control and reduce complications, especially if the targeted levels for both blood sugar and HbA1c were achieved. Hypoglycaemia should not be a restricting factor when initiating second-line therapy, especially with better patient education and closed-home glucose monitoring. Improved diabetes control was reflected in improved quality of life in terms of the Mental and Physical Component Scores. Individualised treatment intensification plans should be developed by concerned physicians, who should weigh the benefits of good glycaemic control against the risk of hypoglycaemia, especially in elderly patients.

Despite the low incidence rate of diabetes complications, this rate is still critical for a country such as Saudi Arabia which is facing a type 2 diabetes epidemic, especially when no active prevention programmes have been adopted or launched. The annual incidence of these complications could affect healthcare.

The study findings serve as a basis for health planners and insurance companies to improve healthcare and reduce the financial impact of the disease. Even though the incidence of hypoglycaemia among patients with type 2 diabetes is low, this complication should not be neglected. Healthcare providers should advocate for patient-centred diabetes care by adopting safe and effective treatment strategies that minimise patient burden, improve quality of life, and reduce risks of both immediate and long-term complications. Addressing hypoglycaemia—by leveraging advances in diabetes technologies, patient engagement and multidisciplinary team-based care—is an essential approach.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the relevant institutional review boards of the selected hospitals namely: Institutional Review Board, College of Medicine, King Saud University, for the university hospitals (IRB# E-14-1229), General Administration for research and studies research ethics committee at Ministry of Health, the institutional review board at International Medical Center and the human research ethics committee of the Saudi German Hospital. All the study subjects signed informed consent forms. The protocol complies with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice.

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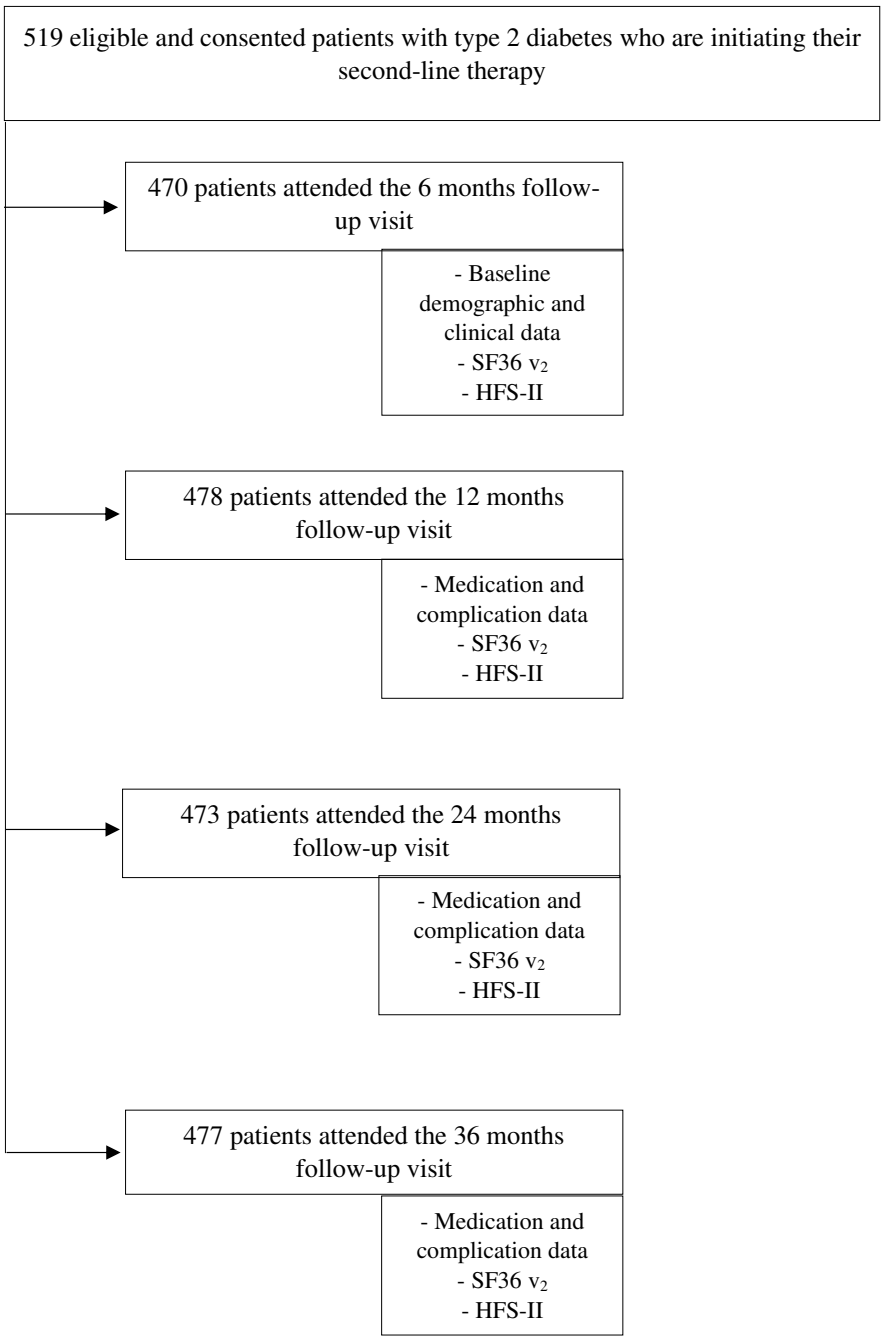
Appendix 1. Study Flowchart



Appendix 2. Baseline characteristics of the studied Saudi cohort of DISCOVER study.

Variables	**Baseline data for 519 patients**
Mean age (years) (SD)	52.4 (±11.0)
Gender n(%)	
Males	284 (54.7)
Females	235 (45.3)
Any Macrovascular Disease n (%)	57 (11)
Coronary artery disease n (%)	38 (7.3)
Myocardial infarction n (%)	8 (1.5)
Angina n (%)	12 (2.3%)
Atrial fibrillation event	4 (0.8)
Heart failure n (%)	8 (1.5)
Peripheral vascular disease n (%)	0 (0)
Stroke n (%)	12 (2.3)
TIA n (%)	6(1.2)
Chronic Kidney Disease n (%)	7 (4)
Albuminuria	16 (3.1)
Retinopathy n (%)	22 (4.3
Peripheral neuropathy n (%)	59 (11)
Autonomic neuropathy n(%)	35 (6.8)
Hypertension n (%)	196 (37.8)
Hyperlipidemia n (%)	226 (43.5)
First-line hypoglycemic medications n (%)	
Biguanides	463 (89.2)
Sulfonylurea	246 (47.5)
DPP-4 inhibitors	48 (9.3)
Thiazolidinedione/ glitazones	2 (0.4)
Second-line hypoglycemic medications n (%)	
Biguanides	475 (91.5)
Sulfonylurea	232 (51.2)
DPP-4 inhibitors	384 (73.9)
Thiazolidinedione/ glitazones	24 (4.6)
Alph-glucosidase inhibitors	5 (1)
Meglitinides/Glinides	3 (0.6)
Incretin mimetics/GLP1	4 (0.8)
Insulin	46 (8.9)

Appendix 3. Mean ± SD and Median (IQR) for clinical, metabolic, and biochemical markers at baseline and during the follow-up period

Parameter	Follow-up Period					P value
	Baseline (n = 519)	**6 months (n = 470)**	**12 months (n = 478)**	**24 months (n = 473)**	**36 months (n = 477)**	
Anthropometric parameters						
Weight (kg)	83.4 ± 17.6 82.0 (71.0, 93.0)	83.3 ± 17.6 81.0 (71.0, 93.0)	84.2 ± 17.5 83.0 (72.0, 94.0)	82.7 ± 16.9 81.0 (71.0, 91.0)	83.2 ± 16.8 82.0 (70.0, 92.0)	0.760
Height (cm)	162.2 ± 9.6 162.0 (155.0, 170.0)	162.0 ± 9.3 161.0 (155.0, 169.0)	162.2 ± 9.3 162.0 (155.0, 169.0)	161.7 ± 9.0 160.5 (155.0, 168.0)	161.9 ± 9.2 161.0 (155.0, 169.0)	0.0942
BMI (kg/m^2)	31.9 ± 6.6 31.1 (27.5, 35.3)	31.9 ± 6.7 31.1 (27.3, 35.6)	32.1 ± 6.6 31.5 (27.8, 35.6)	32.0 ± 6.6 31.5 (27.4, 35.1)	32.2 ± 6.6 32.0 (27.7, 35.4)	0.948
Waist circumference (cm)	104.1 ± 14.4 104.0 (95.0, 112.0)	103.2 ± 14.1 103.0 (96.0, 111.0)	105.2 ± 13.8 104.0 (97.0, 114.0)	104.1 ± 12.5 103.0 (96.0, 110.5)	107.2 ± 10.3 108.0 (105.0, 116.0)	0.0002
Clinical paraments **Pulse rate at rest (/min)**	82.0 ± 10.8 81.0 (75.0, 88.0)	80.7 ± 10.2 80.0 (74.0, 88.0)	80.1 ± 10.5 80.0 (72.0, 87.0)	79.8 ± 10.3 80.0 (72.0, 86.0)	81.0 ± 9.8 80.0 (76.0, 87.5)	0.1274
Systolic BP (mmHg)	133.7 ± 17.5 132.0 (122.0, 143.0)	132.4 ± 15.8 131.5 (120.0, 141.0)	132.5 ± 15.6 133.0 (120.0, 142.0)	132.0 ± 16.2 130.0 (120.0, 140.0)	133.0 ± 16.0 130.0 (120.0, 141.0)	0.3482
Diastolic BP (mmHg)	79.2 ± 10.9 80.0 (72.0, 87.0)	78.4 ± 9.9 80.0 (70.0, 85.0)	78.0 ± 10.1 78.0 (70.0, 86.0)	77.1 ± 10.5 80.0 (70.0, 85.0)	77.5 ± 9.8 80.0 (70.0, 83.0)	0.0025
Metabolic markers **HbA1C %** **(mmol/mol)**	8.8 ± 1.7 (73) 8.6 (71) 7.6 (60), 9.8 (84)	7.8 ± 1.4 (62) 7.5 (59) 6.8 (51), 8.4 (68)	8.0 ± 1.5 (64) 7.7 (61) 6.9 (52), 8.8 (73)	8.1 ± 1.7 (65) 7.7 (61) 6.9 (52), 9.1 (76)	8.2 ± 1.7 (66) 7.8 (62) 7.0 (53), 9.1 (76)	< 0.0001
Fasting Glucose (mg/dL)	185.9 ± 65.5 169.4 (135.1, 225.2)	152.3 ± 50.0 140.5 (119.1, 173.0)	154.6 ± 50.0 146.0 (117.1, 179.0)	152.2 ± 55.4 136.4 (117.1, 174.8)	146.3 ± 55.1 137.5 (107.9, 167.6)	< 0.0001
Random Glucose (mg/dL)	227.0 ± 79.2 215.3 (173.0, 278.0)	199.1 ± 67.2 191.0 (151.0, 225.2)	215.7 ± 70.7 203.5 (167.6, 251.0)	241.1 ± 86.4 234.2 (183.0, 298.0)	205.6 ± 72.8 192.5 (155.0, 240.0)	< 0.0001
Post Prandial Glucose (mg/dL)	256.2 ± 78.5 252.1 (200.9, 289.5)	208.6 ± 70.9 189.0 (160.4, 254.1)	197.0 ± 63.5 180.1 (153.2, 235.0)	206.5 ± 68.5 200.0 (160.0, 231.0)	167.3 ± 31.0 161.1 (144.0, 189.0)	< 0.0001

Parameter	Follow-up Period					P value
	Baseline (n = 519)	**6 months (n = 470)**	**12 months (n = 478)**	**24 months (n = 473)**	**36 months (n = 477)**	
Lipid profile **Total Cholesterol (mg/dL)**	190.0 ± 52.7 184.0 (160.2, 210.0)	175.8 ± 40.8 169.9 (150.0, 196.0)	177.0 ± 42.9 170.3 (150.6, 199.6)	174.6 ± 35.6 172.2 (152.9, 197.7)	177.6 ± 40.5 176.0 (151.4, 201.2)	0.0001
HDL (mg/dL)	44.0 ± 11.5 42.7 (36.1, 52.1)	44.4 ± 12.5 42.1 (36.7, 49.0)	44.3 ± 11.1 43.1 (37.5, 50.0)	45.6 ± 10.9 44.0 (37.0, 53.0)	47.0 ± 11.0 45.9 (39.8, 54.8)	< 0.0001
LDL (mg/dL)	112.0 ± 35.7 112.4 (90.3, 134.0)	101.6 ± 33.6 101.4 (81.1, 119.7)	103.2 ± 33.2 99.2 (84.2, 121.0)	101.1 ± 29.8 100.8 (81.1, 120.0)	106.2 ± 35.8 101.2 (83.4, 130.0)	0.0083
Triglycerides (mg/dL)	190.7 ± 160.5 152.0 (110.0, 212.4)	166.7 ± 121.2 133.6 (106.0, 185.0)	172.0 ± 115.9 144.2 (107.1, 200.0)	171.3 ± 117.3 145.0 (104.4, 204.4)	153.7 ± 82.9 134.2 (108.8, 181.4)	< 0.0001
Renal function **Albumin/Creatinine ratio (mg/g)**	45.3 ± 62.6 18.4 (8.0, 59.0)	28.8 ± 44.3 8.4 (5.9, 34.0)	63.6 ± 139.0 9.8 (6.4, 31.7)	89.9 ± 252.6 15.2 (2.9, 34.5)	83.5 ± 134.8 37.7 (9.0, 62.0)	< 0.0001
Serum Creatinine	1.0 ± 1.2 0.8 (0.7, 1.0)	1.2 ± 1.5 0.8 (0.7, 1.0)	1.3 ± 1.8 0.8 (0.7, 1.0)	2.1 ± 2.7 0.9 (0.7, 1.2)	1.9 ± 2.5 0.8 (0.7, 1.2)	< 0.0001
Uric acid (mg/dL)	4.7 ± 1.3 4.7 (3.7, 5.6)	5.1 ± 1.6 4.9 (4.0, 5.9)	5.1 ± 1.5 5.0 (4.1, 5.6)	4.7 ± 1.9 4.7 (4.0, 5.5)	4.8 ± 1.2 4.6 (4.0, 5.3)	0.0001
Liver function **Serum Albumin (g/dL)**	4.2 ± 0.4 4.2 (4.0, 4.5)	4.2 ± 0.5 4.2 (4.0, 4.5)	4.2 ± 0.7 4.2 (3.9, 4.4)	4.0 ± 0.5 4.1 (3.8, 4.4)	4.1 ± 0.4 4.1 (3.8, 4.5)	0.0001
Alanine transaminase (ALT, IU/L)	34.1 ± 21.9 28.0 (19.0, 41.0)	31.0 ± 19.5 26.0 (19.1, 37.0)	29.9 ± 15.7 27.0 (18.9, 38.5)	30.7 ± 21.0 25.0 (17.2, 34.5)	31.6 ± 18.4 26.5 (18.0, 43.0)	0.1207
Aspartate transaminase (AST, IU/L)	22.1 ± 13.0 18.7 (15.0, 25.0)	21.4 ± 11.6 18.5 (15.0, 24.0)	23.0 ± 18.0 18.5 (15.0, 23.4)	21.7 ± 10.7 19.0 (15.0, 24.0)	21.1 ± 9.2 20.0 (15.7, 23.0)	0.1648
Gamma Glutamyl transpeptidase (GGT, IU/L)	46.2 ± 40.1 35.0 (22.0, 57.5)	40.0 ± 27.0 33.0 (23.0, 46.0)	48.1 ± 45.5 36.0 (23.0, 60.0)	55.9 ± 73.9 35.0 (27.0, 50.0)	45.2 ± 95.3 32.0 (20.3, 39.0)	0.8268
CBC **White Blood Cell Count**	8.1 ± 2.3 7.7 (6.5, 9.4)	7.8 ± 2.2 7.9 (6.2, 8.9)	8.3 ± 2.5 8.1 (6.4, 9.6)	8.0 ± 2.5 7.7 (6.1, 9.5)	7.8 ± 3.3 7.2 (5.8, 8.7)	0.942
Hemoglobin	13.5 ± 1.7 13.6 (12.4, 14.6)	13.5 ± 1.8 13.6 (12.5, 14.8)	13.1 ± 2.0 13.3 (12.1, 14.6)	13.4 ± 1.9 13.6 (12.1, 14.8)	13.8 ± 1.6 14.0 (12.4, 15.0)	< 0.0001
Hematocrit	41.6 ± 5.0 41.4 (38.2, 44.9)	41.9 ± 5.2 41.8 (38.9, 45.8)	41.8 ± 5.2 42.5 (37.7, 44.9)	40.9 ± 4.9 41.9 (37.4, 44.5)	41.8 ± 4.6 41.7 (39.1, 45.4)	0.0138
Platelets	268.0 ± 72.7 257.5 (215.0, 313.0)	251.3 ± 55.1 238.0 (211.0, 287.0)	268.4 ± 75.4 257.0 (203.0, 313.0)	291.4 ± 61.7 295.0 (253.0, 333.0)	264.1 ± 79.1 261.5 (214.5, 303.5)	0.4058

Appendix 4. The crude prevalence and calculated incidence of micro and macro angiopathy for the studied cohort since the previous follow-up visit.

Clinical condition	Follow-up period				INCIDENCE (/1000 patient-years)
	6 months, n = 470 Number (%)	12 months, n = 478 Number (%)	24 months, n = 473 Number (%)	36 months, n = 477 Number (%)	
Albuminuria	10 (2.7)	8 (2.2)	2 (0.5)	11 (3.2)	31 (22.71) [14.75-30.81]
Retinopathy Events	14 (4.9)	15 (4.9)	18 (6.0)	21 (6.5)	68 (47.00) [36.98-60.37]
Maculopathy	0	1 (0.2)	2 (0.5)	3 (0.6)	6 (4.20) [1.54-9.14]56
Non-proliferative	13 (2.8)	14 (2.9)	12 (2.5)	17 (3.6)	(39.22) [29.62-50.92]
Proliferative	1 (0.2)	0	4 (0.9)	1 (0.2)	6 (4.20) [1.54-9.14]
Peripheral neuropathy Events	42 (9.2)	46 (10.0)	56 (12.2)	54 (11.7)	88 (61.62) [49.42-75.92]
Autonomic neuropathy	2 (0.5)	3 (0.7)	6 (1.4)	7 (1.6)	18 (12.61) [7.47-19.92]
Erectile disfunction	10 (4.2)	13 (5.1)	17 (7.0)	17 (7.1)	57 (39.92) [30.23-51.72]
Outpatient neuropathy test	2 (0.5)	4 (0.9)	1 (0.2)	6 (1.4)	13 (9.10) [4.84-15.86]
Hypertension since last follow-up	70 (15.2)	68 (14.5)	109 (23.2)	144 (30.3)	74 (51.82) [40.69-65.06]
Hyperlipidemia since last follow-up	63 (14.5)	63 (14.4)	135 (29.4)	177 (38.0)	114 (79.83) [65.85-95.90]
Thyroid Disease Events	21 (4.8)	17 (3.8)	28 (6.1)	30 (6.4)	96 (67.23) [54.45-82.10]
Hyperthyroidism	0	0	1 (0.2)	3 (0.6)	4 (2.80) [0.76- 7.17]
Hypothyroidism	21 (4.8)	16 (3.3)	27 (5.7)	26 (5.5)	90 (63.03) [50.68-77.47]
Arthritis event	5 (1.1)	9 (2.0)	11 (2.4)	10 (2.1)	35 (24.51) [17.07-34.09]
Cancer Events	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)	6 (4.20) [1.54-9.14]
Cancer site Breast	0	0	1 (0.2)	0	1 (0.70) [0.017-3.90]
Colorectal	0	1 (0.2)	1 (0.2)	0	2 (1.40) [0.17-5.05]
Other	1 (0.20)	0	0	2 (0.5)	3 (2.10) [0.43-6.14]
Urinary tract infection Events	10 (2.2)	3 (0.6)	7 (1.5)	10 (2.1)	30 (21.01) [14.17-29.99]
Genital infection events	2 (0.4)	0	4 (0.9)	3 (0.6)	9 (6.30) [2.88-11.96]
Respiratory disease	2 (0.5)	3 (0.7)	4 (0.9)	9 (2.1)	18 (12.61) [7.47-19.92]
Depression event	1 (0.2)	2 (0.5)	3 (0.7)	5 (1.1)	11 (7.70) [3.84-13.78]

Appendix 5. The annual incidence of clinical events related to various conditions during the three-year follow-up period