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Treatment Patterns and Associated Clinical Outcomes in Type 2 Diabetes Patients Initiating Second-Line Glucose-Lowering Therapy: Interim Analysis of Baseline Data from Turkey Arm of the Global DISCOVER Study

İkinci-Sıra Glukoz Düşürücü Tedaviye Başlanan Tip 2 Diyabet Hastalarında Tedavi Uygulamaları ve İlişkili Klinik Sonuçlar: Global DISCOVER Çalışması Türkiye Kolu Başlangıç Verilerinin Ara Analizi

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Abstract

Objective: To evaluate the treatment patterns and associated clinical outcomes in Type 2 diabetes (T2D) patients initiating a second-line glucose-lowering therapy. **Material and Methods:** This paper presents a preliminary subgroup analysis of the baseline data collected from 536 patients [mean (standard deviation) age: 55.1 (10.0) years, 50.2% were males] in the Turkey arm of global observational DISCOVER study among T2D patients initiating second-line glucose-lowering therapy. Patient demographics, disease (duration, complications) and treatment (type of regimens, modifications) characteristics, hemoglobin A1c (HbA1c), low-density lipoprotein-cholesterol (LDL-C), and systolic blood pressure (BP) target achievement rates and the patient-reported outcomes were recorded at the initiation of second-line therapy. **Results:** Overall, 11.7% of patients were HbA1c target of <7% at baseline, 62.5% were systolic BP target of <140 mmHg and 21.2% were LDL-C target of <100 mg/dL. Major and minor hypoglycemic events were noted in 5.5% and 10.7% of patients, while macro and microvascular complications in 17.2% and 20.1% of patients, respectively. Metformin monotherapy (47.9%) and metformin+sulfonylurea combination (22.6%) were the two most common first-line therapies. However, insulin (32.3%) was the most commonly prescribed second-line agent. Lifestyle assessment revealed a healthy lifestyle in 50.7% of patients. **Conclusion:** Our finding revealed a failure to achieve HbA1c, LDL-C, and systolic BP targets and a high rate of diabetes-related complications before initiation of second-line therapy in a significant proportion of Turkish T2D patients. Thus, emphasizing a need for more aggressive risk factor screening and modification at early disease stages and earlier treatment intensification among T2D patients.

Keywords: Type 2 diabetes; first-line therapy; second-line therapy; metformin; insulin; complications; glycemic control; dyslipidemia; patient-reported omes

Özet

Amaç: İkinci-sıra glukoz düşürücü tedaviye başlanan Tip 2 diyabet (T2D) hastalarında, tedavi uygulamaları ve ilişkili klinik sonuçların değerlendirilmesidir. **Gereç ve Yöntemler:** Bu makalede, ikinci-sıra glukoz düşürücü tedaviye başlanan T2D hastaları ile yürütülen küresel gözlemsel DISCOVER çalışması Türkiye kolunda yer alan 536 hastanın [ortalama (standart sapma) yaş: 55,1 (10,0) yıl, %50,2 erkek hasta], başlangıç verilerine yönelik ara analiz sunulmaktadır. Hastaların demografik özellikleri, hastalık özellikleri (süre, komplikasyonlar) ve tedavilerin (uygulanan rejimler, değişimler) yanı sıra hemoglobin A1c (HbA1c), düşük yoğunluklu lipoprotein-kolesterol [low-density lipoprotein-cholesterol (LDL-C)] ve sistolik kan basıncı (KB) hedeflerine ulaşan hasta yüzdesi ve hasta bildirimli sonuçlar, ikinci-sıra tedavi başlangıcında kaydedildi. **Bulgular:** Toplamda hastaların %11,7'sinde HbA1c (<%7), %62,5'inde KB (<140 mmHg) ve %21,2'sinde LDL-C (<100 mg/dL) hedef değerlerde bulundu. Majör ve minör hipoglisemik olaylar hastaların sırasıyla %5,5 ve %10,7'sinde gözlenirken; makrovasküler ve mikrovasküler komplikasyon oranları sırasıyla %17,2 ve %20,1 olarak saptandı. Metformin monoterapisi (%47,9) ve metformin+sülfonilüre kombinasyonu (%22,6) en yaygın 2 ilk-sıra tedavi seçeneği olup, insülin (%32,3) en sık reçetelenen ikinci-sıra ajandı. Hastaların %50,7'sinde, sağlıklı yaşam biçimi varlığı tespit edildi. **Sonuç:** Sonuç olarak bulgularımız, Türk T2D hastalarında ikinci-sıra tedaviye geçiş öncesi HbA1c, LDL-C ve sistolik KB hedeflerinin, hastaların önemli bir kısmında karşılanamadığına ve mikrovasküler ve makrovasküler komplikasyon oranlarının yüksekliğine işaret etmektedir. Bu doğrultuda, erken evre hastalık döneminde risk faktörü tarama ve modifikasyonları açısından daha sıkı bir stratejiye ve daha erken dönemde tedavi yoğunlaştırmasına gereksinim olduğunu vurgulamaktadır.

Anahtar kelimeler: Tip 2 diyabet; ilk-sıra tedavi, ikinci-sıra tedavi; metformin; insülin; komplikasyonlar; glisemik kontrol; dislipidemi; hasta bildirimli sonuçlar

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Introduction

Global estimates indicate a rapidly increasing prevalence of diabetes worldwide, with about 700 million people estimated to be affected by the disease, primarily by Type 2 diabetes (T2D), by 2045 (1). According to 1997-1998 data from the Turkish Diabetes Prevalence Study (2) and Turkish Diabetes Hypertension Obesity and Endocrine Disease Prevalence Study (3) conducted 12 years later, an increase from 7.2% to 16.5% (7.5% new diagnosis, 13.7% in the age-adjusted population) in the prevalence of T2D (≥20 years of age) was noted in Turkey.

Diabetes is responsible for 10.7% of global all-cause mortality in the age group of 20-79 years, with diabetes-related complications the leading cause of disease-related premature deaths (1). Achievement in optimal glycemic control is of critical importance in T2D, given a causal link between dysglycemia and the development of micro/macrovascular complications (4-7).

According to current guidelines, a standard treatment for T2D involves metformin therapy plus lifestyle changes and treatment intensification in case of failure to achieve glycemic control (8). Albeit atherosclerotic cardiovascular disease (CVD)-based treatment recommendations per guidelines were not evident at the time of the study enrollment. Currently, treatment intensification for patients with clinical CVD is recommended to be based on the addition of a sodium-glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit (8). Moreover, T2D is a risk factor for CVD due to the high prevalence of concomitant modifiable cardiovascular risk factors such as obesity, hypertension, and dyslipidemia (9,10). Therefore, the management of T2D is considered a complex and multifactorial process that should address co-morbidities besides glycemic control (9,11-14).

Despite the potential association of different prescribing patterns with differences in disease control, diabetes-related complication, quality of life, healthcare resource utilization, limited data are available on the efficacy and clinical outcomes of treatment options available for use following the failure of first-line treatment in T2D in the clinical practice (7,14). DISCOVER is a global, prospective, observational study designed to address this gap by providing a comprehensive overview of the real-world data on current practice patterns after initiation of second-line therapy in treating patients with T2D (14). The primary objective of the DISCOVER study program was to describe the disease management patterns in patients with T2D initiating a second-line glucose-lowering therapy after failure of the first-line oral treatment concerning potential determinants (patient, physician, and healthcare system-related) and outcomes (glycemic parameters, complications, healthcare resource utilization, patient-reported outcomes) of treatment patterns (14).

The present study, representing the Turkey arm of a multi-national, non-interventional prospective DISCOVER study, described the preliminary baseline data on patient profile, diabetes-related complications, glycemic control, treatment patterns, and patients' reported clinical outcomes in T2D patients initiating a second-line glucose-lowering therapy.

Material and Methods

Study population

DISCOVER is a global, prospective, observational study (ClinicalTrials.gov Identifier: NCT02322762) involving 14,668 patients with T2D from 37 countries across 6 regions initiated with second-line glucose-lowering therapy (add-on or switching) following first-line oral treatment (mono, dual or triple) (14,15). As per the study protocol, the study was estimated to last from 2014 to 2019, including the patient enrollment (December 2014-June 2016) phase and the subsequent 3-year follow-up period. The study was based on the data collected at baseline (onset of second-line therapy) and 3-year follow-up (6, 12, 24, and 36 months after onset of second-line therapy) periods (14) (Figure 1). This paper presents a preliminary sub-group analysis of baseline data collected from 536 patients in Turkey.

Diagnosis of T2D, age ≥18 years, and initiated with second-line therapy (add-on or switching) were the study's inclusion criteria. Diagnosis of T1D, pregnancy, injectable agent (i.e., insulin or a GLP-1-receptor agonist) as first-line therapy, first-line treatment

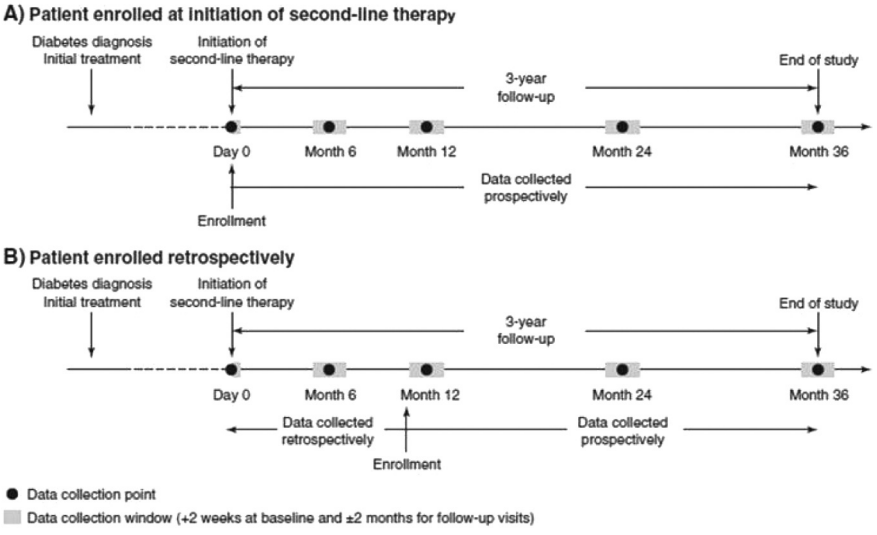

Figure 1. Study timelines. A) Patients enrolled on the day of initiation of second-line glucose-lowering therapy. B) Patients enrolled retrospectively (after initiation of second-line glucose-lowering therapy).

with herbal remedies/natural medicine alone, and ongoing dialysis or previous renal transplantation were the exclusion criteria. Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by The Erciyes University Faculty of Medicine Ethics Committee approved the study (Date of approval: 19/06/2015; reference number/protocol no: 2015/295).

Data collection

Baseline data included socio-demographic characteristics of patients, diabetes history, rate of hemoglobin A1c (HbA1c), low-density lipoprotein-cholesterol (LDL-C) and systolic blood pressure (BP) target achievement, hypoglycemic events and macro/microvascular complications at baseline, co-morbid disorders and concomitant treatments, anthropometrics and vital signs, laboratory findings, diabetes treatment (first-line and second-line therapies, reasons for treatment modifications), target goals set for HbA1c, fasting, casual and post-prandial plasma glucose at the initiation of second-line therapy, and the patient-reported outcomes.

All patients underwent routine clinical assessments and received standard medical care, as determined by the treating physician. Complications were according to the judgment of the investigators. Hypoglycemia was based on patient recall within the past month for minor events and since the last follow-up for major events.

Patient-reported outcomes

Patient-reported outcomes at baseline were collected via four self-administered questionnaires, including the 36-item Short-form Health Survey version 2 (SF-36v2) (16), the 33-item revised Hypoglycemia Fear Survey (HFS-II) (17), a seven-item lifestyles questionnaire to assess (18), and a two-item questionnaire on avoidance of healthcare and/or medication due to the cost.

SF-36 measured the health-related quality of life across eight domains, including physical functioning, physical and emotional role limitations, body pain, general health perception, vitality, social functioning, and mental health (16,19). Total scores ranged from 0 to 100, with higher scores indicating better health status (16,19). The two summary scales include the physical component summary and mental component summary (16,19).

HFS-II is a survey with two subscales to assess behaviors (HFS-B, 15 items) and worries (HFS-W, 18 items) relating to fear of hypoglycemia using a five-point Likert scale from 0 (never) to 4 (always).

The total score ranged from 0 to 132, and higher scores indicate increased fear of hypoglycemia (17, 20).

Statistical Analysis

All statistical analyses were performed using the SAS statistical software system (SAS Institute, Inc., Cary, NC). Descriptive statistics were used to summarize the study parameters. Data were expressed as "mean (standard deviation)", median [interquartile range (IQR)], and percent (%) where appropriate.

Results

Socio-demographic and clinical characteristics of patients

Overall, 50.2% of the cohort was male, with a mean±standard deviation age of 55.1±10.0 years. Higher education was noted in 16.8% of patients, while 45.2% were unemployed and 22.8% retired. Majority of patients were either non-smoker (60.0%) or ex-smoker (22.4%) and lifetime abstainer (78.6%) (Table 1).
Co-morbidity was noted in 27.6% of patients, while anti-hypertensive drugs (38.8%), lipid-lowering drugs (28.0%), and anti-platelet drugs (18.8%) were the most commonly prescribed concomitant medications (Table 1).

Anthropometrics and vital signs, laboratory findings

Mean body mass index (BMI) was 31.7±6.4 kg/m2, while systolic and diastolic BP values were 131.6±15.9 mmHg and 81.0±9.9 mmHg, respectively. Median (IQR) levels of LDL-C, total cholesterol and triglyceride were 126.0 (104.0-153.0) mg/dL, 204.0 (175.0-231.0) mg/dL and 172.0 (130.0-254.0) mg/dL, respectively (Table 2).

Diabetes history, glycemic control, hypoglycemic events, and diabetes-related complications at baseline

The median diabetes duration was 70.8 months (range, 35.8 to 110.5 months). Overall, 63.4% of patients were using glucose monitoring, and 70.8% had diabetes education in the past year (Table 3).
Mean (standard deviation) values for HbA1c was 8.8±1.8%, while HbA1c level was <7.0% in 11.7% of patients and ≥9% in 40.6% of patients. The prevalence of major and minor hypoglycemic events were 5.5% and 10.7%, respectively. Overall, 17.2% of patients had any macrovascular disease (coronary artery disease in 12.9%), and 20.1% had microvascular disease (peripheral neuropathy in 11.2%) at baseline (Table 3).

First-line and second-line therapies

Metformin monotherapy (47.9%) and metformin+sulfonylurea combination (22.6%) were the most common first-line therapies. Insulin was initiated in 32.3% of patients (7.7% in global and 10.1% in European cohort) as the most commonly prescribed second-line agent, followed by metformin+dipeptidyl peptidase-4 (DPP-4) inhibitor (20.1%) (Table 4, Figure 2).

Table 1. Socio-demographic characteristics of patients.

Age (year), mean (SD, IQR)	55.1 (10.0, 48.2-61.2)
(n=536) Gender, n (%) (n=536)	
Male	269 (50.2)
Female	267 (49.8)
Education level, n (%) (n=452)	
No formal education	37 (8.2)
Primary (1-6 years of education)	181 (40.0)
Secondary (7-13 years of education)	158 (35.0)
University/higher education (13+ years)	76 (16.8)
Main working status, n (%) (n=469)	
Employed	149 (31.8)
Unemployed	212 (45.2)
Retired	107 (22.8)
Tobacco smoking, n (%) (n=495)	
Non-smoker	297 (60.0)
Ex-smoker	111 (22.4)
Current smoker	87 (17.6)
Alcohol drinking, n (%) (n=490)	
Lifetime abstainer	385 (78.6)
Former drinker	71 (14.5)
Drinker	34 (6.9)
Co-morbidity, n (%)	148 (27.6)
Concomitant medications, n (%)	
Anti-hypertensive drugs	208 (38.8)
Lipid-lowering drugs	150 (28.0)
Anti-platelet drugs	101 (18.8)
Anticoagulant drugs	8 (1.5)
Antidepressants	27 (5.0)
Non-steroidal anti-inflammatory drugs	24 (4.5)
Proton-pump inhibitor	69 (12.9)
Thyroid replacement drugs	35 (6.5)

SD: Standard deviation; IQR: Interquartile range.

Table 2. Anthropometrics and vital signs, laboratory findings.

Anthropometrics	n	Mean±SD
Weight (kg)	471	86.5±17.4
Height (cm)	472	165.4±9.8
BMI (kg/m^2)	471	31.7±6.4
Vital signs		**Mean (SD)**
Systolic blood pressure (mmHg)	419	131.6±15.9
Diastolic (mmHg)	419	81.0±9.9
Pulse rate at rest (bpm) (n=371)	371	81.9±8.4
Laboratory findings		**Median (IQR)**
WBC (x10^9/L)	412	8.2 (6.9-9.7)
Hemoglobin (g/dL)	413	14.0 (12.8-15.1)
Hematocrit (%)	410	42.6 (39.4-45.5)
Platelets (x10^9/L)	412	266.5 (225.0-313.0)
HDL (mg/dL)	391	42.0 (36.0-50.0)
LDL (mg/dL)	425	126.0 (104.0-153.0)
Total cholesterol (mg/dL)	393	204.0 (175.0-231.0)
Triglycerides (mg/dL)	415	172.0 (130.0-254.0)
Serum creatinine	436	0.8 (0.7-0.9)
ALT (IU/L)	449	25.0 (18.0-40.0)
AST (IU/L)	422	21.0 (16.1-29.5)

SD: Standard deviation; BMI: Body mass index; IQR: Interquartile range; WBC: White blood cell count; HDL: High-density lipoprotein, LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Metformin was the most commonly used first-line agent either as a monotherapy (47.9%) or combination therapy (47.0%). However, metfor min was discontinued at the initiation of second-line treatment in 3.9% of patients (Table 4).

Setting and reasons for changing first-line therapy at baseline

The decision to change first-line therapy was made in an outpatient setting in most patients (92.4%). Lack of efficacy (90.9%) was the most common reason for changing first-line therapy, followed by weight gain (11.6%). Selection of the second-line therapy was based on expected efficacy in most cases (75.9%), followed by tolerability (27.1%) and advantages regarding weight control (20.9%) and hypoglycemia (13.1%) (Table 5).

HbA1c, LDL-C and systolic BP target achievement at baseline

Overall, 11.7% of patients were at HbA1c target of <7% (17.6% in global, 18.7% in European cohort), 62.5% at systolic BP target of <140 mmHg (67.7% in global, 56.5% in European cohort) and 21.2% at LDL-C target of <100 mg/dL (43.5% in global, 43.2% in European cohort) (Table 6, Figure 3).

Considering ≤65 vs. >65 year age groups, rates for HbA1c (<7%), systolic BP (<140

Table 3. Diabetes history, glycemic control, hypoglycemic events, and macro/micro-vascular complications at baseline.

Diabetes history	
Duration of diabetes (month), median (IQR)	70.8 (35.8-110.5)
Use of glucose monitoring, n (%) (n=415)	263 (63.4)
Education on diabetes in the past 1 year, n (%) (n=465)	329 (70.8)
Glycemic control	
HbA1c (%), mean±SD (IQR) (n=497) HbA1c category, n (%)	8.8±1.8 (7.5-9.7)
<7.0%	58 (11.7)
7.0%-<8.0%	118 (23.7)
8.0%-<9.0%	119 (23.9)
≥9%	202 (40.6)
Fasting glucose (mg/dL) mean±SD (n=487)	187.0±63.0
Post-prandial glucose (mg/dL), mean±SD (n=124)	281.5±81.1
Hypoglycemic events, n (%) (n=506)	
Major hypoglycemic events	28 (5.5)
Minor hypoglycemic events	54 (10.7)
Macrovascular complications, n (%)	
Any macrovascular disease	92 (17.2)
Coronary artery disease	69 (12.9)
Angina	22 (4.1)
Myocardial infarction	17 (3.2)
Heart failure	11 (2.1)
Diabetic foot	10 (1.9)
Atrial fibrillation	7 (1.3)
Stroke	6 (1.1)
Severe valve disease	5 (0.9)
Peripheral artery disease	4 (0.7)
Transient ischemic attack	2 (0.4)
Microvascular complications, n (%)	
Any microvascular disease	108 (20.1)
Peripheral neuropathy	60 (11.2)
Retinopathy	33 (6.2)
Erectile dysfunction	21 (3.9)
Chronic kidney disease	11 (2.1)
Albuminuria	8 (1.5)
Autonomic neuropathy	6 (1.1)

IQR: Interquartile range; HbA1c: Hemoglobin A1c; SD: Standard deviation.

Table 4. First-line and second-line glucose-lowering therapies.

First-line therapy		
Metformin monotherapy		257 (47.9)
Sulfonylurea monotherapy		11 (2.1)
DPP4 monotherapy		2 (0.4)
Other monotherapy		6 (1.1)
Metformin+sulfonylurea		121 (22.6)
Metformin+DPP4 inhibitor		32 (6.0)
Metformin+other		44 (8.2)
Other dual combinations		5 (0.9)
Metformin+sulfonylurea+DPP4 inhibitor		20 (3.7)
Metformin+sulfonylurea+thiazolidinedione		15 (2.8)
Other triple combinations		21 (3.9)
4 or 4+therapy		2 (0.4)
Second-line therapy		
Metformin monotherapy		1 (0.2)
Sulfonylurea monotherapy		1 (0.2)
DPP4 monotherapy		2 (0.4)
Other monotherapy		3 (0.6)
Metformin+sulfonylurea		45 (8.4)
Metformin+DPP4 inhibitor		108 (20.1)
Metformin+other		61 (11.4)
Sulfonylurea+thiazolidinedione		3 (0.6)
Other dual combinations		11 (2.1)
Metformin+sulfonylurea+DPP4 inhibitor		65 (12.1)
Metformin+sulfonylurea+thiazolidinedione		12 (2.2)
Metformin+sulfonylurea+alpha glucosidase		1 (0.2)
Other triple combinations		40 (7.5)
4 or 4+therapy		10 (1.9)
Insulin (May also receive oral therapy)		173 (32.3)
Metformin data		
First-line metformin, n (%)	None	25 (4.7)
	Monotherapy	257 (47.9)
	Combination	252 (47.0)
Metformin discontinuation at second-line therapy, n (%)		20 (3.9)

DPP4: Dipeptidyl peptidase-4.

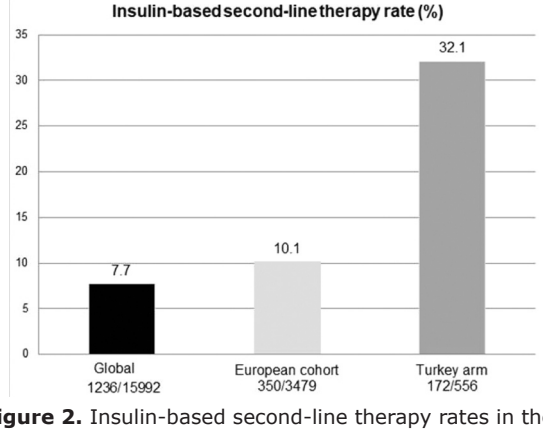

Figure 2. Insulin-based second-line therapy rates in the global DISCOVER population, European cohort, and Turkey arm.

Table 5. Reasons for changing first-line therapy and choosing a second-line treatment at baseline.

Reasons for changing first-line therapy	**n (%)**
Lack of efficacy	487 (90.9)
Hypoglycemic event	17 (3.2)
Weight gain	62 (11.6)
Side effect	34 (6.3)
Developed acute disease	16 (3.0)
Developed chronic disease	14 (2.6)
Affordability	0 (0.0)
Inability to self-administer	0 (0.0)
Patient request	16 (3.0)
Poor adherence	5 (0.9)
Patient convenience	7 (1.3)
Prescriber access reasons	1 (0.2)
Drug interaction	0 (0.0)
Physician preference	46 (8.6)
Reasons for choosing a second-line therapyn (%)	
Efficacy	407 (75.9)
Tolerability	145 (27.1)
Weight	112 (20.9)
Hypoglycemia	70 (13.1)
Patient request	49 (9.1)
Convenience	36 (6.7)
Access reason	10 (1.9)
Cost	9 (1.7)
Other	23 (4.3)

mmHg) and LDL-C (<100 mg/dL) target achievement were 10.8 vs. 20.9%, 64.7 vs. 40.5% and 20.7 vs. 25.6%, respectively (Table 6). Considering males vs. females, rates for HbA1c (<7%), systolic BP (<140 mmHg) and LDL-C (<100 mg/dL) target achievement were 11.2 vs. 12.1%, 65.5 vs. 59.6% and 20.5 vs. 21.9%, respectively (Table 6).

Glycemic targets set at second-line therapy initiation

Glycemic targets were set in 76.7% of patients at initiation of second-line therapy, including HbA1c target set to mean (standard deviation) 7.0 (0.5) % in 76.7% of patients, fasting plasma glucose target set to 194.2 (384.4) mg/dL in 54.9% of patients, casual plasma glucose target of 184.5 (341.6) mg/dL in 15.5% of patients and post-prandial plasma glucose target of 270.5 (529.0) mg/dL in 44.6% of patients (Table 6).

Table 6. HbA1c, LDL-cholesterol, and systolic BP target achievement at baseline and glycemic targets set at the time of second-line therapy initiation.

Target achievement at baseline		**n (%)**
HbA1c <7%	Total (n=536)	58 (11.7)
	≤65 year (n=490)	49 (10.8)
	>65 year (n=46)	9 (20.9)
	Male (n=269)	28 (11.2)
	Female (n=267)	30 (12.1)
Systolic BP <140 mmHg	Total (n=536)	262 (62.5)
	≤65 year (n=490)	247 (64.7)
	>65 year (n=46)	15 (40.5)
	Male (n=269)	135 (65.5)
	Female (n=267)	127 (59.6)
LDL <100 mg/dL	Total (n=536)	90 (21.2)
	≤65 year (n=490)	80 (20.7)
	>65 year (n=46)	10 (25.6)
	Male (n=269)	44 (20.5)
	Female (n=267)	46 (21.9)
Glycemic targets set at second line therapy initiation		
Overall, n (%)	Yes	411 (76.7)
	No	79 (14.7)
	Not known	46 (8.6)
For HbA1c (n=411)	Yes, n (%)	411 (76.7)
	Mean (SD)	7.0 (0.5)
For fasting plasma glucose (n=294)	Yes, n (%)	294 (54.9)
	Median (IQR)	120.0 (110.0-130.0)
For post-prandial plasma glucose (n=239)	Yes, n (%)	239 (44.6)
	Median (IQR)	160.0 (150.0-180.0)

HbA1c: Hemoglobin A1c; BP: Blood pressure; LDL: Low-density lipoprotein; IQR: Interquartile range; SD: Standard deviation.

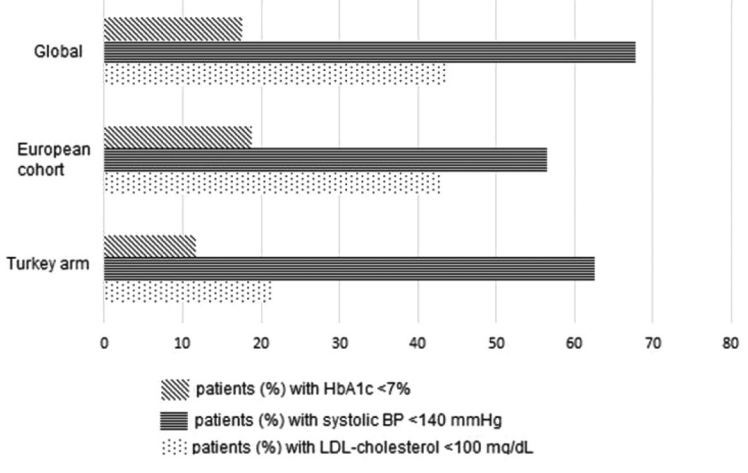

Figure 3. HbA1c, systolic BP, and LDL-cholesterol target achievement rates at baseline in the global DISCOVER population, European cohort, and Turkey arm.
HbA1c: Hemoglobin A1c; BP: Blood pressure; LDL: Low-density lipoprotein.

Patient-reported outcomes

Lifestyle assessment revealed a healthy lifestyle in 50.7% of patients, while the lifestyle was categorized as unhealthy or intermediate unhealthy in 35.9% of patients (Table 7).

Mean (standard deviation) HFS-II subscale scores were 9.8 (10.2, range 1.0 to 16.0) for behaviors and 14.1 (15.5, range 0.0 to 24.0) for worries (Table 7). Mean (standard deviation) physical and mental component scores in SF-36 were 47.9 (8.4) and 41.1 (10.7), respectively (Table 7).

Discussion

This preliminary analysis of baseline data from the Turkey arm of the global DISCOVER study revealed metformin therapy either as a monotherapy or in combination to be the most common first-line agent. It also revealed the failure to achieve HbA1c, LDL-C, and systolic BP targets in a considerable portion of patients and high rates of micro and macrovascular complications before initiating second-line therapy. Lack of efficacy was the main reason for switching to second-line therapy, while second-line treatment choice was also primarily based on its expected efficacy. Accordingly, insulin was the most commonly prescribed second-line agent, followed by metformin+DPP4 inhibitor therapy, with discontinuation of metformin only in 3.6% of patients.

When compared to the global cohort, the Turkish cohort seemed to be composed of patients with a longer diabetes duration [mean (standard deviation) 7.1 (5.9) vs. 5.7 (5.3) years], higher BMI values [mean (standard deviation) 31.7 (6.4) vs. 29.4 (6.0) kg/m2] and a lower rate of high educational attainment (16.8% vs. 32.0%) (15). The nationwide TEMD Obesity Study also reported that among T2D patients (n=4,648) in the cohort, only 10% of patients had normal BMI and overweight (31%) or obesity (59%) in the majority of patients (21).

Before second-line therapy initiation, the percentage of patients at target HbA1c (<7%), as well as those at target LDL-C (<100 mg/dL), were lower in Turkey (11.7% and 21.2%, respectively) as compared to global (17.4% and 43.5%, respectively) and European (18.7% and 43.2%, respectively) cohorts (22,23). In addition, mean (standard deviation) HbA1c levels [8.8(1.8)%], as well as the rate of HbA1c levels >9% (40.6%), were higher among Turkish patients, as compared to data from global [8.3 (1.7)% and 26.7%, respectively] and European [8.1 (1.6)% and 21.8%, respectively] cohorts (22,23). The rate of target systolic BP (<140 mmHg) achievement in Turkey (62.5%) was consistent with rates reported in global (67.7%) and European (56.5%) cohorts (22,23).

Notably, baseline BP control data analysis from patients with high cardiovascular risk in the LEADER Study (n=9,349) across 32 countries reported that rates of BP control (50-54%) could not be considered satisfactory at baseline along with higher rates of poor BP control in the European cohort, including Turkey (only 20.3%, 42.4%, and 46.2% were at target BP <130/80 mmHg, <140/85 mmHg and <140/90 mmHg, respectively) (24). Lower rate of LDL-C target achievement in our cohort compared with global and European cohorts is important given the lower rates of statin prescription in Turkey (24.8%) than in Europe (45.8%) and the global population (42.9%) (25).

Table 7. Patient-reported outcomes.

Lifestyle at baseline (n=412)		**n (%)**
Unhealthy (0-2)		56 (13.6)
Intermediate unhealthy (3)		92 (22.3)
Healthy (4-5)		209 (50.7)
Very healthy (6-7)		55 (13.3)
Hypoglycemic Fear Survey-II scores	**n**	**Median (IQR)**
HFS-II-behaviors	341	7.0 (1.0, 16.0)
HFS-II-worries	377	10.0 (0.0, 24.0)
Total score	320	17.0 (4.0, 39.0)
SF-36 HRQoL scores	**n**	**Mean (SD)**
Physical functioning score	435	46.8 (10.1)
Role-physical score	427	45.0 (9.5)
Bodily pain score	414	44.8 (10.6)
General health score	436	45.2 (9.2)
Vitality score	410	47.6 (10.0)
Social functioning score	429	45.0 (9.8)
Role-emotional score	427	40.1 (12.8)
Mental health score	411	40.4 (10.8)
Physical component score	402	47.9 (8.4)
Mental component score	403	41.1 (10.7)

HFS: Hypoglycemic Fear Survey; IQR: Interquartile range; SD: Standard deviation; HRQoL: Health-related quality of life.

Similarly, in a previous study among 707 patients with T2D in Turkey, only 33% of the patients were reported to receive statin therapy. In contrast, most of the patients had LDL-C levels of >100 mg/dL (77%), with only 5% with LDL-C levels of <70 mg/dL (26).

The rate of glycemic control (HbA1c <7%) achievement in Turkish T2D patients was 15.6% in a nationwide multi-center ADMIRE Study (n=1,790, mean age 58.7 years, average 7.7 years of diabetes duration) a decade ago (27), whereas much higher rates of glycemic control were reported in recent studies, including the Turkey arm of international IDMPS Study (n=842, mean age: 56.9 years, average 8.7 years of diabetes duration) (28) and TEMD Study (n=4,756, mean age 58.5 years, average 13.7 years of diabetes duration) (29), which reported 28% and 40.2% glycemic control rate in 2016 and 2018, respectively.

In addition, TEMD Study also revealed that LDL-C <100 mg/dL and home BP <135/85 mmHg targets were achieved by 37.3% and 69.1% of patients, respectively, whereas only 10.1% of patients achieved the triple metabolic targets, including HbA1c <7.0%, LDL-C <100 mg/dL, home BP <135/85 mmHg (29). The LDL-C (<100 mg/dL) and BP (<130/80 mmHg) goal achievement rates were 25% and 23% in the ADMIRE study (27), while 35% and 20% in the IDMPS study, respectively (28). In the TEMD Dyslipidemia Study among 4,504 T2D patients, only 8.4% of patients attained target LDL-C levels, and 44.8% of patients were on statin treatment despite the need for statin therapy in 89.5% along with achieving target LDL-C levels by only a quarter of patients on statin therapy (30). Data from TEMD Hypertension Study in 4,756 T2D patients revealed hypertension in 67.5% of patients and 87.4% of hypertensive patients received treatment; BP was on target only in 52.7% of patients (31). Due to the higher rates for glycemic, LDL-C, and BP goal achievement as compared with previous studies in Turkey, authors of the TEMD study emphasized the potential role of an improved healthcare system in Turkey over the years, as well as adherence to regular, follow up in better diabetes care and improved rates for triple target achievement by patients (29).

Overall, at baseline, 17.2% of Turkish patients had macrovascular, and 20.1% had the microvascular disease. In the global cohort, micro and macrovascular complications were evident in 19.4% and 14.7% of patients, respectively (15), indicating slightly higher rates for microvascular complications in the Turkey arm of the DISCOVER study. Minor (10.7% vs. 3.5%) or major (5.5% vs. 1.0%) hypoglycemia history was also evident in a higher percentage of patients in our cohort as compared with the global cohort (15). Similarly, data from ADMIRE study in 1,790 T2D patients from Turkey revealed 58.6% of patients to have at least one chronic complication, including neuropathy (40.0%), while hypoglycemia (19%) was reported to be the most common acute complication (26). Data from the Turkey arm of the international IDMPS study revealed that 88% of T2D patients had at least one microvascular complication, and 99% had at least one cardiovascular risk factor (28).

Multivariate regression analysis of global data revealed a positive association of microvascular complication rates with higher HbA1c levels, older age, male gender, low educational status, active smoking, longer diabetes duration, and hypoglycemia history (25). Accordingly, the high prevalence of microvascular complications in our cohort was consistent with higher HbA1c levels, higher hypoglycemia prevalence, longer diabetes duration, lower educational levels, and higher smoking rates than in the overall global cohort. These findings emphasize a need for more aggressive risk factor screening and modification at early stages of T2D in Turkish patients (25).

Metformin monotherapy (47.9%) and metformin+sulfonylurea (22.6%) were the most common first-line therapies, whereas insulin (32.3%) was the most commonly prescribed second-line agent, followed by metformin+DPP4 inhibitor (20.1%) in our cohort. It was consistent with the global data that indicated that the most commonly prescribed first-line glucose-lowering therapies were metformin monotherapy (57.9%) and combinations of metformin and sulfonylurea (14.6%) (15). However, despite being among the most commonly selected first-line treatment options, in real-life clinical practice,

the rate of metformin+DPP4 inhibitor therapy was meager in both the Turkey arm (6.0%) and global cohort (3.3%) (15).

In addition, metformin+sulfonylurea (21.3%) and metformin+DPP4 inhibitor (25.1%) were the most commonly initiated second-line therapies in the global cohort, with insulin prescribed only in 6.2% cases (15). Notably, anti-diabetic treatment findings from the nationwide ADMIRE Study and Turkey arm of IDMPS Study was consistent with our results in terms of rates for oral antidiabetic drug (OAD) alone (61% and 52%, respectively), insulin alone (15% and 18%, respectively), and OAD+insulin (20% and 29%, respectively) regimens (27,28). Data from the TEMD Treatment study on 4,678 T2D patients revealed that 50.7% of patients (45% on insulin) were on injectable regimens with or without OADs, and 49.3% were on OADs alone (32). The authors also noted that metformin (93.5%) was the most common OADs, followed by secretagogues (40.1%) and DPP-4 inhibitors (37.2%), while basal, basal-bolus, and premix insulin was used by 26.5%, 39.5%, and 22.4% of patients, respectively (32).

Nonetheless, a higher rate of insulin as a second-line agent in Turkey vs. the global cohort was consistent with a lower rate of HbA1 target achievement and higher prevalence of HbA1c levels >9% at the time of initiating second-line therapy and longer diabetes duration in the Turkey cohort. A higher likelihood of treatment intensification with insulin was also reported in T2D patients with HbA1c levels ≥9.0% vs. ≥8.0% under OAD therapy (33). In addition, data from Germany and UK cohorts of the DISCOVER study also revealed very high HbA1c levels while initiating second-line therapy with baseline HbA1c ≥9.0% in one-third of patients (7). Authors suggested a delay in treatment intensification, indicating a need for earlier treatment intensification (7), supporting the data from several real-world studies, including Turkey (34-38).

Hence, based on an average of 7.1 years of diabetes duration and high rates of HbA1c values >9% and macro and microvascular complications in our cohort at the time of second-line therapy initiation, our findings support data from observational studies. Previous studies suggested that patients are often exposed to a prolonged glycemic load before the onset of insulin treatment following a long disease history and average HbA1c levels above 9% worldwide, in a population in which diabetes-related complications are already highly prevalent (38,39).

Lack of efficacy (90.9%) was the most common reason for changing first-line therapy in the Turkey arm, and the second-line therapy selection was also based on its expected efficacy in most cases (75.9%), followed by tolerability (27.1%), concordant with the global data (40). However, global and European reports revealed that metformin was discontinued in over one-third of patients initiating a second-line therapy, considered more than expected if guideline recommendations were applied (7,9,40). Accordingly, discontinuation of metformin only in 3.6% of patients initiating second-line therapy in our cohort was per guideline recommendations and consistent with the benefits of continuing metformin therapy, including reduced mortality risk and reduced micro/macrovascular complications (7,9,40).

For patients with a known CVD who failed to reach the HbA1c target under first-line therapy, the addition of an agent with proved cardiovascular benefit (i.e., SGLT2-inhibitors or GLP-1A) due to their association with reduced risk of cardiovascular event and mortality is recommended in TEMD 2018 Guideline for Diagnosis, Treatment, and Monitoring of Diabetes Mellitus and Its Complications (41). SGLT2-inhibitors (dapagliflozin) were not covered by insurance and not reimbursed in Turkey within the study period.

Lifestyle assessment revealed a healthy lifestyle in 50.7% of patients, while moderate scores in terms of quality of life and hypoglycemia fear at baseline before initiating second-line therapy. In a study with 5,813 patients with T2D, the treatment intensification was associated with quality of life change and the predictive role of insulin alone on quality of life and hypoglycemia worry. Thus, our findings support the importance of measuring patient-reported outcomes after second-line therapy to increase treatment adherence and the likelihood of long-term glycemic control (42). Besides, it is also notable given the role of clinical inactivity, poor treatment compliance, and side

effects in the delay of necessary treatment intensification in patients receiving OAD treatment (39), as well as the association of prolonged delays in initiation of insulin with fear of injection pain, hypoglycemia and weight gain, and the reduced quality of life (43-47).

The major strength of the global DISCOVER study was the inclusion of patients from diverse clinical settings in 37 countries with careful selection of physicians and geographic regions, enabling findings to be representative of real-life practice in each country. However, there are two limitations to this study. First, the observational design indicated the likelihood of bias and confounding. Second, underestimating negative outcomes is another limitation given the higher possibility of loss on follow-up among patients with poorly controlled diabetes.

Conclusion

In conclusion, this preliminary analysis of baseline data from the Turkey arm of the global DISCOVER study revealed metformin monotherapy or combination therapy was the most common first-line therapy, and lack of efficacy was the main reason for switching to second-line therapy. However, the choice of second-line treatment was also primarily based on its expected efficacy. Accordingly, insulin was the most commonly prescribed second-line agent, followed by metformin+DPP4 inhibitor therapy, with discontinuation of metformin only in 3.6% of patients. Compared to global and European cohorts, longer diabetes duration, higher BMI values, higher rate of HbA1c levels of >9%, and failure to achieve HbA1c and LDL-C targets were noted in the Turkish cohort when initiating second-line therapy. Our findings emphasized a need for more aggressive risk factor screening and modification at early stages of T2D in Turkish patients and earlier treatment intensification to reduce prolonged glycemic load and better management of dyslipidemia and hypertension to prevent further complication risks.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Fahri Bayram; Design: Fahri Bayram, Ramazan Sarı, Ferit Kerim Küçükler, Mustafa Araz; Control/Supervision: Fahri Bayram, Ramazan Sarı, Ferit Kerim Küçükler, Mustafa Araz; Data Collection and/or Processing: Fahri Bayram, Ramazan Sarı, Ferit Kerim Küçükler, Mustafa Araz, Ramis Çolak, Osman Başpınar, Yaşar Küçükkardalı, Mehmet Çalan, Ceren Yılmaz, Onur Utebay, Tamer Tetiker; Analysis and/or Interpretation: Fahri Bayram, Ramazan Sarı, Ferit Kerim Küçükler, Mustafa Araz; Literature Review: Fahri Bayram, Ramazan Sarı, Ferit Kerim Küçükler, Mustafa Araz, Ramis Çolak, Osman Başpınar, Yaşar Küçükkardalı, Mehmet Çalan, Ceren Yılmaz, Onur Utebay, Tamer Tetiker; Writing the Article: Fahri Bayram, Ramazan Sarı, Ferit Kerim Küçükler, Mustafa Araz; Critical Review: Fahri Bayram, Ramazan Sarı, Mustafa Araz; References and Fundings: Ceren Yılmaz, Onur Utebay.

References

1. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019. [Link]
2. Satman I, Yilmaz T, Sengül A, Salman S, Salman F, Uygur S, Bastar I, Tütüncü Y, Sargin M, Dinççag N, Karsidag K, Kalaça S, Ozcan C, King H. Population-based study of diabetes and risk characteristics in Turkey: results of the turkish diabetes epidemiology study (TURDEP). Diabetes Care. 2002;25:1551-1556. [Crossref] [PubMed]
3. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir B, Tuomilehto J; TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol. 2013;28:169-180. [Crossref] [PubMed] [PMC]

4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-1589. [Crossref] [PubMed]
5. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560-2572. [PubMed]
6. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-853. Erratum in: Lancet 1999;354:602. [Crossref] [PubMed]
7. Khunti K, Godec TR, Medina J, Garcia-Alvarez L, Hiller J, Gomes MB, Cid-Ruzafa J, Charbonnel B, Fenici P, Hammar N, Hashigami K, Kosiborod M, Nicolucci A, Shestakova MV, Ji L, Pocock S. Patterns of glycaemic control in patients with type 2 diabetes mellitus initiating second-line therapy after metformin monotherapy: Retrospective data for 10256 individuals from the United Kingdom and Germany. Diabetes Obes Metab. 2018;20:389-399. [Crossref] [PubMed] [PMC]
8. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018;61:2461-2498. Erratum in: Diabetologia. 2019;62:873. [Crossref] [PubMed]
9. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58:429-442. [Crossref] [PubMed]
10. Preis SR, Pencina MJ, Hwang SJ, D'Agostino RB Sr, Savage PJ, Levy D, Fox CS. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. Circulation. 2009;120:212-220. [Crossref] [PubMed] [PMC]
11. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, Davidson MB, Einhorn D, Garber JR, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez G, Davidson MH. AACE/ACE comprehensive diabetes management algorithm 2015. Endocr Pract. 2015; 21:438-447. [Crossref] [PubMed]
12. International Diabetes Federation. Global Guideline for Type 2 Diabetes. Brussels, Belgium: International Diabetes Federation; 2012. [Link]
13. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012;156:218-231. Erratum in: Ann Intern Med. 2012;157:152. Erratum in: Ann Intern Med. 2012;156:756. [Crossref] [PubMed]
14. Ji L, Bonnet F, Charbonnel B, Gomes MB, Kosiborod M, Khunti K, Nicolucci A, Pocock S, Rathmann W, Shestakova MV, Shimomura I, Watada H, Fenici P, Hammar N, Hashigami K, Macaraeg G, Surmont F, Medina J. Towards an improved global understanding of treatment and outcomes in people with type 2 diabetes: Rationale and methods of the DISCOVER observational study program. J Diabetes Complications. 2017;31:1188-1196. [Crossref] [PubMed]
15. Nicolucci A, Charbonnel B, Gomes MB, Khunti K, Kosiborod M, Shestakova MV, Shimomura I, Watada H, Chen H, Cid-Ruzafa J, Fenici P, Hammar N, Surmont F, Tang F, Pocock S. Treatment patterns and associated factors in 14 668 people with type 2 diabetes initiating a second-line therapy: Results from the global DISCOVER study programme. Diabetes Obes Metab. 2019;21:2474-2485. [Crossref] [PubMed] [PMC]
16. Ware Jr JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's Manual for the 36v2® Health Survey. 2nd ed. Lincoln: Quality Metric Incorporated; 2007. [Link]
17. Stargardt T, Gonder-Frederick L, Krobot KJ, Alexander CM. Fear of hypoglycaemia: defining a minimum clinically important difference in patients with type 2 diabetes. Health Qual Life Outcomes. 2009;7:91. [Crossref] [PubMed] [PMC]
18. Carlsson AC, Wändell PE, Gigante B, Leander K, Hellenius ML, de Faire U. Seven modifiable lifestyle factors predict reduced risk for ischemic cardiovascular disease and all-cause mortality regardless of body mass index: a cohort study. Int J Cardiol. 2013; 168:946-952. [Crossref] [PubMed]
19. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med. 2016;4:20503121166 71725. [Crossref] [PubMed] [PMC]
20. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, Cox DJ. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. Diabetes Care. 2011;34:801-806. [Crossref] [PubMed] [PMC]
21. Sonmez A, Yumuk V, Haymana C, Demirci I, Barcin C, Kıyıcı S, Güldiken S, Örük G, Ozgen Saydam B, Baldane S, Kutlutürk F, Küçükler FK, Deyneli O, Çetinar slan B, Sabuncu T, Bayram F, Satman I; TEMD Study Group. Impact of obesity on the metabolic control of Type 2 diabetes: Results of the Turkish nationwide survey of glycemic and other metabolic parameters of patients with diabetes mellitus (TEMD Obesity Study). Obes Facts. 2019;12:167-178. [Crossref] [PubMed] [PMC]
22. Khunti K, Chen H, Cid-Ruzafa J, Fenici P, Gomes MB, Hammar N, Ji L, Kosiborod M, Pocock S, Shestakova MV, Shimomura I, Tang F, Watada H, Nicolucci A; DISCOVER investigators. Glycaemic control in patients with type 2 diabetes initiating second-line therapy: Results from the global DISCOVER study programme. Diabetes Obes Metab. 2020;22:66-78. [Crossref] [PubMed] [PMC]

23. Gomes MB, Charbonnel B, Cid-Ruzafa J, Fenici P, Hammar N, Khunti K, Kosiborod M, Nicolucci A, Pocock S, Shestakova MV, Watada H, Shimomura I, Tang F, Ji L; on behalf of the DISCOVER study investigators. Glycaemic, lipid and blood pressure control according to guidelines in patients initiating second-line glucose-lowering therapy: results from the global DISCOVER study. Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD); 2017 Sep 11-15; Lisbon, Portugal, P301. Diabetologia. 2017;60(Suppl 1): S1-S608. [Link]
24. Petrie JR, Marso SP, Bain SC, Franek E, Jacob S, Masmiquel L, Leiter LA, Haluzik M, Satman I, Omar M, Shestakova M, Van Gaal L, Mann JF, Baeres FM, Zinman B, Poulter NR; LEADER investigators. LEADER-4: blood pressure control in patients with type 2 diabetes and high cardiovascular risk: baseline data from the LEADER randomized trial. J Hypertens. 2016;34:1140-1150. [Crossref] [PubMed] [PMC]
25. Shestakova MV, Cid-Ruzafa J, Fenici P, Gomes MB, Hammar N, Kosiborod M, Nicolucci A, Pocock S, Rathmann W, Shimomura I, Tang F, Watada H, Khunti K; on behalf of the DISCOVER study investigators. Global prevalence of type 2 diabetes complications in 14 178 patients initiating second-line therapy: the DISCOVER study. Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD); 2017 Sep 11-15; Lisbon, Portugal, P1126. Diabetologia. 2017; 60 (Suppl 1):S1-S608. [Link]
26. Kahya Eren N, Harman E, Dolek D, Emren S, Tütüncüoğlu AP, Nazli C, Ergene O. The gap between the current dyslipidemia guidelines and the physicians' treatment targets in patients with type 2 diabetes in Turkey. Minerva Cardioangiol. 2014; 62:287-295. [Crossref] [PubMed]
27. Satman İ, İmamoğlu S, Yılmaz C; ADMIRE Study Group. Physician adherence to the SEMT guidelines for the management of Type 2 diabetes in Turkey: ADMIRE study. Turk Jem. 2010;14:66-72. [Link]
28. İlkova H, Damcı T, Karşıdağ K, Çömlekçi A, Ayvaz G. The International Diabetes Management Practices Study (IDMPS)-Turkey's 5th wave results. Turk J Endocrinol Metab. 2016;20:88-96. [Crossref]
29. Sonmez A, Haymana C, Bayram F, Salman S, Dizdar OS, Gurkan E, Kargili Carlıoglu A, Barcin C, Sabuncu T, Satman I; TEMD Study Group. Turkish nationwide survEy of glycemic and other Metabolic parameters of patients with Diabetes mellitus (TEMD study). Diabetes Res Clin Pract. 2018;146:138-147. [PubMed]
30. Bayram F, Sonmez A, Haymana C, Sabuncu T, Dizdar OS, Gurkan E, Carlioglu AK, Agbaht K, Ozdemir D, Demirci I, Barcin C, Salman S, Tetiker T, Balci MK, Kebapci N, Ersoy C, Yumuk V, Toth PP, Satman I; TEMD Study Group. Utilization of statins and LDL-cholesterol target attainment in Turkish patients with type 2 diabetes - a nationwide cross-sectional study (TEMD dyslipidemia study). Lipids Health Dis. 2020;19:237. [Crossref] [PubMed] [PMC]
31. Sabuncu T, Sonmez A, Eren MA, Sahin I, Çorapçioğlu D, Üçler R, Akin Ş, Haymana C, Demirci İ, Atmaca A, Ersöz HÖ, Satman I, Bayram F; TEMD Study Group. Characteristics of patients with hypertension in a population with type 2 diabetes mellitus. Results from the Turkish nationwide survey of glycemic and other metabolic parameters of patients with diabetes mellitus (TEMD Hypertension Study). Prim Care Diabetes. 2021;15:332-339. [PubMed]
32. Haymana C, Sonmez A, Demirci I, Fidan Yaylalı G, Nuhoglu I, Sancak S, Yilmaz M, Altuntas Y, Dinccag N, Sabuncu T, Bayram F, Satman I; TEMD Study Group. Patterns and preferences of antidiabetic drug use in Turkish patients with type 2 diabetes - A nationwide cross-sectional study (TEMD treatment study). Diabetes Res Clin Pract. 2021;171: 108556. [Crossref] [PubMed]
33. Rubino A, McQuay LJ, Gough SC, Kvasz M, Tennis P. Delayed initiation of subcutaneous insulin therapy after failure of oral glucose-lowering agents in patients with Type 2 diabetes: a population-based anal ysis in the UK. Diabet Med. 2007;24:1412-14 18. [Crossref] [PubMed]
34. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care. 2013;36:3411-3417. [Crossref] [PubMed] [PMC]
35. Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? Diabetes Care. 2005;28:600-606. [Crossref] [PubMed]
36. Fu AZ, Qiu Y, Davies MJ, Radican L, Engel SS. Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy. Diabetes Obes Metab. 2011;13:765-769. [Crossref] [PubMed]
37. Damci T, Kultursay H, Oguz A, Pehlivanoglu S, Tokgozoglu L; Vascular Risk Study Group. Sub-optimal drug treatment of diabetes and cardiovascular risk in diabetic patients in Turkey. A countrywide survey. Dia betes Metab. 2004;30:327-333. [Crossref] [PubMed]
38. Damci T, Emral R, Svendsen AL, Balkir T, Vora J; SOLVE™ study group. Lower risk of hypoglycaemia and greater odds for weight loss with initiation of insulin detemir compared with insulin glargine in Turkish patients with type 2 diabetes mellitus: local results of a multinational observational study. BMC Endocr Disord. 2014;14:61. [Crossref] [PubMed] [PMC]
39. Owens DR. Clinical evidence for the earlier initiation of insulin therapy in type 2 diabetes. Diabetes Technol Ther. 2013;15(9):776-785. [Crossref] [PubMed] [PMC]
40. Khunti K, Cid-Ruzafa J, Fenici P, Gomes MB, Hammar N, Kosiborod M, Nicolucci A, Pocock S, Rathmann W, Shestakova MV, Watada H, Shimomura I, Tang F, Ji L; on behalf of the DISCOVER study investigators. Factors associated with the discontinuation of metformin therapy: results from 11 452 patients in the global DISCOVER study. Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD); 2017 Sep 11-15; Lisbon, Portugal, P906. Diabetologia. 2017; 60 (Suppl 1):S1-S608. [Link]

41. Satman I, Imamoglu S, Yilmaz C, Akalin S, Salman S, Dinccag N; on behalf of Turkish Society of Endocrinology and Metabolism Diabetes Mellitus Study and Training Group. Turkish Society of Endocrinology and Metabolism 2018 Guideline for Diagnosis, Treatment and Monitoring of Diabetes Mellitus and Its Complications. Ankara: Miki Press; 2018. Available from: [Link]
42. Bradley C, Eschwège E, de Pablos-Velasco P, Parhofer KG, Simon D, Vandenberghe H, Gönder-Frederick L. Predictors of quality of life and other patient-reported outcomes in the PANORAMA multinational study of people with type 2 diabetes. Diabetes Care. 2018;41:267-276. [Crossref] [PubMed]
43. Khunti K, Gomes MB, Pocock S, Shestakova MV, Pintat S, Fenici P, Hammar N, Medina J. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: A systematic review. Diabetes Obes Metab. 2018;20:427-437. [Crossref] [PubMed] [PMC]
44. Karter AJ, Subramanian U, Saha C, Crosson JC, Parker MM, Swain BE, Moffet HH, Marrero DG. Barriers to insulin initiation: the translating research into action for diabetes insulin starts project. Diabetes Care. 2010;33:733-735. [Crossref] [PubMed] [PMC]
45. Escalada J, Orozco-Beltran D, Morillas C, Alvarez-Guisasola F, Gomez-Peralta F, Mata-Cases M, Palomares R, Iglesias R, Carratalá-Munuera C. Attitudes towards insulin initiation in type 2 diabetes patients among healthcare providers: A survey research. Diabetes Res Clin Pract. 2016;122:46-53. [Crossref] [PubMed]
46. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, Landgraf R, Kleinebreil L; International DAWN Advisory Panel. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care. 2005;28:2673-2679. [Crossref] [PubMed]
47. Nakar S, Yitzhaki G, Rosenberg R, Vinker S. Transition to insulin in Type 2 diabetes: family physicians' misconception of patients' fears contributes to existing barriers. J Diabetes Complications. 2007;21:220-226. [Crossref] [PubMed]