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ORIGINAL RESEARCH

Adherence to the National Guidelines for Follow-Up Protocol in Subjects with Type 2 Diabetes Mellitus in Greece: The GLANCE Study

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ABSTRACT

Introduction: Physician adherence, or lack therefore, to diabetes care and follow-up guidelines may be linked to the rates of achieving suboptimal glycaemic, blood pressure and lipid targets in people with type 2 diabetes mellitus (T2DM). In this cross-sectional study we evaluated physician adherence to the patient follow-up protocol (PFP) of the 2017 Hellenic Diabetes Association (HDA) guidelines and also assessed glycated haemoglobin (HbA_{1c}), blood pressure and lipid control achievement rates in the routine care setting in Greece.

Methods: Eligible subjects were adults with T2DM receiving oral hypoglycaemic agents (OHAs) for $\geq$ 1 year who had $\geq$ 2 HbA_{1c} measurements in the previous year and an HbA_{1c} target $< 7\%$. Overall adherence at the subject level was defined as the percentage of the 62 HDA PFP items that had been met during the past year.

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Results: Between June and December 2018, 601 eligible subjects (54.6% men; mean age 65.2 years; median T2DM duration 5.9 years, of whom 96.5% had ≥ 1 medical condition/co-morbidity), were enrolled into the study by 53 hospital- and office-based endocrinologists, internists and general practitioners. The main OHAs prescribed at enrolment were metformin (91.0%), dipeptidyl peptidase-4 inhibitors (60.7%), sodium-glucose co-transporter-2 inhibitors (23.5%) and sulphonylureas (16.3%). Mean overall physician adherence to the PFP was 43.6%. Predictors of greater higher physicans' adherence were female sex ($p = 0.026$), > 3 medical conditions/comorbidities ($p = 0.043$) and diabetic complications ($p < 0.001$). HbA_{1c}, low-density lipoprotein-cholesterol, systolic/diastolic blood pressure and composite metabolic targets were achieved by 82.1, 57.0, 42.6 and 21.6% of subjects, respectively.

Conclusions: In Greek routine care, physician adherence to the PFP of the 2017 HDA guidelines is suboptimal. Future efforts should focus on identifying the barriers to an adequate adherence by physicians to the full PFP, with the aim to provide optimal patient care.

Keywords: Follow-up; Glycated haemoglobin A1c; Guideline adherence; Target attainment; Type 2 diabetes mellitus

Key Summary Points

Inadequate adherence to diabetes care and to follow-up guidelines by physicians may contribute to suboptimal glycaemic, lipid and blood pressure target attainment rates in subjects with type 2 diabetes (T2DM).

The aim of the GLANCE study was to assess the level of physician adherence to the patient follow-up protocol (PFP) of the Hellenic Diabetes Association (HAD) 2017 T2DM guidelines, the achievement rates for glycaemic, blood pressure and low-density lipoprotein-cholesterol (LDL-C) targets and physician adherence to the HDA-recommended pharmacological treatment algorithm.

Overall, physician adherence to the PFP of the national guidelines for T2DM was found to be suboptimal, but the glycaemic target was achieved by eight of ten subjects.

It is important to identify the barriers to an adequate adherence by physicians to the full PFP provided in the 2017 HDA guidelines, with the aim to optimally support subjects with T2DM and improve outcomes.

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DIGITAL FEATURES

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INTRODUCTION

Diabetes is an emerging global epidemic of the twenty-first century, with an ever-increasing prevalence [1]. The International Diabetes Federation (IDF) 2019 estimate of diabetes prevalence in Greece was 7.4% of the national population [1]. Similarly, a study based on 2014–2015 Greek national electronic prescription database data estimated the prevalence of medication-prescribed diabetes at 8.2% for adults in general and at 30.3% for those aged ≥ 75 years [2].

Type 2 diabetes (T2DM) accounts for about 90% of all cases of diabetes [3]. Persons with T2DM carry a high risk of developing micro- and macrovascular complications, with atherosclerotic cardiovascular disease (CVD) being the primary source of morbidity and mortality [4–6]. Current management goals include achieving adequate glycaemic control and addressing vascular risk factors, notably blood pressure (BP), lipids, among others [7–10]. In general, the achievement of therapeutic targets in T2DM is not optimal [11, 12]; this also holds true for Greece [13–16], where the achievement rates of glycated haemoglobin (HbA_{1c}) and BP targets have been reported to be 53 and 27%, respectively [15]. Achievement of therapeutic targets may be linked to adherence to diabetes standards of medical care recommendations [17–19]. In Greece, the Hellenic Diabetes Association (HDA) issues and regularly updates practice guidelines for the management and care of persons with diabetes [20], which are aligned with the guidelines of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [21–23]. The 2017 HDA guidelines include a patient follow-up protocol (PFP) that lists 62 items that should be part of a patient's medical history and clinical and laboratory evaluations, with the aim to achieve optimal diabetes management [20].

To date, the adherence of Greek physicians to the PFP has not been systematically explored. The aims of this study were to assess (1) the adherence level of physicians to the PFP of the HDA 2017 T2DM guidelines [20] and (2) the achievement rates of glycaemic, BP and low-density lipoprotein-cholesterol (LDL-C) control; and (3) to examine physician adherence to the HDA-recommended pharmacological treatment algorithm.

METHODS

Study Design

The present study (GLANCE) was a nationwide, multi-centre, cross-sectional study conducted in 15 hospital-based outpatient clinics and 38 private practices located across Greece. A total of 610 persons with T2DM were consecutively enrolled in the study (referred to as subjects) by 14 endocrinologists, 35 internists and four general practitioners with a special interest in diabetes between 27 June and 20 December 2018. The study was conducted in accordance with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice, the ethical principles of the Declaration of Helsinki of 1964 and its later amendments and all standing regulations. The study was approved by the ethics committees of all participating hospitals (see Electronic Supplementary Material Table S1). Signed written informed consent was obtained from all participants.

The study included non-insulin-dependent persons with T2DM who were aged ≥ 19 years at enrolment, had ≥ 2 HbA_{1c} measurements during the past year, had a HbA_{1c} target < 7% and

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were receiving oral hypoglycaemic agents (OHAs) for ≥ 1 year. Exclusion criteria were patients who were insulin dependent; had type 1 DM or gestational diabetes; were hospitalised; were participating in any clinical trial at time of enrolment; had in the current or past (preceding) year a history of alcohol or drug abuse; were pregnant/lactating (at enrolment or within the previous year); subjects who did not have $HbA_{1c} < 7\%$ as a therapeutic target were also excluded.

In order to ensure country-wide representation of clinical practices, the sample of patients was distributed according to the percentage of the Greek population residing in the various regions. Consecutive patients from those attending the selected centres during a prespecified period were invited to participate in the study.

Data were collected using a web-based data system during the single study visit, which occurred at enrolment, and through patient self-report and medical chart review. For the evaluation of adherence by physicians to the HDA guidelines, we used information available in participants' medical records within the last 365 days and up tol the most recent visit prior to enrolment. For the assessment of metabolic target attainment rates, we used laboratory assessments available at enrolment or within 1 month prior to enrolment. Compliance of participants to their current antidiabetic treatment regimen and their adherence to physician-provided nutritional recommendations were rated by the physicians using a five-level Likert-type scale with responses of "very good", "good", "moderate", "poor" and "very poor".

Outcomes

The primary outcome was overall physican adherence to the PFP of the HDA guidelines, at a participant level. Other outcomes included: (1) glycaemic control, defined as the proportion of subjects attaining the HbA_{1c} target < 7%; (2) adherence to the HDA-recommended therapeutic algorithm; (3) physician adherence to each domain and each item of the PFP; (4) adherence to the PFP according to each physician's specialty (endocrinologist, internist, general practitioner); and (5) target achievement for LDL-C, BP and composite metabolic control, in accordance with the HDA T2DM guidelines [20], as follows: (1) systolic BP (SBP) < 140 mmHg (< 130 mmHg for subjects < 65 years old) and diastolic BP (DBP) < 85 mmHg (< 80 mmHg for subjects < 65 years old); (2) composite SBP/DBP target of SBP < 140 and DBP < 85 mmHg for subjects aged ≥ 65 years old, and SBP < 130 and DBP < 80 mmHg for those aged < 65 years; (3) LDL-C < 100 mg/dL or < 70 mg/dL in subjects with pre-existing CVD (i.e. coronary artery disease, peripheral arterial disease, stroke, transient ischaemic attack, carotid artery stenosis (> 50%) and abdominal aortic aneurysm); (4) composite metabolic control, i.e. simultaneous attainment of HbA_{1c}, LDL-C, SBP and DBP targets as defined above.

Follow-Up Protocol

The PFP of the HDA 2017 guidelines [20] comprises 62 items (Table 1), organised in three distinct domains: complete medical history (items 1–30), physical examination (items 31–42) and laboratory evaluation (items 43–62). For the following items to be considered to be completed, the respective information should have been available in the patient's medical record: items 1, 3–10, 13, 21–29, 31–37, 40, 43 on every visit, and items 44–58 and 62 at least once in the year prior to enrolment. The remaining items were considered fulfilled if the physician confirmed they had been evaluated.

Statistical Analyses

Statistical analyses were performed using SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA). Categorical variables are presented as frequencies (*n*, %), while continuous variables are presented as the mean and standard deviation (SD) or as the median and interquartile range (IQR). Normality of distribution was assessed using the Kolmogorov–Smirnov test. For each subject, a crude score of overall adherence was estimated as the sum of fulfilled

Table 1 Items and domains based on the patient's follow-up protocol of the Hellenic Diabetes Association guidelines and physicians' adherence to each item

Item no.	Domains of the 2017 HDA guidelines	Patients for whom sufficient information was available for the item [*n* (%)]
	Complete medical history domain	
	A) Demographic characteristics	
1	Age (or date of birth)	589 (98.0)
2	Profession	471 (78.4)
3	Year of T2DM diagnosis	560 (93.2)
4	Mode of T2DM diagnosis	297 (49.4)
5	Medication applied to T2DM since diagnosis	503 (83.7)
6	Smoking status (no. of cigarettes, etc.)	63 (10.5)
7	Alcohol consumption	59 (9.8)
8	Use of toxic substances	172 (28.6)
9	Vaccinations	96 (16.0)
	B) Factors that should have been recorded on the last visit prior to enrolment	
10	Present symptoms	181 (30.1)
11	Current antidiabetic treatment	601 (100.0)
12	Response to treatment	564 (93.8)
13	Other medications received (concomitant medication)	214 (35.6)
14	Dietary habits	405 (67.4)
15	Diet to be followed	341 (56.7)
16	Nutrition state	314 (52.2)
17	Physical activity	375 (62.4)
18	Patient's compliance with medication intake	422 (70.2)
19	Willingness for dietary and lifestyle modifications	299 (49.8)
	C) Information that the patient has to provide	
20	Blood sugar self-measurement results	331 (55.1)
21	Hypoglycaemic events	123 (20.5)
22	Ketoacidosis events (Incidence, severity/cause)	60 (10.0)
23	Diabetic complications (time and method of diagnosis)	73 (12.1)
	D) Other clinical history information	
24	Hypertension	119 (19.8)
25	Dyslipidaemia	119 (19.8)

Table 1 continued

Item no.	Domains of the 2017 HDA guidelines	Patients for whom sufficient information was available for the item [*n* (%)]
26	Body weight changes over time	141 (23.5)
27	Concomitant diseases (e.g., depression, obstructive sleep apnoea, non-alcoholic liver disease, osteoporosis, periodontal disease, neoplasms)	110 (18.3)
28	Psychosocial problems	48 (8.0)
29	Surgical procedures	42 (7.0)
	E) Family history	
30	Diabetes mellitus presence in parents, siblings or children	514 (85.5)
	Physical examination domain	
	A) At the first visit and repeated on a yearly basis	
31	Clinical examination relates to all systems (respiratory, cardiovascular, digestive, urinary, nervous system), skin, skull, muscles, joints, sensory organs	302 (50.2)
32	Measurement of height, body weight, BMI calculation	130 (21.6)
33	Waist circumference measurement	85 (14.1)
34	Pulse and arterial pressure measurement (systolic and diastolic, in a seated and standing position, as well as assessment of the difference in blood pressure measurements between the two upper extremities)	300 (49.9)
35	Lower-extremity examination for the diagnosis of diabetic peripheral neuropathy (foot architecture, Achilles reflexes, examination of small- and large nerve fibre sensation)	163 (27.1)
36	Examination of the lower extremities for the diagnosis of peripheral arterial disease (peripheral arteries pulses, ankle/brachial index, skin colour and temperature, examination of hair distribution and state of nails and examination for: oedema, sensitivity, pain, ulcers, gangrene, infection, bubbles, abrasions, skin ruptures, bunions, keratoses)	181 (30.1)
37	Examination for the diagnosis of autonomous nervous system neuropathy (gustatory sweating, persistent tachycardia at rest, orthostatic hypotension, hypoglycaemia unawareness, sexual dysfunction)	66 (11.0)
38	Thyroid gland palpation	211 (35.1)

Table 1 continued

Item no.	Domains of the 2017 HDA guidelines	Patients for whom sufficient information was available for the item [*n* (%)]
39	Skin examination: Search of acanthosis nigricans and possible hypertrophy/atrophy at the sites of insulin injection	66 (11.0)
	Ophthalmology examination	
40	Fundoscopy upon dilation at diagnosis	218 (36.3)
41	If, during the first fundoscopy, there are no findings, this is being repeated after 1 year, and then every year	201 (33.4)
42	If there are lesions, the examination is performed every six months or more frequently depending on the severity of the lesions	328 (54.6)
	Laboratory evaluation	
	A) At every visit	
43	Glucose measurement, either at a fasting state or 2 h after the meal or randomly, depending on the time of the visit	258 (42.9)
	B) Every 3–6 months (at least once within the year prior to enrolment)	
44	HbA_{1c} % measurement	601 (100.0)
	C) Every year (At least once within the year prior to enrolment)	
45	Complete blood count, ESR	96 (16.0)
46	Total cholesterol	427 (71.0)
47	Triglycerides	432 (71.9)
48	HDL-C	420 (69.9)
49	LDL-C	412 (68.6)
50	Urea	373 (62.1)
51	Creatinine	432 (71.9)
52	Potassium	253 (42.1)
53	Sodium	231 (38.4)
54	Glomerular filtration calculation (eGFR) as per MDRD or CKD-EPI	116 (19.3)
55	Aminotransferases (AST, ALT)	374 (62.2)
56	Alkaline phosphatase	184 (30.6)
57	γGT	234 (38.9)
58	CPK	157 (26.1)
59	Thyroid function (TSH): in patients with dyslipidemia and in women aged > 50 years	395 (65.7)

Table 1 continued

Item no.	Domains of the 2017 HDA guidelines	Patients for whom sufficient information was available for the item [*n* (%)]
60	Urine examination (if albuminuria is determined, examination of its origin)	246 (40.9)
61	Examination for urinary albumin excretion by calculating the albumin/creatinine ratio at a random sample of morning urine	102 (17.0)
62	ECG at rest	59 (9.8)

AST Aspartate transaminase, *ALT* alanine transaminase, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *CPK* creatine phosphokinase, *γGT* gamma-glutamyl-transferase, *ECG* electrocardiogram, *eGFR* estimated glomerular filtration rate, *ESR* erythrocyte sedimentation rate, *HbA1c* haemoglobin A1c, *HDA* Hellenic Diabetes Association,*HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *MDRD* Modification of Diet in Renal Disease, *T2DM* type 2 diabetes mellitus, *TSH* thyroid stimulating hormone

items, divided by the total number of PFP items ($n = 62$), multiplied by 100. Each item was scored 1 point if fulfilled or 0 if not. The mean overall adherence 95% confidence interval (CI) was calculated. The 95% Wald CI for binomial proportions is presented for the glycaemic control rate.

To identify patient- and physician-related factors associated with physicians' adherence to the HDA guidelines PFP, we performed univariable and multivariable linear regression analyses. The initial multivariable model included the following factors: participant's age at enrolment (≥ 65 vs. < 65 years), sex, T2DM duration (> 5 vs. ≤ 5 years), obesity, number of past or ongoing medical conditions/comorbidities (> 3 vs. ≤ 3), presence of diabetic complications and physicians' specialty (endocrinologist vs. general practitioner, internist vs. general practitioner). The final multivariable model was derived through a stepwise procedure based on the minimisation of the Akaike information criterion.

Sample Size

Due to the descriptive nature of the study, sample size calculation was based on the study's primary endpoint, and no hypothesis-specific calculation was performed. Assuming that the estimated SD of the overall adherence score could range from 0.5 to approximately 1, a sample size of 600 participants was considered appropriate to estimate the adherence level with a 95% CI half-width < 0.1, with at least 80% power.

RESULTS

Baseline Characteristics at Enrolment

A total of 610 subjects were enrolled. Of these, 601 [mean (SD); age 65.2 (10.3) years; 54.6% men] were included in the analysis (Fig. 1). Participants' demographic and anthropometric characteristics are presented in Table 2. Mean (SD) age at T2DM diagnosis was 57.3 (10.4) years, with a median disease duration of 5.9 years (Table 2). Median (IQR) subject follow-up duration was 2.6 (1.5–4.7) years, with 29.5% of subjects having been diagnosed with T2DM by the study physicians.

Overall, 96.5% of participants had ≥ 1 [median (IQR): 3.0 (2.0–4.0)] clinically relevant medical condition/comorbidity. Conditions/comorbidities reported in $\geq 10\%$ of the participants are shown in Table 2. At enrolment, 93.8% (563/600) of subjects were receiving at least one concomitant medication other than antidiabetics. Medication classes received by $> 10\%$ of the participants included lipid-modifying agents (73.5%), cardiac therapy/antihypertensives (66.5%) and antithrombotic or antiplatelet agents (30.5%).

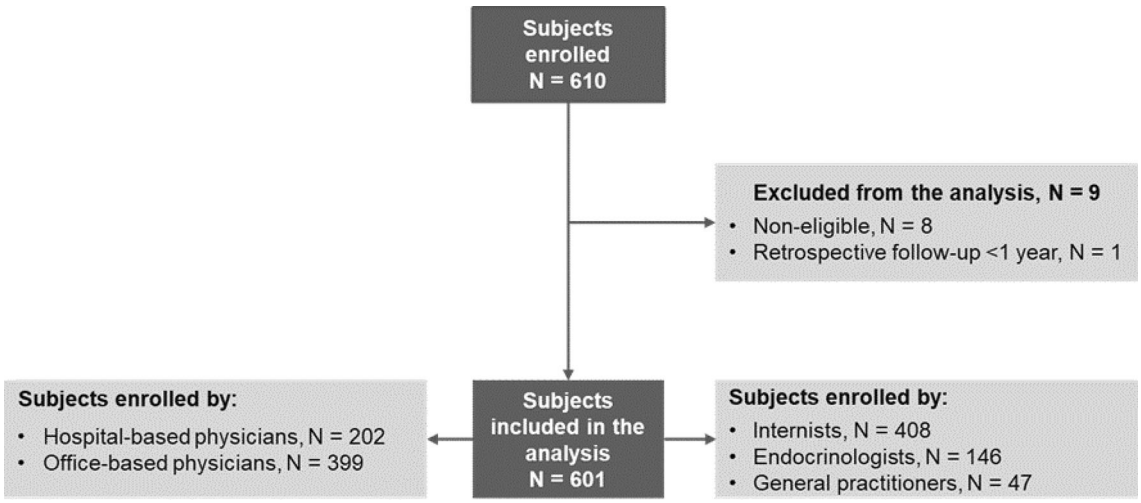

Fig. 1 Subject disposition and flow chart. Flow chart displaying the number of subjects enrolled and analysed, and the number of enrolled subjects analysed per physician specialty and healthcare setting

Frequency of diabetic complications was 16.1%: 6.5% of the subjects had macrovascular, 6.0% microvascular and 7.0% other diabetic complications (Table 3). Additionally, 12 months prior to enrolment, 4.4% of the 571 evaluable subjects had experienced a total of 134 (median 3) hypoglycaemic events. The latter included 75 of unknown severity and 59 mild ones. Prior to enrolment, most subjects had received training on diabetes self-management and personalised nutrition counselling, and most were using a self-monitoring glucose device (Table 3).

Treatment for T2DM and Subjects' Compliance to Medication

Antidiabetic therapy since T2DM diagnosis was known for 509 (84.7%) of subjects. Among these, 30.5% had received one, 31.2% two and 38.3% ≥ 3 antidiabetic agents (Table 4). A median (IQR) of 4.0 (2.1–9.0) years had elapsed from first receipt of an OHA to enrolment.

At enrolment, all subjects were receiving OHAs with a median (IQR) treatment duration of 3.8 (2.0–8.9) years. Specifically, 27.6% of subjects were receiving metformin monotherapy, 63.4% were receiving metformin + other OHAs and 9.0% were receiving therapy that did not include metformin (Table 4). Participants' compliance with antidiabetic medication was rated by the physicians on a five-level scale: 67.5% (400/593) of the subjects were rated as having very good compliance, 26.0% (154/593) as good, 3.9% (23/593) as moderate and 2.7% (16/593) as poor or very poor. In addition, compliance was rated very good/good in 95.4% (188/197) of those receiving monotherapy, in 95.4% (208/218) of those on dual therapy, in 88.8% (135/152) of those receiving triple therapy and in 92.0% (23/25) of those on quadruple therapy.

Guidelines Followed by Physicians

Physicians followed the HDA therapeutic guidelines for managing 77.2% of the subjects, the ADA/EASD guidelines for 43.4% and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines for 8.8%, while different guidelines were followed according to physicians' specialty (Fig. 2). Hospital-based and office-based physicians followed the HDA guidelines for managing 85.6% (173/202) and 72.9% (291/399) of the subjects, the ADA/EASD guidelines for 40.1% (81/202) and 45.1% (180/399), and the AACE/ACE guidelines for 12.4% (25/202) and 7.0% (28/399), respectively.

Table 2 Demographic and anthropometric characteristics of persons enrolled in the study

Demographic and anthropometric characteristics of subjects	Values
Age [mean (SD), years], *N* = 601	65.2 (10.3)
Sex, *N* = 601	
Male	328 (54.6%)
Race, *N* = 601	
Caucasian	601 (100.0%)
Residence, *N* = 601	
Urban	453 (75.4%)
Semi-urban	64 (10.6%)
Rural	84 (14.0%)
Educational level, *N* = 451	
No education	6 (1.3%)
1–12 years	335 (74.3%)
≥ 13 years	110 (24.4%)
Employment status, *N* = 536	
Employed	170 (31.7%)
Unemployed	11 (2.1%)
Retired[a]	255 (47.6%)
Household duties	95 (17.7%)
Other	5 (0.9%)
BMI [median (IQR), kg/m^2], *N* = 505	29.0 (26.2–32.6)
BMI categories	
Normal BMI (18.5 ≤ BMI < 25 kg/m^2)	76 (15.0%)
Overweight (25 ≤ BMI < 30 kg/m^2)	218 (43.2%)
Obese (BMI ≥ 30 kg/m^2)	211 (41.8%)
Smoking, *N* = 567	
Never smoker	379 (66.8%)
Current smoker	89 (15.7%)
Former smoker	99 (17.5%)
Pack-years for former/current smokers [median (IQR)], *N* = 135	30.0 (20.0–45.0)
Alcohol consumption, *N* = 568	
Occasional (1–2 units/week)	184 (32.4%)
Regular (daily or most days/week)	31 (5.5%)
Physical activity, *N* = 538	
No physical activity	203 (37.7%)
Physical activity of vigorous intensity	15 (2.8%)
Physical activity of moderate intensity	110 (20.4%)
Physical activity of low intensity	210 (39.0%)
Conditions/comorbidities in > 10% of the participants (MEdDRA PT), *N* = 601	
At least one	580 (96.5%)
Dyslipidaemia	452 (75.2%)
Hypertension	394 (65.6%)
Hypothyroidism	139 (23.1%)
Obesity	116 (19.3%)
Coronary artery disease	64 (10.6%)
Family history of premature cardiac disease in a first-degree relative, *N* = 601	11 (1.8%)

Values in table are given as a frequency (number with percentage in parentheses), unless otherwise indicated
BMI Body mass index, *IQR* interquartile range, *MedDRA PT* Medical Dictionary for Regulatory Activities Preferred Term, *N* number of subjects for whom information was available, *SD* standard deviation
[a] Two subjects had retired due to T2DM or diabetic complications

Physicians' Adherence to the PFP of the HDA Guidelines

Mean overall physician adherence to the HDA guidelines PFP was 43.6% [95% CI 42.3–45.0, median (IQR) 41.9% (32.3–54.8)] (Fig. 3). The highest adherence was noted for the laboratory

Table 3 Type 2 diabetes history, training on diabetes self-management, nutrition counselling and healthcare resource utilisation in the year prior to enrolment

Clinical aspects of subjects	Values
Characteristics of patient history of T2DM	
Age at T2DM diagnosis [mean (SD), years], *N* = 591	57.3 (10.4)
Duration of T2DM [median (IQR), years], *N* = 591	5.9 (2.9–11.7)
Family history of diabetes mellitus, *N* = 511	323 (63.2%)
Number of HbA_{1c} assessments during the last year prior to enrolment [median (IQR)], *N* = 601	2.0 (2.0–3.0)
Diabetes complications, *N* = 601	97 (16.1%)
Macrovascular complications	39 (6.5%)
Coronary artery disease	28 (4.7%)
Peripheral arterial disease	8 (1.3%)
Transient ischaemic attack	3 (0.5%)
Cerebrovascular event	2 (0.3%)
Cardiac failure	1 (0.2%)
Carotid artery stenosis (> 50%)	1 (0.2%)
Microvascular complications	36 (6.0%)
Peripheral neuropathy	14 (2.3%)
Chronic kidney disease	10 (1.7%)
Autonomic neuropathy	9 (1.5%)
Retinopathy	9 (1.5%)
Diabetic foot	2 (0.3%)
Erectile dysfunction	2 (0.3%)
Other diabetic complications	42 (7.0%)
Patients' training and blood glucose monitoring	
Training on diabetes self-management (during the last year prior to enrolment), *N* = 601	536 (89.2%)
Personalised nutrition counselling for achieving glycaemic control, *N* = 601	549 (91.3%)
Patients' adherence to nutrition recommendations as assessed by the physician, *N* = 529	
Very good/good	312 (59.0%)
Moderate	163 (30.8%)
Poor/very poor	54 (10.2%)
Current use of blood glucose self-monitoring device, *N* = 601	527 (87.7%)
Current use of blood glucose self-monitoring device for at least 1 year prior to enrolment, *N* = 601	522 (86.9%)
Current use of continuous blood glucose monitoring system, *N* = 601	0 (0%)
Healthcare resource utilisation in the 12 months prior to enrolment, *N* = 601	
Total number of visits to study physicians' clinic/office	1307
Number of visits [median (IQR)]	2.0 (1.0–3.0)

Values in table are given as a frequency (number with percentage in parentheses), unless otherwise indicated
N Number of subjects for whom information was available

evaluation domain (mean 48.3%, 95% CI 46.2–50.3), followed by the complete medical history domain (mean 45.5%, 95% CI 43.9–47.1) and then by the physical examination domain (mean 31.2%, 95% CI 29.3–33.2) (Fig. 2).

Mean overall adherence and the results for adherence to each PFP domain according to physicians' specialty are presented in Fig. 2. The percentage of subjects for whom each of the 62 PFP items was completed are shown in Table 1. Items completed in > 90% of subjects included the items "current antidiabetic treatment", "age or date of birth", "response to treatment", "year of T2DM diagnosis" and "HbA_{1c} measurement". Items fulfilled in < 10% of the subjects were the

Table 4 Medications used by study subjects for management of type 2 diabetes mellitus prior to study enrolment and at enrolment

Medications	Number of subjects (%)
Antidiabetic treatment prior to study enrolment	
Subjects for whom the treatment classes received prior to enrolment were fully known, $N = 601$	509 (84.7)
Treatment classes, $N = 509$	
Biguanides/metformin	495 (97.2)
DPP4i	311 (61.1)
SGLT2i	130 (25.5)
Sulphonylureas	123 (24.2)
Glitazones	57 (11.2)
Meglitinides	7 (1.4)
Insulin	4 (0.8)
GLP-1 analogues	3 (0.6)
Alpha-glucosidase inhibitors	2 (0.4)
Combinations of prior drug classes, $N = 509$	
Metformin only	148 (29.1)
Metformin and DPP4i	121 (23.8)
Metformin, DPP4i and SGLT2i	56 (11.0)
Metformin, sulphonylureas and DPP4i	51 (10.0)
Other combinations of drug classes including metformin	119 (23.4)
Combinations not including metformin	14 (2.8)
Antidiabetic treatment at enrolment	
Any treatment, $N = 601$	601 (100.0)
Treatment classes, $N = 601$	
Biguanides/metformin	547 (91.0)
DPP4i	365 (60.7)
SGLT2i	141 (23.5)
Sulphonylureas	98 (16.3)
Glitazones	57 (9.5)
Meglitinides	3 (0.5)
Number of drug classes, $N = 601$	
1	198 (32.9)
2	223 (37.1)
3	154 (25.6)
4	25 (4.2)
5	1 (0.2)
Patterns of drug classes, $N = 601$	
Metformin only	166 (27.6)
Metformin + DPP4i	164 (27.3)
Metformin + DPP4i + SGLT2i	72 (12.0)
Metformin + Sslphonylureas + DPP4i	42 (7.0)
Metformin + other	103 (17.1)
Combinations not including metformin	54 (9.0)

DPP4i Dipeptidyl peptidase-4 inhibitors, *GLP-1* glucagon-like peptide-1, *N* number of subjects for whom information was available, *SGLT2i* sodium-glucose co-transporter-2 inhibitors

items "alcohol consumption", "psychosocial problems", "surgical procedures" and "electrocardiogram at rest'.

The overall adherence of physicians to the PFP was higher for female subjects ($p = 0.026$), subjects with > 3 medical conditions/comorbidities ($p = 0.043$), those with diabetic complications ($p < 0.001$) and those seen by endocrinologists versus general practitioners ($p < 0.001$) and by internists versus general practitioners ($p = 0.001$), when adjusted for other factors in the final multivariable model (Table 5). Significant predictors of physicians' adherence overall and to each of the PFP domains are shown in Table 5.

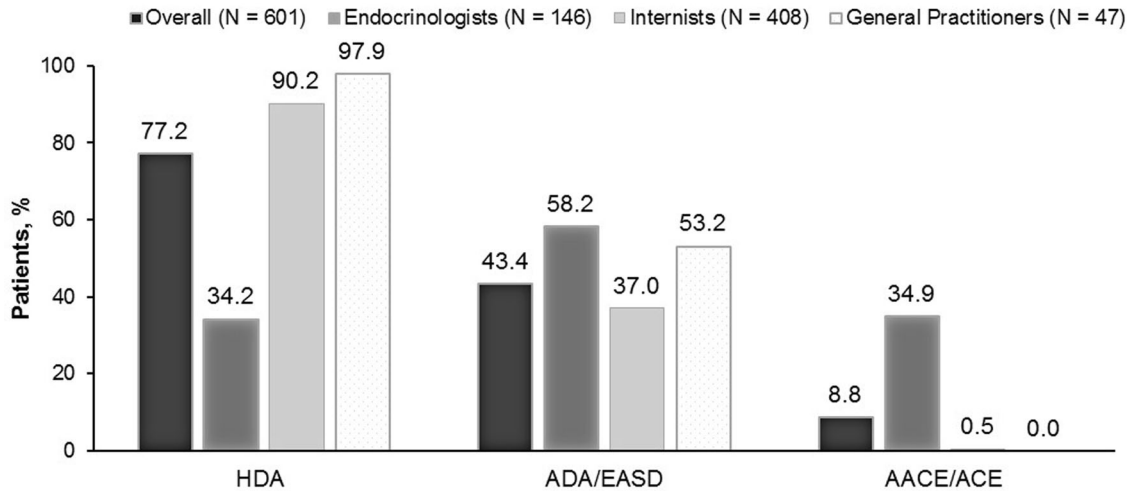

Fig. 2 Diabetes guidelines followed by physicians overall and according to physicians' specialty. Bars and labels indicate percentage of subjects for which each guideline was followed. More than one guideline was followed for some participants. *AACE/ACE* American Association of Clinical Endocrinologists/American College of Endocrinology, *ADA/EASD* American Diabetes Association/European Association for the Study of Diabetes, *HDA* Hellenic Diabetes Association

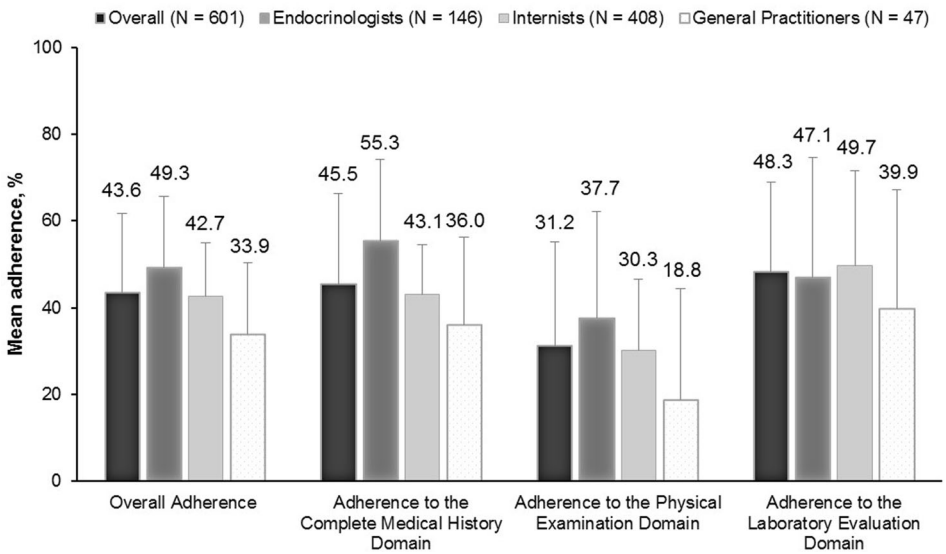

Fig. 3 Adherence to the patient follow-up protocol (PFP) of the HDA guidelines overall and according to physicians' specialty. Bars represent the mean and standard deviation, while the labels indicate means

Achievement of Glycaemic Control at Enrolment

Based on available HbA_{1c} measurements, adequate glycaemic control ($HbA_{1c} < 7\%$) was achieved by 82.1% of all participants (363/442, 95% CI 78.6–85.7; Fig. 4a). Among the 79 (17.9%) subjects without adequate glycemic control, 71 had HbA_{1c} 7–8.5%, one had $HbA_{1c} > 8.5$ and $\leq 9\%$, and seven had

Table 5 Predictors of physicians' adherence to the type 2 diabetes mellitus patient follow-up protocol (PFP) of the Hellenic Diabetes Association guidelines (multivariable linear regression), overall and for each PFP domain

Adherence to PFP overall and for each PFP domain	Comparison	OLS estimate	Standard error	95% Wald CI		*p* value
				Lower limit	Upper limit	
Overall adherence (N = 526)						
Sex	Male vs. female	− 3.163	1.417	− 5.947	− 0.380	0.026*
Duration of T2DM	> 5 vs. ≤ 5 years	1.819	1.427	− 0.985	4.623	0.203
Number of medical conditions/comorbidities	> 3 vs. ≤ 3	3.342	1.644	0.112	6.571	0.043*
Diabetic complications	Yes vs. no	7.929	1.941	4.116	11.742	< 0.001*
Physicians' specialty	Endocrinologist vs. GP	16.062	3.072	10.027	22.097	< 0.001*
	Internist vs. GP	9.083	2.831	3.521	14.645	0.001*
Complete medical history domain (N = 536)						
Sex	Male vs. female	− 3.482	1.616	− 6.658	− 0.307	0.032*
Diabetic complications	Yes vs. no	10.935	2.106	6.797	15.072	< 0.001*
Physicians' specialty	Endocrinologist vs. GP	22.684	3.390	16.025	29.342	< 0.001*
	Internist vs. GP	10.060	3.137	3.898	16.221	0.001*
Physical examination (N = 591)						
Sex	Male vs. female	− 4.072	1.935	− 7.871	− 0.272	0.036*
Duration of T2DM	> 5 vs. ≤ 5 years	3.029	1.958	− 0.815	6.874	0.122
Number of medical conditions/comorbidities	> 3 vs. ≤ 3	8.714	2.097	4.596	12.833	< 0.001*
Physicians' specialty	Endocrinologist vs. GP	16.525	4.052	8.566	24.484	< 0.001*
	Internist vs. GP	9.174	3.721	1.867	16.482	0.014*
Laboratory evaluation (N = 591)						
Age at enrolment	≥ 65 vs. < 65 years	4.020	2.185	− 0.271	8.312	0.066
Duration of T2DM	> 5 vs. ≤ 5 years	3.882	2.181	− 0.401	8.164	0.076

Table 5 continued

Adherence to PFP overall and for each PFP domain	Comparison	OLS estimate	Standard error	95% Wald CI		*p* value
				Lower limit	Upper limit	
Number of medical conditions/comorbidities	> 3 vs. ≤ 3	6.383	2.295	1.876	10.890	0.006*

CI Confidence interval, *GP* general practitioner, *HDA* Hellenic Diabetes Association, *N* Number of subjects for whom information was available, *OLS* ordinary least squares
*Significant difference at $p < 0.05$

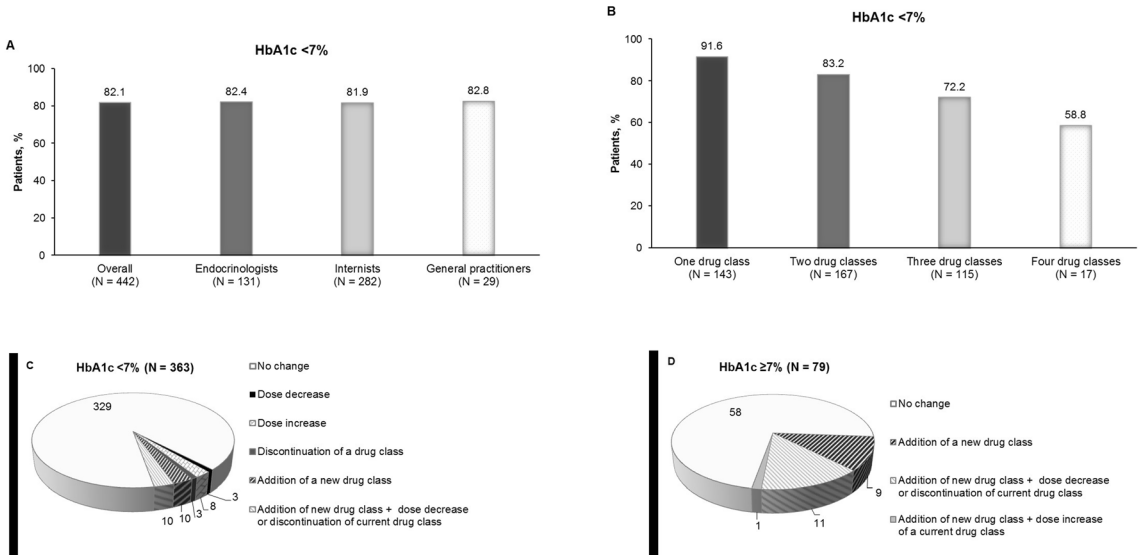

Fig. 4 Achievement of glycaemic control and action taken with current antidiabetic medication by physicians at enrolment. **a** Glycaemic control achievement rate, overall and according to physicians' specialty. Labels indicate the percentages of participants achieving control, and *N* is the number of patients for whom data were available on haemoglobin A_{1c} (HbA_{1c}). **b** Glycaemic control achievement rate by number of antidiabetic treatment classes received. Labels indicate the percentages of participants achieving control, and *N* is the number of patients for whom data were available on HbA_{1c}. **c** Distribution of participants [in absolute numbers (*N*)] attaining the target $HbA_{1c} < 7\%$ according to the action to be taken with their antidiabetic medication at enrolment. **d** Distribution of participants [in absolute numbers (*N*)] failing to attain the target $HbA_{1c} < 7\%$ according to the action to be taken with their antidiabetic medication at enrolment

$HbA_{1c} > 9\%$. The glycaemic control achievement rate according to the physicians' specialty is shown in Fig. 4a. The glycaemic control rate decreased as the number of OHAs increased, ranging from 91.6% in those receiving antidiabetic monotherapy to 58.8% in those receiving four OHAs (Fig. 4b).

LDL-C, Blood Pressure, and Composite Metabolic Control at Enrolment

Overall, the percentages of subjects achieving the LDL-C, SBP, DBP, composite SBP/DBP and composite metabolic targets were 57.0% (174/305) [with established CVD: 26.7% (12/45), without CVD: 62.3% (162/260)], 55.2% (289/

524), 60.7% (318/524), 42.6% (223/524) [≥ 65 years: 59.6% (159/267), < 65 years: 24.9% (64/257)] and 21.6% (58/268), respectively. The corresponding rates for SBP/DBP target achievement per physicians' specialty were 44.4% (59/133), 42.2% (152/360, and 38.7% (12/31) for endocrinologists, internists and general practitioners respectively; achievement of the composite metabolic target was 21.6% (21/97), 21.5% (34/158) and 23.1% (3/13) for the aforementioned specialties.

Changes in OHAs at Enrolment

For 89.4% (537/601) of subjects, OHAs were not changed. Conversely, antidiabetic treatment was changed for 64 subjects (10.6%), including 34 with $HbA_{1c} < 7\%$, 21 with $HbA_{1c} \geq 7\%$ (Fig. 4c, d), and nine for whom HbA_{1c} data were unavailable. Changes in OHAs adhered to the HDA-recommended therapeutic algorithm in 83.5% (369/442) of subjects with available HbA_{1c} [in 96.7% (351/363) of those with $HbA_{1c} < 7\%$ and in 22.8% (18/79) of those with $HbA_{1c} \geq 7\%$ at enrolment].

DISCUSSION

The GLANCE study provides novel evidence on the adherence of Greek physicians to the PFP of the HDA guidelines in the routine care setting. It also provides data on the achievement rates for glycemic, blood pressure and lipid and composite metabolic control targets of non-insulin dependent subjects with T2DM in routine care settings.

The mean overall adherence of physicians to the PFP of the HDA guidelines was below 50%. Physican adherence was highest for the laboratory evaluation domain (48%), followed by the complete medical history domain (46%) and then the physical examination domain (31%). Slightly higher physician adherence rates were reported in the ADMIRE (Adherence of physicians to guidelines for the management of type 2 diabetes) study [18, 24], which had a similar design as the GLANCE study and evaluated physician adherence to the Turkish diabetes guidelines PFP in 1790 patients [18, 25]. The Turkish and Greek PFP have several items in common, and the former separates the items into the same three domains as examined in the GLANCE study [20]. In ADMIRE, the mean overall adherence score for the 12 months prior to study enrolment was 70%, with the scores (on 10-point scales) being 8.8 for the 5-item medical history domain, 6.3 for the 3-item laboratory evaluation domain, and 5.9 for the 10-item physical examination domain [18]. The difference in the adherence scores between the two studies may be partly due to all 62 items of the HDA PFP being considered in the GLANCE study, whereas only 18 of the 39 items of the Turkish guidelines were evaluated in the ADMIRE study [18, 24, 25]. Additionally, the higher physician adherence rate in ADMIRE could, at least partly, be attributed some items of the PFP examined possibly being among those more commonly performed by physicians. For example, mean adherence score for the laboratory domain in the present study would be about 60% (and thus similar to the mean of 6.3 on a 10-point scale reported in ADMIRE), if it was based on the laboratory domain items included in ADMIRE [18, 24]. However, caution is needed when comparing the results of these two studies given that they differ in terms of patient characteristics. Importantly, in ADMIRE [24], 35% of subjects received insulin, which was an exclusion criterion in the present study. Moreover, female sex was more frequent in ADMIRE (62%) [24] than in the present study (45%), and this has been shown to affect adherence, both in the present study and in a Luxembourg study [26]. Finally, in both the present study and in ADMIRE, diabetic complications and physicians' specialty were associated with adherence [18].

The results from the multivariable model on the factors affecting the overall PFP adherence require further investigation. For example, there are no specific cultural characteristics that may explain the increased adherence related to female subjects; and mixed findings have been reported in published data on the sex differences affecting the management of people with diabetes [27]. Furthermore, subjects with multiple comorbidities may have more regular access to the healthcare system and they also

may receive more attention from their treating physician related to diabetes management and regular follow-up. In addition, the specialised and continuous education of endocrinologists and internal medicine physicians in diabetes could further provide a potential explanation of these results.

The general reasons reported for the poor adherence of physicians to guidelines include, among others, a lack of awareness or familiarity with the guidelines and/or the absence of any education on the use of the guidelines [17, 28, 29]. Indeed, in the ADMIRE study, overall physican adherence increased following the introduction of an education programme on the guidelines and diabetes complications [18]. Additional barriers to adherence may include poor healthcare finances and resources, inadequate healthcare system infrastructure and logistic support, excessive physician workload and the fact that physicians often doubt the utility of guidelines [29]. During the financial crisis in Greece, it was reported that prescriptions for OHAs were not affected [30], but decreased income and unemployment were identified as the major factors affecting access to healthcare services [31]. Specifically, the concerns of subjects with T2DM about treatment costs may affect their adherence to treatment and frequency of prescription fulfilment or even influence physicians' prescription behaviour towards choosing less expensive treatment options [32]. Moreover, budget cutbacks related to biochemical testing for and poor follow-up of diabetic complications that may prevent regular patient monitoring [32] could also play an important role in physician adherence to PFP. However, an inquiry into these factors was beyond the scope of GLANCE.

Of note, some studies have reported high adherence to guideline recommendations in terms of laboratory tests but inadequate glycemic control [33–35]. We found the reverse discrepancy, i.e. inadequate PFP adherence, but high glycaemic control (82.1%). Impressively, this glycaemic control rate is the highest reported over the last decade in multi-centre studies in routine care Greek settings. In the recent AGREEMENT registry of 1191 adult patients with T2DM, adequate glycaemic control was achieved by 53% of subjects overall and by 65% of non-insulin-treated subjects [36]. Other studies have reported glycaemic control rates of 53–67% [15, 30, 37]. In the GLANCE study, the LDL-C target was achieved by 57% of subjects, compared to 31% [15] and 60% [36] in previous Greek studies. In addition, adequate SBP control was achieved in the GLANCE study by 55% of subjects compared to a previously reported rate of 27% [15], while the composite metabolic control rate was 22% in this work compared to about 5% in a previous study [15]. Arguably, our results point to some improvement—or at least some degree of stability—in the observed rates compared to those reported previously. Nonetheless, it should be mentioned that the present work was of a different design to those of the aforementioned Greek studies and had the primary aim to assess physician adherence to the HDA diabetes care guideline, with a secondary aim to capture the rates of achievement of glycemic, blood pressure and lipid targets.

Patient adherence to medication is known to affect the achievement of therapeutic targets [38, 39]. In the present study, physicians reported that compliance to OHAs was very good/good in the vast majority (93%) of subjects. Importantly, therapeutic decisions for changes in OHAs adhered to the HDA therapeutic algorithm in nearly nine of ten subjects. This high percentage probably reflects the wide acceptability of the HDA guidelines and the quality of the HDA-initiated physician education initiative on antidiabetic therapy.

Overall, the findings of GLANCE indicate that further efforts should focus on identifying potential barriers to the suboptimal adherence of physicians to the 62 PFP items and towards increasing physician awareness of the importance of comprehensive medical evaluation as outlined by HDA and international diabetes guidelines [20–23]. Moreover, given the available resources of physicians and taking into consideration potential financial and time constraints in routine care, it may be useful to take a closer look at the 62 items in the national PFP that were most met and least commonly met and potentially prioritise some items in the PFP. This could possibly optimise care for

subjects with T2DM under the realistic situations encountered by physicians in daily practice [40]. On the other hand, the rapid evolution in digital solutions for diabetes management could further support patient follow-up protocols and improve outcomes [41]. However, as highlighted by the EASD and the ADA Diabetes Technology Working Group, several issues regarding the standardisation of diabetes digital applications should be addressed so that they can be validated in terms of their clinical significance and ensure patient safety and data privacy [42].

The strengths of the study include the large sample size and its multi-centric and nationwide nature. The recruitment of subjects from 10 of the 13 administrative regions of Greece (residence to 93.4% of the country's population) and the inclusion of endocrinologists, internists and general practitioners reflect variations in clinical practice. However, the study also has a number of limitations. First, bias in subject selection and information cannot be entirely ruled out. The former was minimised by consecutive enrolment. Regarding the latter, the rate of missing data on HbA_{1c}, LDL-C and SBP/DBP measurements was between 13% (SBP/DBP) and 49% (LDL-C). Moreover, data on diabetic complications were only collected from medical records; therefore, underestimation of their actual prevalence cannot be ruled out. A further limitation is that we did not use a central laboratory for measurements. Moreover, the inclusion of subjects with ≥ 2 HbA_{1c} measurements may have contributed to overestimation of adherence. Also, the Likert scale used by physicians to evaluate patient compliance to antidiabetic treatment as well as patient adherence to physicians' recommendations represents per se a subjective rating method, which does not necessarily reflect the real situation. Lastly, results should be interpreted with caution, and a prospective study using all subjects with T2DM from the national diabetes registry could shed more light on current T2DM management in Greece.

CONCLUSIONS

The adherence of Greek physicians to the full PFP of the national diabetes guidelines is suboptimal. Of note, this adherence is affected by physicians' specialty as well as patient characteristics, such as sex, comorbidities and diabetic complications. Hence, future efforts should strive to identify potential barriers to guideline adherence in order to improve it and potentially prioritise the items included in the PFP, with the ultimate goal to optimally support subjects with T2DM.

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Compliance with Ethic Guidelines. The study was conducted in accordance with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice, the ethical principles of the Declaration of Helsinki of 1964 and its later amendments and all standing regulations. The study was approved by the ethics committees of all participating hospitals (see Electronic Supplementary Material Table S1). Signed written informed consent was obtained from all participants.

Prior Presentation. Part of the manuscript was presented as an abstract in ISPOR Europe 2019 Congress, Copenhagen, Denmark.

Data Availability. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request. MSD is committed to providing qualified scientific researchers access to anonymised patient-level data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. The company is also obliged to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The process includes submission of data requests to the Merck data sharing website (available at http://engagezone.merck.com/ds_documentation.php).

There are circumstances that may prevent Merck from sharing the requested data.

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