Thieme

Real-World Adequacy of Glycaemic Control in Treatment-Naïve Greek Patients with Type 2 Diabetes Mellitus Initiating Treatment with Metformin Monotherapy at the Maximum Tolerated Dose: The Reload Study

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Key words
clinical inertia, glycaemic control, metformin, type 2 diabetes mellitus

received 14.10.2018
revised 15.12.2018
accepted 18.12.2018

Bibliography
DOI https://doi.org/10.1055/a-0824-6607
Published online: 2019
Exp Clin Endocrinol Diabetes

ISSN 0947-7349

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ABSTRACT

Background Metformin, in the absence of contraindications or intolerance, is recommended as first-line treatment for patients with type 2 diabetes mellitus (T2DM). This observational, retrospective study assessed the real-world adequacy of glycaemic control in Greek patients with T2DM initiating metformin monotherapy at maximum tolerated dose.

Methods Included patients received metformin monotherapy for ≥ 24 months; relevant patient data were collected immediately prior to metformin initiation (baseline) and at other prespecified time points. The primary objective was to report, after 9 months of metformin treatment, the percentage of patients with baseline glycated haemoglobin (HbA_{1c}) levels ≥ 6.5 % (≥ 48 mmol/mol) achieving HbA_{1c} < 6.5 %. Secondary objectives included the assessment of time spent with poor glycaemic control and time to treatment intensification. A sensitivity analysis assessed the percentage of patients with baseline HbA_{1c} ≥ 7 % (≥ 53 mmol/mol) achieving HbA_{1c} < 7 % (< 53 mmol/mol).

Results Of the enrolled patients (N = 316), 247 had baseline HbA_{1c} ≥ 6.5 %; following 9 months on metformin, 90 (36.4 %) patients achieved HbA_{1c} < 6.5 % (mean HbA_{1c} change − 1.3 % [− 14 mmol/mol]). Median time of exposure to HbA_{1c} ≥ 6.5 % was 23.4 months and time to treatment intensification was 28.0 months. The sensitivity analysis revealed that the proportion of patients achieving HbA_{1c} < 7.0 % was 50 % (mean HbA_{1c} change − 1.6 % [− 17 mmol/mol]).

Conclusion Irrespective of HbA_{1c} target assessed, most patients with T2DM do not achieve the recommended HbA_{1c} goals after 9 months on metformin while remained on monotherapy for up to 24 months. Addressing clinical inertia could improve disease outcomes and, possibly, economic burden.

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive and complex metabolic disorder that is associated with a risk of developing microvascular and macrovascular complications when blood glucose is not adequately controlled [1]. The Hellenic Diabetes Association (HDA), in agreement with American and European positioning statements for the management of hyperglycaemia [2, 3], recommends that glycated haemoglobin (HbA_{1c}) levels should be maintained < 7 % (53 mmol/mol) for the majority of patients with T2DM [4]; for patients with long life expectancy and without serious comorbidities or apparent cardiovascular disease the recommended level is < 6.5 % (48 mmol/mol) provided that the treatment does not cause hypoglycaemia episodes. The HDA treatment algorithm for T2DM recommends the initiation of metformin concurrently with lifestyle modifications at diagnosis [4]. Metformin, in the absence of contraindications or intolerance, is recommended as first-line treatment on the basis of its proven efficacy and tolerability [5, 6]. As a result, metformin is used widely in the treatment of T2DM, either as monotherapy or in combination with other agents [7].

Despite the recommendations for strict glucose control, numerous studies have shown that increased HbA_{1c} levels may persist for long periods of time in patients with T2DM [8, 9]; these findings likely reflect the progressive nature of the disease but are also attributed to 'clinical inertia' which is defined as a failure to 'intensify therapy when indicated, or a failure to act despite recognition of the problem' [10]. Clinical inertia in the management of patients with T2DM may result in suboptimal glycaemic control, which is associated with increased incidence of cardiovascular events [11]. Following metformin treatment failure, clinical inertia has been reported to affect almost half of the patients assessed [12], with delays in treatment intensification with additional anti-hyperglycaemic agents exceeding one year [13–15].

In Greece, more than 2 thirds of patients with T2DM receiving anti-hyperglycaemic monotherapy are treated with metformin [16], which is in alignment with the HDA treatment guidelines [4]. However, 32.9 % to 47.0 % of actively treated patients have HbA1c levels ≥ 7 % (≥ 53 mmol/mol) for significant periods of time [17, 18]. In the Europe-wide PANORAMA study, which included Greece, one of the barriers to glycaemic control attainment is clinical inertia [19].

At present, treatment adequacy of glycaemic control with metformin monotherapy and subsequent treatment intensification practices have not been studied in Greece, representing a knowledge gap for both physicians and health authorities. This real-world study was designed to explore the adequacy of glycaemic control metformin monotherapy on maximum tolerated doses in patients with T2DM.

Methods

Study design and patients

RELOAD was an observational, retrospective, real-world study conducted in a total of 18 primary and secondary care sites in Greece (12 primary care physician practices and 6 hospital outpatient clinics); participating physicians were diabetologists, endocrinologists, pathologists and general practitioners. Ethical approval was sought and obtained from all coordinating centres. Sites were selected on the basis of availability of patient medical charts (electronic or hard-copy). To ensure random patient selection, investigators were required to select the first 10 eligible patients visiting the centre on a given practice day.

Eligible patients were diagnosed with T2DM as based on HDA criteria [4], were aged 40 years or older at the time of diagnosis and initiated and were maintained on treatment with metformin monotherapy at maximum tolerated doses for ≥ 24 months during the 60-month period prior to study enrolment, irrespective of the baseline HbA_{1c} measurement.

Patients were excluded from the study if at baseline, they were treated with insulin or oral hypoglycaemic agents other than metformin, had a cardiovascular event, diabetes mellitus secondary to other conditions (such as surgical procedures, medications, infections etc.) or a condition affecting glucose metabolism during the 24-month treatment period with metformin.

Procedures

At study entry, demographic and current clinical data were collected. Furthermore retrospective clinical data were collected from the medical charts for the following time-points: immediately before initiating metformin treatment (baseline), at 9, 17–20 and 24 months, and then at any time point from 24–60 months prior to the decision to intensify metformin monotherapy with the addition of at least one anti-hyperglycaemic agent (▶ **Fig. 1**); glycaemic control with metformin is usually optimised after 9 months of treatment, while secondary treatment failure with metformin typically occurs after 17–20 months [15].

Demographic data included age, gender, age at time of T2DM diagnosis and disease duration, body mass index, smoking habits, alcohol consumption and amount of physical activity (defined as mild if it occurred for < 20 min per week, or intense if it occurred in multiple bouts of ≥ 20 min per week). Current or retrospective recorded clinical data included microvascular and macrovascular diabetes complications, comorbidities, HbA_{1c} measurements, fasting plasma glucose, blood pressure, lipidemic profile and treatment dates and dosages for all anti-hyperglycaemic medications used. Apart from the HbA_{1c} measurements recorded along with other detailed information at the selected time-points, intervening HbA_{1c} measurements which were part of the daily clinical practice were also recorded for the assessment of the time of exposure to

DCP

1 : Immediately prior to metformin monotherapy initiation (during study period; up to 60 months prior to enrolment date)
2 : After 9 months of metformin monotherapy
3 : Between months 17 to 20 of metformin monotherapy
4 : Any time point between months 24 to 60, at treatment intensification
5 : Up to 60 months from metformin initiation (Study enrolment)

▶ **Fig. 1** DCP, data collection point.

HbA_{1c} ≥ 6.5 % and time to treatment intensification following metformin failure.

Definitions

Glycaemic control was defined as the achievement of HbA_{1c} levels < 6.5 % (< 48 mmol/mol) following 9 months of metformin monotherapy at maximum tolerated doses. Metabolic control was defined as the combined achievement of HbA_{1c} < 7 % (< 53 mmol/mol), high- and low-density lipoprotein values of > 40 mg/dL (> 1.0 mmol/l) and < 100 mg/dL (< 2.6 mmol/l), respectively, and systolic and diastolic blood pressure values of < 130 and < 80 mmHg, respectively. Metformin failure was defined as the non-attainment of glycaemic control from treatment initiation through to 9 months or, subsequently, the inability to maintain glycaemic control. Treatment intensification was defined as the addition of at least one anti-hyperglycaemic agent to metformin.

Objectives

The primary objectives were to assess the percentage of patients achieving HbA_{1c} < 6.5 % (< 48 mmol/mol) after 9 months of metformin monotherapy at maximum tolerated doses and the mean absolute HbA1c reduction from baseline to 9 months, both for the subgroup of patients with baseline HbA1c ≥ 6.5 % (≥ 48 mmol/mol).

Secondary objectives included the assessment of the percentage of patients with baseline HbA_{1c} ≥ 6.5 % (≥ 48 mmol/mol) who achieved glycaemic control at 17–20 months; the mean absolute HbA_{1c} reduction from baseline, after 9 and 17–20 months of metformin monotherapy for the entire study population (i. e., irrespective of baseline HbA1c level); the average time spent with HbA_{1c} at levels ≥ 6.5 % (≥ 48 mmol/mol) or ≥ 7 % (≥ 53 mmol/mol) while on metformin monotherapy for the entire study population; time to treatment intensification with one (or more) anti-hyperglycaemic agents for these patients who had their treatment intensified during the observation period (60 months); and factors influencing the probability of achieving metabolic control.

Statistical analysis

Sample size was estimated based on the assumption that among those patients with baseline HbA_{1c} ≥ 6.5 % (≥ 48 mmol/mol) the expected percentage achieving HbA_{1c} < 6.5 % (< 48 mmol/mol) would be 50 %. This assumption is the most conservative from a statistical perspective since it provides the widest confidence interval (CI). Thus, with a sample of 250 evaluable subjects the 95 % CI of such percentage has an error margin of ± 6 %. In this study 316 patients had to be enrolled in total so as to have 247 patients with had baseline HbA_{1c} ≥ 6.5 % (≥ 48 mmol/mol).

Descriptive analysis was performed with standard methods to summarize socio-demographic and clinical variables of study patients. Continuous variables are presented as mean with standard deviation (SD) and categorical variables as counts and proportions, along with the respective 95 % CIs.

The impact of comorbidities and diabetes complications on the probability of attaining glycaemic control was evaluated with univariate logistic regression analysis; no multivariate analysis was conducted, since none of these variables was statistically significantly associated with the probability of attaining glycaemic control. For the impact of a variety of demographic and clinical patient variables on the probability of attaining metabolic control, univariate analyses were initially performed (see supplement), followed by a model selection procedure. For the model selection, the exclusion criterion for Type I error was set at 10 %. The odds ratios (ORs) along with the respective 95 % CIs are presented. Statistical significance was set at the level of $p < 0.05$. Analysis was carried out with SAS® release 9.3 (SAS Institute, Inc., Cary, NC, USA).

A sensitivity analysis, evaluated the percentage of patients with baseline HbA_{1c} ≥ 7 % attaining levels of < 7 % (< 53 mmol/mol) after 9 months of metformin treatment, as this HbA_{1c} treatment goal is recommended by the HDA for the majority of patients with T2DM [4].

Results

Patient demographic and clinical characteristics

A total of 316 patients with T2DM were enrolled in the study. At study entry, patients had a mean age of 65.8 years, 49.4 % had a family history of T2DM diabetes, 87.6 % had no or mild weekly physical activity and almost half were on diabetes dietary regimens as recommended by HDA (▶ **Table 1**) [4]. A small percentage of patients (7.6 %) had microvascular and macrovascular diabetes-related complications and 87.3 % had comorbidities, mainly hypertension and dyslipidaemia. The majority of patients (96.8 %) were receiving metformin, either alone or in combination, followed by dipeptidyl peptidase-4 inhibitors, sulfonylurea and insulin in descending order. One patient did not contribute to the HbA_{1c} analysis due to missing baseline measurement

The clinical characteristics at baseline (defined as immediately before metformin treatment initiation) are shown in ▶ **Table 1**. The mean HbA_{1c} for the entire population was 7.2 % (55 mmol/mol); specifically, 247 patients had HbA_{1c} ≥ 6.5 % (≥ 48 mmol/mol; mean HbA_{1c}: 7.4 % [57 mmol/mol]) and 68 patients had HbA_{1c} < 6.5 % (< 48 mmol/mol; mean HbA_{1c}: 6.1 % [43 mmol/mol]). The sensitivity analysis included 150 patients who had baseline HbA_{1c} ≥ 7.0 % (≥ 53 mmol/mol; mean HbA_{1c}: 7.9 % [63 mmol/mol]). Overall, patients were initiated at a mean metformin daily dose of 1,527.3 mg.

The mean HbA_{1c} values for the entire study population following 9, 17–20 and 24 months of metformin monotherapy and at treatment intensification are shown in ▶ **Fig. 2**. The mean metformin daily dose was 1,560.5 mg, 1,621.3 mg, 1,642.8 mg and 1,871.7 mg at 9, 17–20 and 24 months, and at treatment intensification, respectively.

Primary objectives

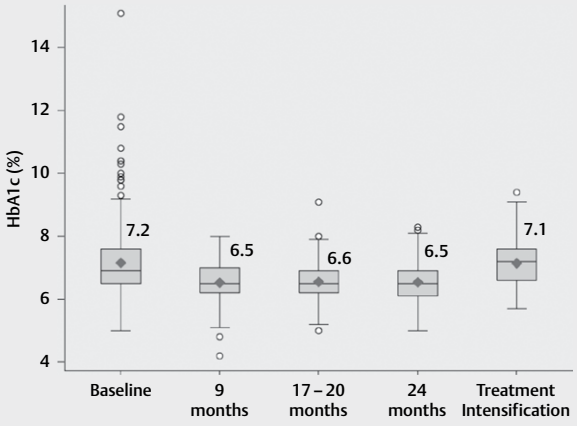
Of the patients with baseline HbA1c ≥ 6.5 % (≥ 48 mmol/mol), 36.4 % (90/247) achieved glycaemic control after 9 months of treatment with metformin monotherapy at maximum tolerated doses; the mean absolute HbA1c was statistically significantly changed by − 1.3 % (− 14 mmol/mol; 95 % CI: − 1.57, − 0.95; $p < 0.001$), from baseline to 9 months (▶ **Fig. 3a**); notably, the mean HbA_{1c} levels for these patients remained < 6.5 % (< 48 mmol/mol) through to 24 months of treatment.

Conversely, 62.4 % (154/247) of patients with baseline HbA_{1c} > 6.5 % (> 48 mmol/mol) did not achieve glycaemic control after 9 months, of treatment with metformin monotherapy and re-

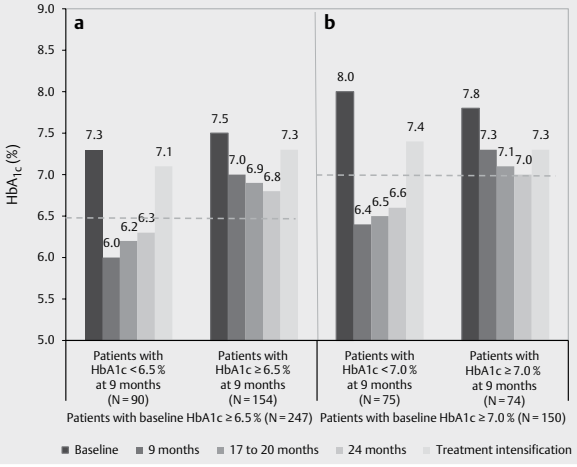
▶ **Table 1** Patient demographic and clinical data at baseline (immediately prior to metformin treatment at maximum tolerated dose) and at study entry (end of observation period).

Characteristics	Baseline (Prior to metformin treatment at maximum tolerated dose)	End of observation period (Study entry, ≤ month 60)
Age, years	62.2 (10.4)	65.8 (10.4)
Female, n (%)	151 (47.8)	
Weight, kg	84.4 (16.1)	84.4 (15.9)
Body Mass Index, n (%)		
18.5–25, kg/m^2	31 (9.8)	35 (11.1)
25–30, kg/m^2	140 (44.3)	131 (41.5)
>30, kg/m^2	134 (42.4)	135 (42.7)
Smoking status, n (%)		
Current smoker	NA	40 (12.7)
Ex-smoker		92 (29.1)
Alcohol consumption, n (%)		
Never	NA	152 (48.1)
Occasionally		148 (46.8)
Every day		13 (4.1)
Physical activity, n (%)		
No activity on a weekly basis	143 (45.3)	141 (44.6)
Only mild activity for most of the weeks	145 (45.9)	136 (43.0)
Intense activity for ≥ 20 min, 1–2 times per week	11 (3.5)	17 (5.4)
Intense activity for ≥ 20 min, ≥ 3 per week	15 (4.7)	22 (7.0)
Special diabetes diet, n (%)	149 (47.2)	161 (50.9)
Positive family history of T2DM, n (%)	156 (49.4 %)	
Comorbidities, n (%)		
Arterial hypertension	187 (59.2)	210 (66.4)
Dyslipidaemia	168 (53.1)	208 (65.8)
Myocardial infarction†	-	8 (2.5)
Diabetes-related complications, n (%)		
Microvascular		
Retinopathy	4 (1.3)	6 (1.9)
Nephropathy	1 (0.3)	3 (0.9)
Neuropathy	3 (0.9)	4 (1.3)
Macrovascular		
Vascular disease	1 (0.3)	2 (0.6)
Cardiovascular disease	4 (1.3)	12 (3.8)
Treatments, n (%) *		
Metformin	-	306 (96.8)
DPP-4 inhibitors	-	84 (26.6)
Sulfonylurea	-	21 (6.6)
GLP-1 agonists	-	14 (3.1)
Insulin	-	9 (2.8)
Other	-	11 (3.5)

Data are n (%) or mean (SD), unless otherwise indicated; †Patients were excluded from the study if they had cardiovascular disease or if they received treatment for T2DM other than metformin; DPP-4, dipeptidyl peptidase; GLP-1, glucagon-like peptide-1; N, number of patients in the analysis; n, number of patients in specified category, NA, non-available.



▶ **Fig. 2** Baseline denotes the HbA_{1c} value prior to treatment initiation with metformin monotherapy. Treatment intensification denotes any time point from 24–60 months prior to the decision to intensify metformin monotherapy with the addition of at least one anti-hyperglycaemic agent. Diamonds represent mean values (which are numerically shown above each box) and circles represent outliers. HbA_{1c} unit conversion: 7.2 %, 55 mmol/mol; 6.5 %, 48 mmol/mol; 6.6 %, 49 mmol/mol; and 7.1 %, 54 mmol/mol. HbA_{1c}, glycated haemoglobin, N, number of patients in the analysis.



▶ **Fig. 3** Panel A shows the HbA_{1c} development for patients with baseline HbA_{1c} ≥ 6.5 % (≥ 48 mmol/mol) who either achieved or failed to achieve the HbA_{1c} target of < 6.5 % after 9 months of metformin monotherapy. Panel B shows the HbA_{1c} development for the HbA_{1c} target of < 7.0 % (< 53 mmol/mol). In both panels, the vertical dashed lines indicate the target HbA_{1c} values. Baseline denotes the HbA_{1c} value prior to treatment initiation with metformin monotherapy. Treatment intensification denotes any time point from 24–60 months prior to the decision to intensify metformin monotherapy with the addition of at least one anti-hyperglycaemic agent. HbA_{1c}, glycated haemoglobin; N, number of patients in the analysis.

mained at HbA_{1c} levels ≥ 6.5 % through to 24 months of treatment (▶ **Fig. 3a**). The percentage of patients who achieved glycaemic control at 9 months was numerically higher among those with ar-

terial hypertension as compared to normotensive patients (65 [40.9 %] vs. 25 [28.4 %], respectively, p = 0.051).

To evaluate the robustness of the results, the primary analysis was repeated excluding patients treated with doses < 1500 mg (104 patients) and patients with HbA_{1c} > 8 % (64 mmol/mol) at baseline (38 patients), with minor changes (glycaemic control after 9 months was not achieved by 67.9 % and 61.2 % of patients respectively).

Secondary objectives

Of the total patients with baseline HbA_{1c} ≥ 6.5 % (≥ 48 mmol/mol), 34.4 % (85/247) achieved glycaemic control after 17–20 months of treatment with metformin monotherapy, with a mean absolute HbA_{1c} change of − 1.2 % (− 13 mmol/mol) from baseline (from 7.3 % [56 mmol/mol] at baseline to 6.1 % [43 mmol/mol] at 17–20 months; 95 % CI: − 1.49, − 0.91).

The median duration of exposure to HbA_{1c} levels ≥ 6.5 % (≥ 48 mmol/mol) or ≥ 7 % (≥ 53 mmol/mol) was 23.4 months (interquartile range [IQR] 10.5–32.7) and 13.6 months (IQR 8.7–23.9), respectively. In patients with metformin monotherapy treatment failure the median time to treatment intensification was 28.0 months (IQR 25.2–35.1) and 27.8 months (IQR 24.6–35.7) for patients with baseline HbA_{1c} levels ≥ 6.5 % (≥ 48 mmol/mol) or ≥ 7 % (≥ 53 mmol/mol), respectively.

During this 24-month period, small improvements were observed in lifestyle modifications (diet and physical activity) and body weight, blood pressure and lipidemic profile. The changes in dietary habits were more common but without any effect on glycaemic control. The median frequency of laboratory tests was 1.6 (IQR 1.1–2.1) times per year. Metformin monotherapy was intensified in 35.4 % (112/316) of patients after ≥ 24 months.

Sensitivity analysis

Of the 150 patients with HbA_{1c} ≥ 7.0 % (≥ 53 mmol/mol), 50.0 % (75/150) achieved HbA_{1c} < 7.0 % (< 53 mmol/mol) after 9 months of metformin, the respective results regarding the mean absolute HbA_{1c} are presented in ▶ **Fig. 3b**. Mean HbA_{1c} levels for these patients remained < 7.0 % (< 53 mmol/mol) through to 24 months.

In contrast, 49.3 % (74/150) of patients from this subgroup failed to achieve HbA_{1c} < 7.0 % (< 53 mmol/mol) at 9 months, reaching a mean HbA_{1c} level of 7.0 % (53 mmol/mol) after 24 months of metformin treatment (▶ **Fig. 3b**).

Factors associated with metabolic control

A variety of demographic and clinical patient variables were investigated for correlation with metabolic control. Arterial hypertension, weight and intense physical activity were predictive of metabolic control (▶ **Table 2**).

▶ **Table 2** Multivariate analysis of factors associated with metabolic control.

	OR	95 % CI	P-value
Weight	0.961	(0.933–0.99)	0.009
Arterial Hypertension			0.046
Yes vs No	0.454	(0.209–0.986)	
Physical Activity			0.020
"Only mild physical activity for most of the weeks" vs. "No activity on a weekly basis"	1.773	(0.736–4.271)	0.202
"Intense physical activity for ≥ 20 min, 1–2 times per week" vs. "No activity on a weekly basis"	0.879	(0.097–7.947)	0.909
"Intense physical activity for ≥ 20 min, 3 or more times per week" vs. "No activity on a weekly basis"	6.716	(1.996–22.595)	0.002

The impact of varying levels (mild or intense) of physical activity and frequency of physical activity (0, 1–2 or ≥ 3 times per week) was compared to 'No activity on a weekly basis'; CI, confidence interval; OR, odds ratio

Discussion

RELOAD was an observational, retrospective, real-world study assessing the treatment adequacy with metformin monotherapy at maximum tolerated doses in patients with T2DM. The main findings for the patients with baseline HbA_{1c} ≥ 6.5 % (≥ 48 mmol/mol), were that: i) only 36.4 % of patients achieved glycaemic control (HbA_{1c} < 6.5 % [< 48 mmol/mol]) after 9 months of metformin monotherapy. In addition, the sensitivity analysis showed that 50.0 % of patients with baseline HbA_{1c} ≥ 7.0 % (≥ 53 mmol/mol) achieved levels < 7.0 % (< 53 mmol/mol) after 9 months of metformin monotherapy. The mean HbA_{1c} for patients achieving HbA_{1c} < 6.5 % (< 48 mmol/ mol) or < 7 % (< 53 mmol/mol) at 9 months was maintained below these cut-offs through to 24 months, in contrast to patients who failed to achieve either HbA_{1c} cut-offs at 9 months while remained on monotherapy for up to 24 months.

The percentages of patients who achieved the HbA_{1c} recommended targets at 9 months are comparable with those reported in the literature. The real-world study of Cook et al. comprising > 3,300 patients with T2DM who initiated metformin treatment showed that only 24.0 % and 45.0 % attained HbA_{1c} < 6.5 % (< 48 mmol/mol) and < 7.0 % (< 53 mmol/mol), respectively, during the first year of monotherapy [20]. However, other studies assessing the attainment of HbA_{1c} < 6.5 % (< 48 mmol/mol) or < 7.0 % (< 53 mmol/mol) with metformin have reported patient percentages ranging from 20.0 % to 56.5 % and 54.0 % to 76.0 %, respectively [21–24]. These differences could be attributed to the heterogeneity in the study designs, including the differences in the daily metformin doses used; in this study, the mean metformin daily dose for the entire cohort at 9 months (1,560.5 mg) was lower than the daily dose of 2,000 mg which provides optimal anti-hyperglycaemic effects [25]. Furthermore, compared with metformin daily doses of 1,000 to 1,500 mg, doses of ≥ 2,000 mg result in a further HbA_{1c} reduction of 0.26 % (2.8 mmol/mol) with a non-significant increase in gastric adverse events [26]. Finally, these differences could be attributed to patient-related variables among studies, as low vs. high baseline HbA_{1c}, older vs. younger age and lower vs. higher body mass index are positively associated with response to metformin [27].

Clinical inertia appears to be evident in routine clinical practice in Greece and this is based on a number of findings in this study.

Firstly, on the low proportion of patients (36.4 %) with baseline HbA_{1c} ≥ 6.5 % (48 mmol/mol) achieving glycaemic control after 9 months of treatment. It is well established that tight glycaemic control in newly diagnosed patients with T2DM is beneficial in terms of microvascular protection [28]. However, at least in some studies, patients treated towards HbA_{1c} ≈ 6.4 % (≈ 46 mmol/mol) experience increased all-cause mortality and cardiac events compared to patients treated to a moderate HbA_{1c} target of ≈ 7.5 % (≈ 58 mmol/mol) [29]. Therefore, it is possible that the latter observation, along with other treatment-related factors could make physicians reluctant in pursuing tight glycaemic goals.

Secondly, clinical inertia could be based on the fact that the mean HbA_{1c} for patients who failed to achieve HbA_{1c} < 6.5 % (48 mmol/mol) or < 7 % (53 mmol/mol) at 9 months was maintained above these cut-offs through to 24 months. However, it is equally possible that the non-attainment of HbA_{1c} goals by these patients is due to the heterogeneity in adult onset T2DM, whereby patients who are less insulin-resistant will not benefit from prolonged treatment with metformin [30].

Finally, clinical inertia could be based on the finding that the time to treatment intensification following metformin failure was also delayed (median of 28.0 and 27.8 months for patients with HbA_{1c} ≥ 6.5 % [≥ 48 mmol/mol]) or ≥ 7 % [≥ 53 mmol/mol], respectively). It is conceivable that the observed delays in the current study relate to baseline characteristics of the enrolled patients which are known to inversely impact on time to treatment intensification, such as older age, higher Charlson Comorbidity Index, patients in treatment with lifestyle modifications or oral monotherapy, or patients on metformin daily doses < 1,500 mg [13, 14, 31, 32].

Other physician-related reasons that could potentially lead to clinical inertia include shortage of time and resources, poor communication with the patient and failure to set and adhere to an individualised care plan aiming to achieve treatment goals [33]. Despite these justifiable reasons, clinical inertia in the management of T2DM is particularly concerning and must be minimised to improve disease outcomes. Focusing on metformin monotherapy failure, Pantalone et al. reported that early intensification resulted in a more rapid attainment of HbA_{1c} goals [31]. Furthermore, Svennson et al. showed that early glycaemic control in patients with T2DM initiating metformin treatment was associated with a lower risk of cardiovascular events and death [34]. Finally, it is also conceivable that by minimising clinical inertia the economic burden of the disease may be reduced, albeit that this is still uncertain [9].

An unexpected finding of this study was that numerically more patients with arterial hypertension achieved glycaemic control at 9 months as compared to normotensive patients (40.9 vs 28.4 %, respectively). Although the antihypertensive medications received by the patients were not recorded in detail, this finding may relate to the fact that patients with hypertension have more frequent visits to physicians' office, which also leads to more frequent glucose control as well as better adherence to antihyperglycemic therapies.

This study has several limitations relating to its retrospective nature. Data on metformin treatment adherence could not be collected and assessed. Most patients had a short history of disease and, therefore, the obtained results cannot be extended to all diabetic patients. Selection bias cannot be ruled out, as the study was conducted in medical sites with available medical records and thus the included patients may not be representative of the general diabetic population in Greece. Finally, the relatively low number of patients might prevented the detection of correlations between confounders and the primary outcome.

In conclusion, this real-world study provides evidence that the adequacy of metformin monotherapy is suboptimal in Greek patients with T2DM. Despite the availability of treatment guidelines, clinical inertia appears to be common and it remains important to further explore the factors that contribute to this phenomenon.

Acknowledgements

The authors thank Georgios Andreopoulos, Vassiliki Prentza, Sotirios Adamidis, Panteleimon Pantelidis, Pavlos Fengos, Anastasios Boniakos, Eleni Rigadi, Vasileios Andreadis, Thekla Chatziadamidou, Eleni Doumala, Evangelos Tavoularis, Maria Chorianopoulou, Ourania Zacharopoulou.

Funding

This study was funded by Merck Sharp & Dohme (MSD) Greece.

Conflict of Interest

Dr Karamousouli and Dr Voss are MSD employees. Prof Tsimihodimos reports honoraria and research grants from Elpen, Servier, MSD, Novartis, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Novo Nordisc. Prof Bargiota reports no conflict of interest. Dr Pagkalos reports contribution in lectures, clinical trials, advisory boards for the following companies: MSD, Sanofi, Eli Lilly, Novo Nordisc, AstraZeneca, Boehringer Ingelheim, Bayer, GSK, WinMedica, Novartis, ELPEN. Dr Manes reports grants from Novo Nordisk, Sanofi, Vianex, MSD, AstraZeneca, Boheringer Ingelheim, ELPEN, Galenica and Angelini. Dr Pappas reports honoraria for advisory boards from MSD, Novo Nordisk and Sanofi and honoraria for lectures from MSD, Boehringer Ingelheim, Novo Nordisk, Sanofi, Vianex, ELPEN, Eli Lilly, Medtronic and AstraZeneca. Prof Elisaf reports honoraria from MSD, Novartis, Chiesi, Bayer, AstraZeneca, Pfizer, Abbott, Mylan, Sanofi, Amgen, Boehringer Ingelheim, Eli Lilly, GSK, Angelini, WinMedica and grants and personal fees from MSD and AstraZeneca. Professor MS Elisaf has given talks and attended conferences sponsored by various pharmaceutical companies, including Bristol-Myers Squibb, Novartis, Chiesi, Bayer, AstraZeneca, Pfizer, Abbott, Mylan, Sanofi, Amgen, Boehringer Ingelheim, Eli Lilly, GSK, Angelini, WinMedica and MSD.

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