

# Clinical characteristics of patients with type 2 diabetes mellitus at the time of insulin initiation: INSTIGATE observational study in Spain

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**Abstract** Little information is available on the management of patients with type 2 diabetes mellitus (DM2) in regular clinical practice, prior to and at the point of initiating treatment with insulin. The INSTIGATE study provides a description of the clinical profile of the patient with DM2 who begins treatment with insulin in both primary and secondary care. A total of 224 patients who had been diagnosed with DM2, were not responding to oral treatment, and began receiving insulin were included in the INSTIGATE study in Spain. Demographic data were collected, as well as data on macro- and microvascular complications of diabetes and comorbidities, past medical history of diabetes and oral treatment administered, the clinical severity of diabetes (HbA1c concentration) and insulin treatment initiated. Mean age of the sample was 65.4 years and 56.7% were men. There were 87% of patients who had a diagnosis of at least one significant comorbidity, notably hypertension and hyperlipidemia. The patient profile for metabolic syndrome was met by 75.1% of the patients. There was a higher incidence of macrovascular complications (38.4%) than microvascular complications (16.1%). Prior to insulin initiation, the most recent mean HbA1c was 9.2%. The majority of patients

had been treated in the last 12 months with sulfonylureas and/or metformin (69.6 and 57.6%). The most common treatment prior to insulinization was the co-administration of two oral antidiabetics (OADs) (37.5%). Patients with DM2 observed in the study presented with elevated mean HbA1c and body mass index levels, comorbidities and complications related to diabetes at the time of insulin initiation. Changes and adjustments in treatment from diagnosis of diabetes occur when HbA1c levels are far above those recommended by the IDF (International Diabetes Federation), a factor which could be contributing to the development of both macrovascular and microvascular complications in the patient profile described in the study.

**Keywords** Type 2 diabetes mellitus · Epidemiology · Treatment · Spain

## Introduction

Type 2 diabetes mellitus (DM2) is a chronic disease that is becoming increasingly prevalent in Western populations. At the beginning of the 1990s, it was estimated that global prevalence would increase by around 40% over the following 10 years, rising from approximately 150–210 million patients [1]. In the absence of adequate glucose control, patients with DM2 present a higher risk of developing macrovascular as well as microvascular complications [2]. The high prevalence and incidence of DM2, including the associated increased morbidity and premature mortality, make diabetes a major pressure on health resources [3].

In Spain, diabetes mellitus is one of the main causes of mortality, ranking third place for women [4]. The prevalence estimations for DM2 in Spain vary between 4.8% [5] and 18.7% [6], with an annual incidence between 8.2 [7]

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and 10.8 cases [8] per 1,000 people. It has been suggested that more than one-third of people with diabetes in Spain have not been diagnosed [9].

The International Clinical Guidelines for the management of glucose control in patients with type 2 diabetes published by the International Diabetes Federation (IDF) recommend implementing changes in the lifestyle of the patient, followed by different treatment patterns, ranging from a single oral antidiabetic drug (OAD) to a combination of oral agents ending up with insulin treatment, always with the objective of maintaining the HbA1c level under 6.5% [10]. In the observation of daily clinical practice, insulin initiation for patients is sometimes delayed due to the potential risk of hypoglycemia, the need to educate patients on the use of insulin, the need to increase glucose control and concern over weight gain [11].

Studies were conducted in the past that describe the pattern of oral antidiabetic and insulin use. These provide data on the level of glucose control achieved with each of these treatments, individually or combined, at different stages of the disease, the development of complications associated with DM2, the duration of therapy for each defined treatment pattern and clinical variables at the time the medication was changed [12–15].

However, the information provided by these studies needs to be updated, since in recent years, significant innovations have appeared within drug treatment options for DM2. In addition, the clinical guidelines for glucose control in type 2 diabetes published by the IDF have recently been reviewed, updating both the recommendations on glucose [10] and metabolic control [16], and the definition of the profile of patients with metabolic syndrome [17]. Therefore, describing treatment patterns in clinical practice and evaluating the proportion of patients who comply with the recommendations of these international guidelines appear to be of major importance in the management of patients with DM2, allowing the implementation of initiatives that improve compliance and thus the clinical situation of the patients.

The present study describes the clinical profile of the DM2 patient who begins insulin treatment in primary and/or secondary care.

## Methods

The present work was conducted with baseline data, relating to a Spanish sample in the European non-interventional, multicenter, prospective, observational INSTIGATE study, in which we provide a description of the profile of the DM2 patient who begins insulin treatment in primary and/or secondary care in Spain. The study was designed to determine the direct costs associated with the first 24 months of

insulin treatment in patients with DM2 and to describe the utilization of resources, the quality of metabolic control and the associated clinical results. This study included patients with DM2 who began treatment with insulin because they did not have acceptable glucose control levels according to clinical judgement and who granted their informed consent. In addition to the baseline data published for the whole European sample [18], the present paper allows a closer look at the Spanish patients within the study, especially in relation to comorbidities at the time of insulin initiation, and treatment patterns before and at the point of initiation of insulin therapy and provides the opportunity to put the data in context within a Spanish environment.

Sites were selected so that the geographic distribution and investigator type (general practitioner or specialist) were representative of the physician population treating patients with type 2 diabetes both up to and through the insulin initiation process. Specialist secondary care centers that did not care for the entire spectrum of patients with diabetic were not included, as these patients were less likely to be representative of the usual patient initiating insulin in Spain.

The participating investigators identified patients with DM2 who (1) began treatment with insulin at that visit to the doctor's office or (2) were promptly sent by the primary care physician to a specialist so that insulin treatment could be initiated, continuing their clinical follow-up at the primary care office.

At the initial visit of this study, the following data were collected:

1. *Demographic and anthropometric characteristics of the patient:* age, sex, ethnic identity, smoking status, height, weight and waist circumference.
2. *Presence of medical complications:* coronary disease, stroke, occlusive peripheral artery disease, congestive heart failure, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, amputation of any limb, hypertension, hyperlipidemia, depression, cancer and other comorbidities.
3. *Past medical history of diabetes:* date of diagnosis, treatment patterns prior to insulin initiation (duration and type of therapy) and OAD drugs (generic name, dose, frequency, start date and end date and the reason for discontinuation) taken during the 12 months prior to insulin initiation.
4. *Clinical severity:* based on HbA1c levels, lipid profile, fasting plasma glucose and blood pressure.
5. *Insulin treatment:* description of insulin treatment initiated at the beginning of the study.

As INSTIGATE is an observational study, results were obtained from the medical records and supported by the clinical judgement of the investigators. All data were

provided as they were generated in usual care and no additional visits, tests or interventions were required as part of the study protocol.

Data on HbA1c (%), lipids (HDL-cholesterol LDL-cholesterol and triglycerides) and blood pressure of each eligible patient were compared with the levels recommended by the IDF to determine what proportion of the Spanish population in the study was achieving target. The following are the current recommended targets:

- HbA1c < 6.5%
- Lipids: HDLc > 39 mg/dL, LDLc < 95 mg/dL and triglycerides < 200 mg/dL
- Blood pressure < 130/80 mmHg [16].

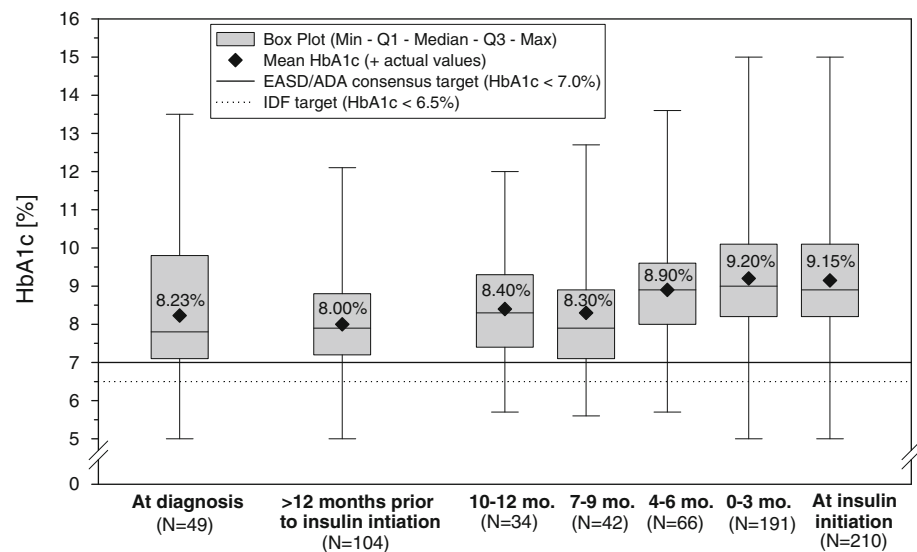
Data on waist circumference, triglyceride level, HDLc, blood pressure and fasting blood glucose levels were used to

**Table 1** Patient characteristics

Parameter	Mean (SD)	n
Weight (kg)	77.72 (15.67)	224
Body mass index (kg/m <sup>2</sup> )	29.54 (5.50)	224
Abdominal perimeter (cm)	99.9 (16.57)	224
Men (cm)	101.9 (15.32)	127
Women (cm)	97.3 (17.81)	97
Systolic blood pressure (mmHg)	137.1 (18.35)	216
Diastolic blood pressure (mmHg)	78.6 (10.79)	216
HDLc (mg/dL)	49.30 (15.07)	209
LDLc (mg/dL)	108.04 (37.28)	208
Triglycerides (mg/dL)	173.7 (98.55)	215
HbA1c at diagnosis (%)	8.23 (1.88)	49
Time since first diagnosed (years)	10.26 (7.14)	220
Current smokers [n (%)]	22 (9.8%)	224

The results are presented as mean results (standard deviation) except for the percentage of smokers

**Fig. 1** Evaluation of the clinical severity of diabetes through HbA1c measurement prior to insulin initiation



evaluate the proportion of patients from the Spanish sample who met the criteria for the diagnosis of metabolic syndrome according to the guidelines published by the IDF [17].

For a patient to be diagnosed with metabolic syndrome, in accordance with the definition by the IDF, European men must have a waist circumference  $\geq 94$  cm and European women  $\geq 80$  cm and, at least two of the following factors:

1. An elevated triglyceride level:  $\geq 150$  mg/dL or a treatment specific to this lipid abnormality.
2. Reduced HDLc level: <40 mg/dL in men and <50 mg/dL in women or a specific treatment for this lipid abnormality.
3. Raised systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg or treatment for previously diagnosed hypertension.
4. Raised blood glucose level: fasting blood glucose  $\geq 100$  mg/dL or previously diagnosed with DM2.

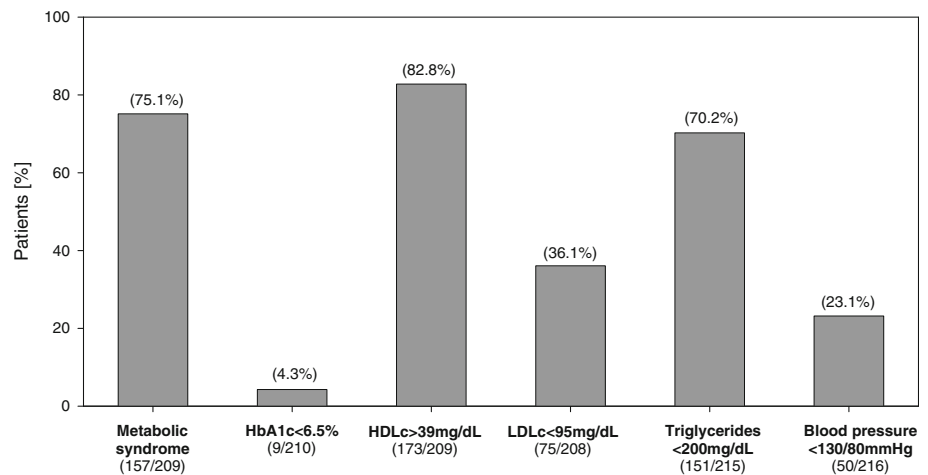
### Statistical analysis

The variables from the study on the demographic, clinical and treatment characteristics were analyzed using descriptive statistics: mean, standard deviation, median, minimum and maximum for quantitative variables and relative and absolute frequencies for qualitative variables. If not stated otherwise, percentages are based on the number of eligible patients. All analyses were conducted using SAS software version 8.2.

### Results

The results refer to the 224 patients included in the INSTIGATE study in Spain, by 24 investigators (9

**Fig. 2** Data on the percentage of patients who meet the criteria for the diagnosis of metabolic syndrome and therapeutic outcomes defined by the IDF. Percentages are based on the number of patients evaluable for the respective criterion



endocrinologists, 8 internal medicine specialists and 7 primary care physicians) at the point of insulin initiation.

The majority of the patients were men (56.7%), Caucasian (97.8%), with a mean age of 65.4 (SD = 12.1) years, with women being older, 67.2 (11.5) than men, 64.1(12.5). The principal patient characteristics are presented in Table 1.

Of the total patient population, 36% were overweight ( $25 \leq \text{BMI} < 30$ ) and 43.3% were obese ( $\text{BMI} \geq 30$ ). Women presented a more elevated mean BMI value than men [30.56 (6.36) vs. 28.77 (4.63)  $\text{kg/m}^2$ , respectively]. Clinical severity was evaluated through HbA1c measurement. Mean HbA1c at diagnosis of the disease and 12 months prior to insulinization were much higher than the glucose control targets recommended by the IDF, reaching a value of 9.2% prior to insulin initiation (Fig. 1). There were a few patients ( $n = 9$ ) who presented HbA1c values below 6.5% at insulin initiation who may have started this treatment due to other clinical factors or comorbidities where clinical judgment advised tight glucose control. Patients with  $\text{HbA1c} > 8.0\%$  versus patients with  $6.5\% < \text{HbA1c} \leq 8.0\%$  had higher rates of chronic complications (88.0 vs. 82.4%, respectively). In addition, patients who had at least one macrovascular complication had higher mean values of HbA1c % (9.29%) than those who did not (8.94%).

Figure 2 presents the percentage of eligible patients who meet the therapeutic goals established by the IDF, with respect to lipid values (LDLc, HDLc and triglycerides), blood pressure, and HbA1c concentration and the criteria for diagnosis of metabolic syndrome.

For the diagnosis of metabolic syndrome at baseline, a smaller sample ( $n = 209$ ) than that included in the study was evaluated, due to the absence of at least one data element necessary for this evaluation for some patients.

There were 75.1% of evaluable patients who met the patient profile for metabolic syndrome, 95.7% who

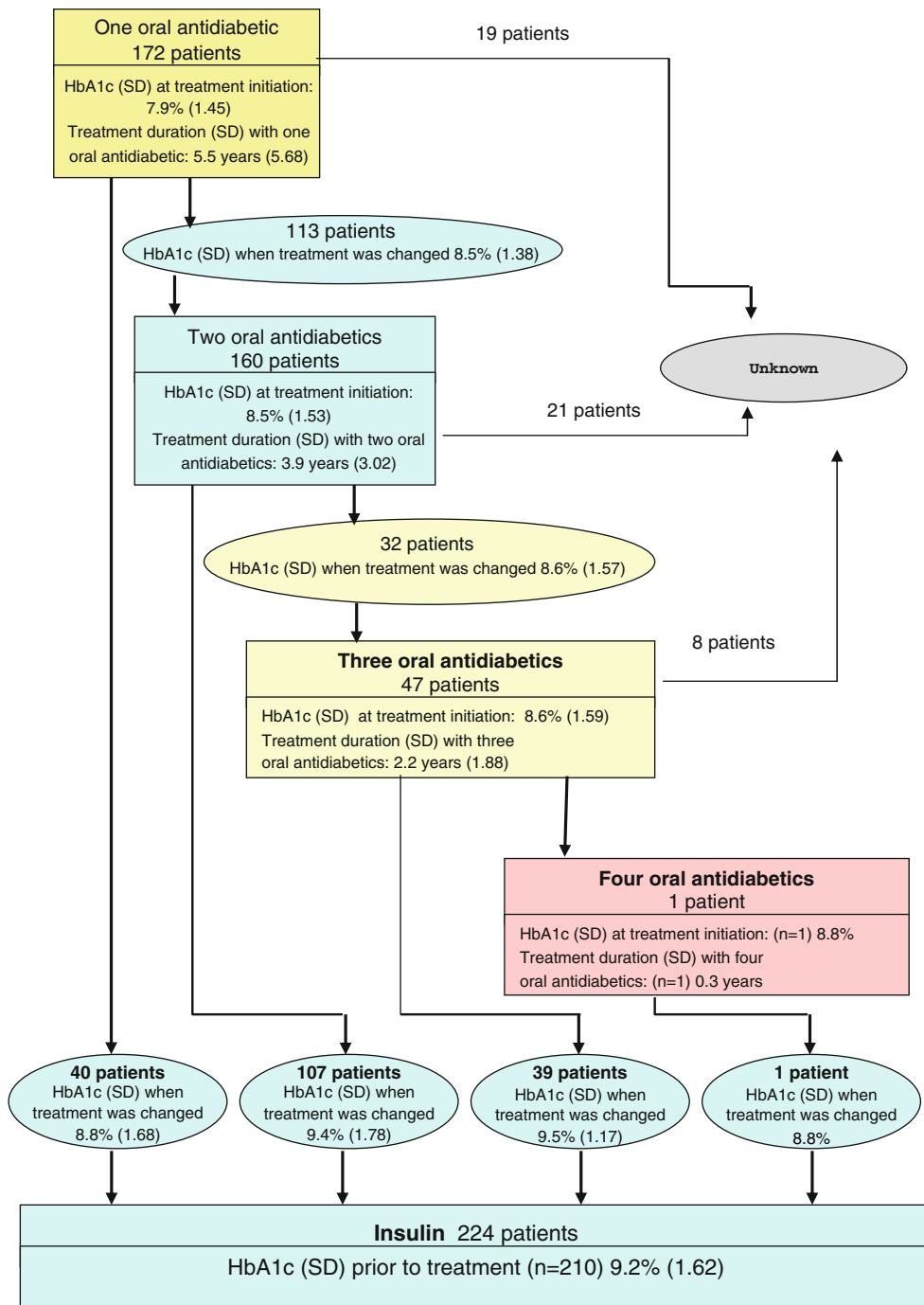
**Table 2** Comorbidity incidence in patients at the time of insulin initiation ( $n = 224$ )

Comorbidity	<i>n</i> (%) of patients with comorbidity
Macrovascular complications (at least 1)	86 (38.4)
Coronary disease	49 (21.9)
Stroke	18 (8.0)
Transient ischemic attack	10 (4.5)
Peripheral occlusive arterial disease	13 (5.8)
Congestive heart failure	24 (10.7)
Amputation	2 (0.9)
Microvascular complications (at least 1)	36 (16.1)
Diabetic retinopathy	15 (6.7)
Diabetic nephropathy	23 (10.3)
Diabetic neuropathy	9 (4.0)
Other comorbidities (at least 1)	182 (81.3)
Hypertension	137 (61.2)
Hyperlipidemia	111 (49.6)
Depression	29 (12.9)
Cancer	12 (5.4)
Others	48 (21.4)

presented an unacceptable HbA1c concentration level ( $>6.5\%$ ) and 63.9% who presented an LDLc level higher than the clinical recommendation (95 mg/dL).

The majority of the population studied (87%) presented with at least one significant comorbidity, 38.4% had macrovascular complications and 16.1% microvascular complications (Table 2). Coronary disease was the most frequent macrovascular complication followed by congestive heart failure; with respect to microvascular complications, diabetic nephropathy was more frequent than retinopathy or neuropathy in the sample studied.

In regard to oral treatment during the 12 months prior to insulin initiation, the majority of the patients had received



**Fig. 3** Different treatment patterns for DM2 before insulinization

sulfonylureas (156 patients; 69.6%) and/or metformin (129 patients; 57.6%) and to a lesser degree, thiazolidinediones (33 patients; 14.7%), alpha-glucosidase inhibitors (29 patients; 12.9%), meglitinides (36 patients; 16.1%) and other drugs (6 patients; 2.7%).

In the period between being diagnosed with DM2 and insulin initiation, 39.5% of the patients had modified their

treatment patterns progressing from 1 to 2 OADs prior to insulin initiation, 17.9% had received only single OAD therapy prior to insulin, 11.2% had progressed from 1 to 2 then 3 OADs, 8.5% had received only dual therapy with OADs, 9.4% did not know the antidiabetic treatment history and 6.3% of the patients had not been treated with OADs. Figure 3 presents the different patterns followed in

**Table 3** Treatment patterns of insulin initiation

Initial administration of insulin	<i>n</i>	Percentage of patients	Mean number of injections	Mean daily dose (IU)	Mean daily dose (IU)/kg of weight
Basal	135	60.3	1.1	16.9	0.23
Pre-established mixtures	42	18.8	2.0	29.9	0.37
Only rapid	21	9.4	2.5	23.6	0.34
Basal/bolus	4	1.8	2.5	24.0	0.36
Other	2	0.9	1.0	15.33	0.21
Basal and mixed	1	0.4	2.0	24.0	–
Unknown	19	8.5	–	–	–
Total	224	100	–	20.0	–

the treatment prior to insulin initiation, demonstrating the mean HbA1c at the time of change in therapy and the duration of treatment on each therapy.

Table 3 describes the insulin regimen initially prescribed for the subjects studied. The most common insulin treatment was a basal insulin only, which was received by 60.3% of the subjects.

## Discussion

The results of the current study suggest patients with DM2 initiating treatment with insulin in Spain are on average aged 65, have had a diagnosis of DM2 for around 10 years and are likely to be overweight or obese. Figure 1 indicates that the majority of patients (>75%) had HbA1c values higher than those recommended by the IDF during the year prior to initiation of insulin. These results are supported by several studies [15, 19, 20], which have evidenced that only a small proportion of patients with diabetes achieve therapeutic objectives in relation to metabolic control, in spite of a number of publications in recent years manifesting the importance of attaining a good control to prevent or delay the development of complications associated with DM2 [12, 13, 16].

The majority of evaluable patients from the INSTIGATE study met the criteria for the diagnosis of metabolic syndrome. These patients are estimated to present twice the risk of mortality and three times the risk of cardiovascular disease, compared to healthy individuals [21].

Glucose control strategies and recommendations on HbA1c targets are currently under discussion since findings from recently published trials, such as ACCORD, ADVANCE and VADT have not demonstrated a significant reduction in cardiovascular disease with intensive glycemic control [22, 23]. However, conversely, the 10-year follow-up data of the UKPDS study did show a reduction in myocardial infarction and all-mortality cause associated to intensive glucose lowering [24].

With regard to treatment patterns followed by patients in the INSTIGATE study, the changes in treatment occurred when the mean HbA1c value was at least 8.5%, which is well above the levels recommended by the IDF guidelines [10] and the consensus treatment algorithm developed by the ADA (American Diabetes Association) in collaboration with the EASD (European Association for the Study of Diabetes) [25]. In addition, at insulin initiation, mean HbA1c was very high (9.15%). Mean HbA1c was lower for patients with one oral antidiabetic than for patients with two or more oral antidiabetics as their immediate previous treatment (Fig. 3).

A limitation of the INSTIGATE study is that although patients were included in a prospective manner from the time of insulin initiation, part of the data collection was retrospective, and obtained from the clinical history. Due to the fact that it was an observational study, all results were provided as they were generated in usual care, and therefore the values of HbA1c% and other lab results were not standardized. Statistical analysis comparing patients from various settings were not carried out since it was not a specified objective of the study to look at possible differences between patients being treated in primary and secondary care. However, this could be an interesting analysis to consider for future studies. Finally, it is possible that a very small number of patients included in the study could have had undiagnosed LADA (Latent Autoimmune Diabetes of the Adult) with an incorrect diagnosis of type 2 diabetes. Given the observational nature of the study, no additional tests could have been run to confirm diabetes type.

The baseline data for the Spanish sample of the INSTIGATE study demonstrate that initiation of insulin therapy in patients with DM2 occurs only after patients have had poor glycemic control for a sustained period of time (Fig. 1). Due to the high prevalence of cardiovascular risk factors and comorbidities related to diabetes, we can consider the studied patients are at high risk of cardiovascular disease and associated mortality. It appears,

therefore, that more needs to be done to encourage earlier intervention to intensify therapy, in accordance with current recommendations for the treatment of DM2, with the final objective of achieving more effective glucose control, and ultimately avoiding or delaying the development of complications associated with diabetes, a cause of high morbidity and mortality in patients with DM2.

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