Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Patterns and trends in insulin initiation and intensification among patients with Type 2 diabetes mellitus in the Middle East and North Africa region

Abdul Jabbar [a,*], *Khalifa Abdallah* [b], *Ahmed Hassoun* [c], *Rachid Malek* [d], *Cagri Senyucel* [e], *Erik Spaepen* [f], *Tamas Treuer* [g], *Indranil Bhattacharya* [h]

[a] *Diabetes and Endocrine Unit, Department of Endocrinology, Medcare Hospital, Jumeira, Dubai, United Arab Emirates*
[b] *Diabetes and Metabolism Unit, Department of Internal Medicine, Alexandria University, Alexandria, Egypt*
[c] *Dubai Diabetes Center, Dubai Health Authority, Dubai, United Arab Emirates*
[d] *Department of Internal Medicine, CHU Setif, Algeria*
[e] *Eli Lilly and Company, Indianapolis, IN, USA*
[f] *Eli Lilly and Company, Bad Homburg, Germany*
[g] *Eli Lilly and Company, Budapest, Hungary*
[h] *Eli Lilly and Company, Gurgaon, India*

ARTICLE INFO

Article history:
Received 10 September 2018
Received in revised form
10 December 2018
Accepted 9 January 2019
Available online 14 January 2019

Keywords:
Type 2 diabetes mellitus
Middle East and North Africa
Observational
Insulin regimens
Clinical inertia

ABSTRACT

Aim: Current and future estimates of the burden of diabetes in the Middle East and North Africa (MENA) region are among the highest in the world. VISION, an 18-month observational study, explored patterns of insulin initiation and intensification in T2DM patients in the MENA region.

Methods: 1192 patients aged ≥18 years were enrolled from Algeria, Egypt, Saudi Arabia and the UAE. Treating physicians recorded participants' data. Patient-reported outcomes (PROs) were assessed using questionnaires completed by participants.

Results: 67.6% patients had HbA1c ≥9% at insulin initiation, with a mean HbA1c of 9.9%, despite 68.3% patients being on ≥2 oral anti-diabetics, indicating a significant delay in insulin initiation. Basal insulin was initiated in 50.6% and premixed insulin in 46.3% patients. After 18 months, changes in insulin therapy were observed in 33.7% patients, while 39.6% patients achieved HbA1c levels of <7.5%. The proportion of patients completely satisfied with their insulin treatment, and the QoL increased over the study course.

Conclusion: Results support that timely initiation and early intensification of insulin therapy are necessary in the region to achieve adequate and timely glycemic control and to prevent diabetic complications.

* Corresponding author at: Medcare Hospital, Jumeira, Dubai 215565, United Arab Emirates.
E-mail address: haj1960@gmail.com (A. Jabbar).

https://doi.org/10.1016/j.diabres.2019.01.017
0168-8227/

1. Introduction

Diabetes is a major burden in the Middle East and North Africa (MENA) region and is responsible for substantial morbidity and mortality, as well as for considerable healthcare expenditure. The International Diabetes Federation 2017 estimated that 9.6% adults (38.7 million people aged 20–79 years) in the MENA region have diabetes and over 49.1% of these are undiagnosed. The healthcare expenditure due to diabetes in the region in 2017 was estimated to be 21.3 billion USD [1]. A high age-adjusted comparative prevalence of diabetes was observed in the MENA region in 2017 (10.8%), with 17.7% in Saudi Arabia, 17.3% both in Egypt and the UAE, and 6.7% in Algeria [1]. A major reason for this dramatic increase in the region has been an increase in risk factors for Type 2 diabetes mellitus (T2DM) such as increased obesity rates due to increased intake of refined carbohydrates and reduced physical activity due to rapid economic development and urbanisation [2,3].

Good glycemic control is important for the prevention of diabetic complications [4], and a stepwise treatment algorithm to achieve glycemic control has been recommended in treatment guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). As insulin has the highest efficacy in lowering blood glucose levels among all antihyperglycemic medications [5], it should be considered as an important component of treatment strategy in patients not achieving an agreed target of HbA1c levels despite maximal oral therapy. However, studies have shown that a large proportion of participants do not achieve their glycated hemoglobin (HbA1c) targets, because of resistance to timely initiation and intensification, termed “clinical inertia” [6]. Adequate and timely insulin initiation and intesification has been shown to reduce HbA1c levels and the risk of complications, leading to considerable economic benefits [7]. Thus, it is of great scientific interest to investigate how long do patients remain on the initial insulin regimen – which depends on country, patients’ glycemic and comorbidity profile, health system, health resources and many other factors – prior to progression, and the reason behind patients’ progression from initial insulin regimen. In addition, it is of economic importance to follow disease progression for the payer to understand the duration of treatment and to confirm assumptions around cost burden of therapy.

Although clinical research is increasing including in the MENA region, many questions remain unanswered even after examining clinical trial or epidemiological research data. Specifically, the profile of patients who are prescribed insulin, the insulin regimens used, clinical effectiveness and psychosocial outcomes associated with patients taking insulin therapy, and cost/resource use and long-term treatment patterns (including duration of insulin treatment) are not well known. Few studies examined influences of physician, patients, and healthcare systems on diabetes management in countries of the MENA region. One of the largest studies, the A1chieve study, investigated the treatment effectiveness and tolerability of insulin analogs in over 65,000 participants in 28 non-Western countries including nine countries in the MENA region (Algeria, Morocco, Libya, Tunisia, Egypt, Iran, Saudi Arabia, the UAE and Yemen) [8]. The MOSAIc study conducted in 18 countries including three countries from MENA region (the UAE, Saudi Arabia and Israel) aimed to identify factors that influence insulin intensification in participants with T2DM using insulin. Baseline data for this study were recently reported [9].

To gain further knowledge on real-world treatment approaches, we conducted an 18-month, non-interventional study Verifying Insulin Strategy and Initial Health Outcome aNalysis (VISION). The aim of this study was to investigate treatment approaches and decisions, treatment patterns, and clinical effectiveness among participants with T2DM initiating insulin therapy in a real-life clinical setting in the MENA and Western Pacific (WP) region. This was investigated by studying the treatment changes in patients who initiated on insulin, the factors which influence insulin intensification patterns in terms of dose and regimen, and HbA1c levels, and the resulting clinical and patient-reported outcomes (PROs).

2. Methods

2.1. Study design

VISION was an 18-month, prospective, observational, non-interventional, multicenter study of patients with T2DM initiating insulin treatment in five countries in the WP region and four countries in the MENA region. Patients were enrolled from April 2014, and prospective data were collected until November 2016 (Supplementary Fig. 1). As per the prospective observational study design, the decision concerning treatment of diabetes including insulin initiation and treatment changes was solely at the discretion of the physician. Insulin therapy for T2DM was prescribed in the usual standard of care and was not to be provided by the study sponsor. Data collected from patient-reported outcome instruments were entered into an electronic database by a contract research organization (Parexel) to avoid any influence on physician decision making. The study was carried out in accordance with the Declaration of Helsinki and the International Conference of Harmonisation – Good Clinical Practices, and was approved by the ethical review boards at each participating site. Written consent was obtained from patients following the decision to initiate insulin therapy.

Because diabetes incidence and prevalence, as well as the treatment approaches differ between regions, we presented results of the WP [10] and MENA regions separately. This is a subgroup analysis of the VISION study, focusing on patients from four countries in the MENA region: Algeria, Egypt, Saudi Arabia and the UAE.

2.2. Patients and procedures

Potential investigators were chosen to reflect a broad and representative sample of general health care for patients with T2DM in each country. VISION included adult (≥18 years) patients who were diagnosed with T2DM (based on the clinical judgement of the investigator) and the treatment decision to initiate insulin therapy was made during a routine clinical

care. Participants also had to have a sufficient understanding of the primary language of the country to complete the questionnaires. Patients were excluded if they had taken insulin in the previous 6 months or were participating in a study of an investigational drug or procedure at the time of enrolment.

2.3. Data collection

Baseline outcome measures included but were not limited to demographics, clinical parameters (disease duration and HbA1c levels), health insurance and PROs. Baseline and follow-up data, other than PROs, were collected by treating physicians.

To understand patterns in treatment intensification/dis continuation by health care providers and factors influencing these decisions for the treatment of T2DM, the following information was captured during the 18-month study period: a change (modification) from one insulin regimen to another; an increase or decrease in daily insulin dose (IU) ≥20% over the last prescribed dose, after titration (optimization); addition of a new medication (any route of administration), after titration (intensification); and discontinuation of insulin initiated at baseline; and insulin re-start after discontinuation.

At baseline, the insulin regimens were classified as basal alone (long-acting insulin), basal bolus (basal plus rapid-acting insulin analogs for all meals), basal plus prandial (basal plus prandial/rapid-acting insulin analogs for main one to two meals), or premixed (premixed insulin regimen with basal and prandial component). The baseline was followed by three follow-up visits, at 6-month intervals (±6 weeks). Visit 2 occurred after 6 months (±6 weeks), Visit 3 at 12 months (±6weeks), and Visit 4 at 18 months (±6 weeks) from the baseline visit. Patient data were collected only at routine clinical visits that fell within these time windows. The first 3-month period after insulin initiation was considered "a titration period," and dose increase was not captured as a treatment change. This was based on the widely used practice guidelines detailed in the ADA and the EASD consensus statement [5] recommending progression if HbA1c levels remain ≥7% after 3 months of basal insulin therapy. Patients discontinuing treatment was considered only if they stopped insulin therapy and did not start again within 30 days. During the follow-up visits, the following data were assessed: antidiabetic treatment history since the last visit, concomitant drug use, diabetes-related laboratory values, clinical and metabolic outcomes, patients' Perceptions of Insulin Therapy Questionnaire (PITQ), EuroQol-Visual Analog Scale (EQ-VAS), and patients' overall satisfaction with diabetes medicines (single global satisfaction question). A full data collection schedule is provided in Supplementary Table 1.

PROs were collected using standardized questionnaires, completed by patients, which were translated to the local language and validated according to current industry standards. Overall satisfaction with diabetes medications was assessed on a 7-point Likert scale from "completely satisfied" to "completely dissatisfied." Expectations about insulin therapy and experiences corresponding to those expectations were assessed using the validated questionnaires - Expectations about Insulin Therapy Questionnaire (EITQ) and PITQ [11,12]. Patients answered each question on a 7-point Likert scale, where higher scores indicated higher expectations. The EITQ comprised 10 questions preceded by 'I expect that…' ranging from 1 (strongly disagree) to 7 (strongly agree) with a maximum total score of 70. The 10 PITQ questions are identical to the EITQ items, but the directions ask the respondent to refer to his/her experience with insulin therapy during the past 4 weeks. Generic health-related quality of life (QoL) was assessed using the EQ-VAS of the three-level version of EQ-5D (EQ-5D-3L) tool [13]. Patients were asked to mark their health state on that specific day on a scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

2.4. Statistical analysis

The sample size was based on the precision (width of the 95% confidence interval [CI]) of the estimate for proportion of patients experiencing significant treatment change within 18 months after initiating insulin therapy within each region (WP and MENA). A sample size of 990 evaluable patients provided a CI width of 0.062, given a true proportion of 0.5. This was the widest width expected since any true proportion other than 0.5 will result in a narrower 95% CI. Assuming a dropout rate of 10%, the sample size of each region was 1100.

The analyses were performed on all patients enrolled in the study. Continuous variables were presented as mean (standard deviation) and categorical variables as number (percentage). Percentages were calculated from the total number of patients with evaluable data (ignoring missing values). We chose the value of HbA1c <7.5% as cut-off for glycaemic control that would be a better fit for most patients in the study, disregarding their co-morbidities. As per the clinical practice recommendations by IDF [13] and ADA/EASD [5], an HbA1c of 6.5% and 7%, respectively, is recommended as the cut off point for blood glucose control. The value chosen was slightly higher than the recommended target due to long disease duration and high percentage of patients with comorbidities, both of these factors allowed for a less stringent HbA1c target according to the guidelines.

3. Results

VISION study screened a total of 2387 participants, of which, 2257 participants were enrolled. In the MENA region, 1192 of the 1213 participants screened fulfilled the inclusion criteria and were enrolled (Supplementary Fig. 2). The most common reason for exclusion from the study was not using oral antidiabetes drugs (OADs) before signing the consent form; these were cases in which insulin was initiated due to an acute hyperglycaemic episode, a hyperglycaemic emergency, and/or other acute medical condition – that is, not a normal clinical care visit (18 patients). The largest number of participants were enrolled in Egypt (645, 54.1%), followed by Saudi Arabia (288, 24.2%), Algeria (181, 15.2%) and the UAE (78, 6.5%). The dropout rate at the end of the study was 32.0%, ranging from 21.6% in Saudi Arabia to 42.3% in the UAE, mainly due to loss of follow-up and withdrawal by subject.

The mean age was 53.5 years, ranging from 49.1 years in the UAE to 56.1 years in Algeria. The percentage of male

patients ranged from 40.9% in Algeria to 61.5% in the UAE, with a mean of 48.7% in the region. The mean body mass index was similar across the countries, with a mean of 30.3 in the region (Table 1). Overall, there was a wide variation in care characteristics between the countries (Table 1). Most importantly, the percentage of patients with full insurance coverage of doctor visits ranged from only 10.4% (n = 67) in Egypt to 70.5% (n = 55) in the UAE. Similarly, the percentage of patients with full insurance coverage of insulin medication ranged from 14.4% (n = 93) in Egypt to 95.0% (n = 172) in Algeria.

The mean duration of diabetes ranged between 8.5 years in Algeria and 10.1 years in the UAE, with an overall mean duration of 8.9 years in the region. The majority of patients (n = 814, 68.3%) used two or more types of OADs at insulin initiation (Table 2). The most common (≥10%) OADs in use at baseline were metformin (n = 759, 63.7%), glimepiride (n = 470, 39.4%), and gliclazide (n = 340, 28.5%). Mean HbA1c level at baseline was 9.9%, ranging from 9.3% in Algeria to 10.1% in the Egypt (Table 2). The most common comorbidities at baseline were dyslipidemia (n = 519 [43.5%]) and hypertension (n = 511 [n = 42.9%]), followed by diabetic neuropathy (n = 392 [32.9%]). The diabetic complications were similar across the countries.

Mostly, patients were initiated on treatment with basal insulin alone (603 patients, 50.6%) or premixed insulin (552 patients, 46.3%), while 30 patients (2.5%) and seven patients (0.6%) started on basal plus prandial and basal bolus insulin, respectively. These percentages differed between the countries (Table 2). Mostly, patients had an HbA1c equal to or more than 9% at baseline irrespective of regimen (57.4% for basal alone [n = 332] and 81.3% for premixed insulin [n = 327]).

The most common concomitant OADs at any post baseline visit were metformin (n = 622, 52.2%), glimepiride (n = 306, 25.7%), and gliclazide (n = 194, 16.3%). At baseline, 83.9% (n = 506) and 76.1% (n = 420) of patients starting on basal alone and premixed insulin, respectively used sulfonylureas. In total, 75.4% (n = 304) and 33.4% (n = 128) of these on basal alone and premixed insulin, respectively, continued to use sulfonylureas at Visit 4.

Over the course of study, a total of 402 patients (33.7%) were advised a change in their diabetes treatment. The modifications in initial insulin treatment were most frequent in those from the UAE (n = 44; 56.4%), followed by those from Algeria (n = 81; 44.8%), Egypt (n = 254; 39.4%) and Saudi Arabia (n = 23; 8.0%) (Table 2).

Overall, the majority of insulin treatment changes occurred during the first 6 months, and between 6 and 12 months, with daily insulin dose increase being the most frequent change (n = 313 [26.3%] [CI: 23.8%, 28.9%]), followed by change from initial insulin regimen to another (n = 105 [8.8%] [CI: 7.3%, 10.6%]). Addition of a new medication was seen in 84 patients (7.0% [CI: 5.7%, 8.7%]), followed by decrease in insulin dose (n = 55, 4.6% [CI: 3.5%, 6.0%]) and discontinuation of initial insulin (n = 14, 1.2% [CI: 0.6%, 2.0%]; Table 2). Between the two most common initial regimens, patients who were initiated on premixed insulin (37.7% [n = 208]) required a modification in insulin dose/regimen more frequently than those who were initiated on basal alone insulin regimen (28.9% [n = 174]; Fig. 1). There was not much

Table 1 – Patient and care characteristics.

Variable	Region MENA (N = 1192)	Algeria (N = 181)	Egypt (N = 645)	Saudi Arabia (N = 288)	UAE (N = 78)
Patient Characteristics					
Age, years, mean (SD)	53.5 (10.4)	56.1 (11.1)	52.4 (9.5)	55.4 (11.1)	49.1 (10.0)
Male, n (%)	581 (48.7)	74 (40.9)	314 (48.7)	145 (50.3)	48 (61.5)
BMI, mean (SD)[1]	30.3 (5.5)	28.3 (5.4)	30.6 (5.0)	31.7 (6.8)	28.8 (5.2)
Smoking					
Never	899 (75.4)	151 (83.4)	443 (68.7)	240 (83.3)	65 (83.3)
Current/former	275 (23.1)	24 (13.3)	196 (30.4)	45 (15.6)	10 (12.82)
Alcohol use, n (%)					
Never	1132 (95.0)	175 (96.7)	617 (95.7)	276 (95.8)	64 (82.1)
Current/former	42 (3.5)	3 (1.66)	20 (3.1)	7 (2.43)	12 (15.38)
Care Characteristics					
Availability of resources, n (%)					
Diabetes nurse educator	534 (44.8)	81 (44.8)	91 (14.1)	288 (100.0)	74 (94.9)
Home blood glucose monitoring	222 (18.6)	0 (0)	222 (34.4)	0 (0)	0 (0)
Physician specialty					
Endocrinologist/diabetologist	723 (60.7)	53 (29.3)	308 (47.8)	288 (100.0)	74 (94.9)
Internal medicine	469 (39.3)	128 (70.7)	337 (52.2)	0 (0)	4 (5.1)
Number of years in practice of diabetes, mean (SD)	29.2 (7.3)	23.3 (6.2)	32.7 (3.9)	25.9 (8.2)	25.9 (11.5)
Health insurance status, n (%)					
Doctor visit fully covered	421 (35.3)	106 (58.6)	67 (10.4)	193 (67.0)	55 (70.5)
Insulin medication fully covered	514 (43.1)	172 (95.0)	93 (14.4)	193 (67.0)	56 (71.8)

Abbreviations: BMI = body mass index; MENA = Middle East and North Africa; UAE = United Arab Emirates; N = total population size; n = number of patients; SD = Standard Deviation.

[1] Calculated based on the following number of participants: Region MENA (N = 983); Algeria (N = 159); Egypt (N = 586); Saudi Arabia (N = 160); UAE (N = 78).

Table 2 – Clinical characteristics.

Variable	Region MENA (N=1192)	Algeria (N=181)	Egypt (N=645)	Saudi Arabia (N=288)	UAE (N=78)
Duration of diabetes, years, mean (%)	8.9 (5.7)	8.5 (5.9)	8.6 (5.6)	9.3 (5.9)	10.1 (5.7)
Number of OADs use, n (%)					
Baseline					
No OADs	57 (4.8)	5 (2.8)	48 (7.4)	1 (0.3)	3 (3.8)
One type	321 (26.9)	57 (31.5)	227 (35.2)	23 (8.0)	14 (17.9)
≥ Two types	814 (68.3)	119 (65.7)	370 (57.4)	264 (91.7)	61 (78.2)
After 18 months[1]					
No OADs	145 (17.9)	9 (7.1)	122 (29.5)	12 (5.3)	2 (4.4)
One type	266 (32.8)	51 (40.5)	180 (43.5)	22 (9.7)	13 (28.9)
≥ Two types	400 (49.3)	66 (52.4)	112 (27.1)	192 (85.0)	30 (66.7)
Initial insulin regimen, n (%)					
Basal	603 (50.6)	130 (71.8)	168 (26.0)	251 (87.2)	54 (69.2)
Premixed	552 (46.3)	29 (16.0)	463 (71.8)	36 (12.5)	24 (30.8)
Basal bolus	7 (0.6)	3 (1.7)	4 (0.6)	0 (0)	0 (0)
Basal plus prandial	30 (2.5)	19 (10.5)	10 (1.6)	1 (0.3)	0 (0)
Change of insulin treatment, n (%)					
All	402 (33.7)	81 (44.8)	254 (39.4)	23 (8.0)	44 (56.4)
Daily insulin dose increase	313 (26.3)	57 (31.5)	221 (34.3)	16 (5.6)	19 (24.4)
Addition of new medication	84 (7.0)	13 (7.2)	37 (5.7)	3 (1.0)	31 (39.7)
Change from initial insulin regimen to another	105 (8.8)	33 (18.2)	57 (8.8)	7 (2.4)	8 (10.3)
Daily insulin dose decrease	55 (4.6)	13 (7.2)	36 (5.6)	3 (1.0)	3 (3.8)
Discontinuation of initial insulin	14 (1.2)	1 (0.6)	7 (1.1)	2 (0.7)	4 (5.1)
Insulin restart after discontinuation	5 (0.4)	1 (0.6)	4 (0.6)	0 (0)	0 (0)
HbA1c, %, mean (SD)					
Baseline[2]	9.9 (1.6)	9.3 (1.6)	10.1 (1.5)	9.9 (1.7)	10.0 (1.6)
After 6 months[3]	8.1 (1.3)	7.6 (1.3)	7.9 (1.0)	8.7 (1.4)	8.2 (1.3)
After 12 months[4]	7.4 (1.2)	7.4 (1.1)	7.2 (0.7)	7.4 (1.6)	8.1 (1.2)
After 18 months[5]	7.3 (0.9)	7.1 (1.0)	7.1 (0.7)	7.6 (1.0)	8.0 (1.1)
Δ HbA1c, %, mean (SD) after 18 months[6]	−2.4 (1.7)	−1.7 (1.3)	−3.2 (1.5)	−2.0 (1.8)	−2.1 (2.0)
HbA1c <7.5%, n (%)[2]					
Baseline	14 (1.4)	3 (1.8)	2 (0.4)	5 (1.8)	4 (5.1)
After 18 months	402 (39.6)	79 (47.0)	196 (40.2)	114 (40.6)	13 (16.7)

Abbreviations: HbA1c = Glycosylated hemoglobin; MENA = Middle East and North Africa; N = total population size; n = number of patients; OAD = oral anti-diabetic; SD = Standard Deviation; UAE = United Arab Emirates.

Note: Baseline HbA1c is from visit 1 lab test. Percentages are based on total number of patients with non-missing values.

Calculated based on the following number of participants:

[1] Region MENA (N = 811); Algeria (N = 126); Egypt (N = 414); Saudi Arabia (N = 226); UAE (N = 45).

[2] Region MENA (N = 1014); Algeria (N = 168); Egypt (N = 487); Saudi Arabia (N = 281); UAE (N = 78).

[3] Region MENA (N = 761); Algeria (N = 145); Egypt (N = 307); Saudi Arabia (N = 252); UAE (N = 57).

[4] Region MENA (N = 685); Algeria (N = 144); Egypt (N = 250); Saudi Arabia (N = 248); UAE (N = 43).

[5] Region MENA (N = 637); Algeria (N = 119); Egypt (N = 259); Saudi Arabia (N = 218); UAE (N = 41).

[6] Region MENA (N = 614); Algeria (N = 109); Egypt (N = 246); Saudi Arabia (N = 218); UAE (N = 41).

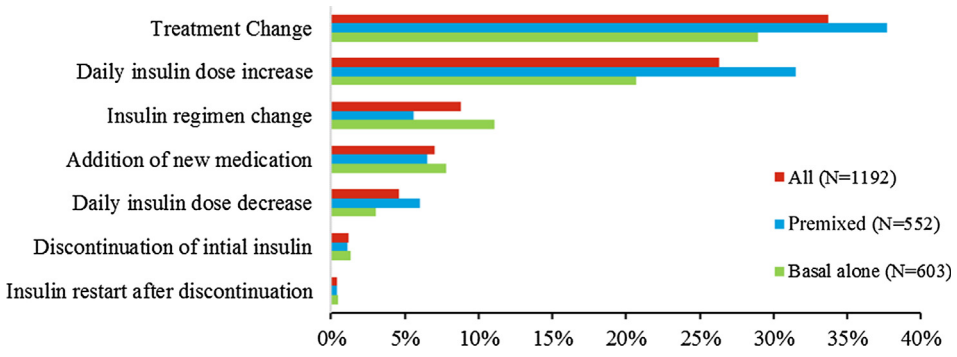

Fig. 1 – Percentage of patients with treatment change.

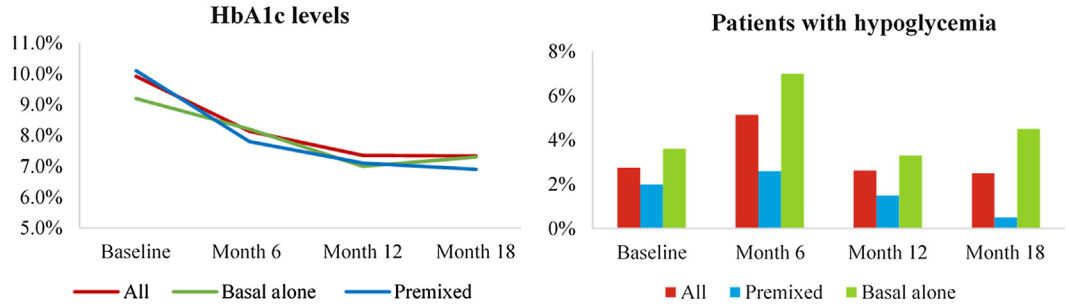

Fig. 2 – (A) Mean HbA1c (%) by initial insulin treatment at baseline after 6, 12, and 18 months. *Abbreviation:* HbA1c = glycated hemoglobin. Note: "all" includes patients who initiated on basal, premixed, basal bolus, and basal plus prandial insulin. Calculated based on the following number of participants: Baseline: all (N = 1014); basal (N = 578); premixed (N = 402); Visit 2: all (N = 761) basal (N = 452); premixed (N = 281); Visit 3: all (N = 685); basal (N = 422); premixed (N = 237); Visit 4: all (N = 637); basal (N = 378); premixed (N = 234). (B) Patients with hypoglycemia (%) at baseline and after 6, 12, and 18 months. *Note:* "all" includes patients who initiated on basal, premixed, basal bolus, and basal plus prandial insulin. Calculated based on the following number of participants: Baseline: all: N = 1192, basal alone: N = 603, premixed: N = 552; Month 6: all: N = 936, basal alone: N = 487, premixed: N = 421; Month 12: all: N = 876, basal alone: N = 459, premixed: N = 389; Month 18: all: N = 811, basal alone: N = 403, premixed: N = 383.

difference in the durability of initial treatment between the patients who were initiated on basal alone and premixed insulin (median 172 days versus 182 days, respectively).

Overall, the mean HbA1c decreased from 9.9% (standard deviation [SD] = 1.6; n = 1014) to 7.3% (SD = 0.94; n = 637) through 18 months (Fig. 2A). The overall mean (SD) change from baseline to Visit 4 was −2.4% (SD = 1.7; n = 614), Supplementary Fig. 3 presents the change in HbA1c from baseline to Visit 4 by initial insulin regime. Among 1014 patients after HbA1c measured at Visit 4, 39.6% reached an HbA1c <7.5% (Table 2). Of these, 42.5% (n = 171) and 37.4% (n = 216) patients who initiated on premixed and basal insulin, respectively, reached HbA1c <7.5% after 18 months of treatment.

The incidence of hypoglycemia was highest (5.1%; n = 48) during the first 6 months and decreased thereafter (Fig. 2B). Hypoglycemia was reported more often in those patients where initial treatment was changed during the study compared with those who did not have any change of treatment. Hypoglycemic events were reported less commonly in those who were initiated on premixed insulin compared with those who were initiated on basal insulin (Supplementary Fig. 4).

At baseline, 66 (6.2%) patients were completely satisfied and 145 (13.7%) were somewhat satisfied with their diabetes medicines. At the end of study, this increased to 168 (29.1%) patients being completely satisfied and 257 (44.5%) patients being somewhat satisfied (percentage based on total number of patients with non-missing values [n = 578, 48.5%]; Table 3, Supplementary Fig. 5).

Overall, there was a strong increase in perception to diabetes treatment with the mean (SD) total EITQ score of 44.1 (8.4, n = 1183) at baseline and PITQ score of 49.4 (8.9, n = 651) at the end of study, with the mean (SD) change of 4.9 (10.5; Table 3, Supplementary Fig. 5). Patients in whom initial treatment was continued without any changes had a greater increase in PITQ score (4.5 [10.2] and 5.7 [11.1] for basal and premixed, respectively) compared to those with changes (3.0 [11.4] and 3.9 [9.8], respectively).

Mean EQ-VAS score ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) was 61.1 (18.38) for 1045 patients at baseline and increased to 77.5 (13.36) for 596 patients at Visit 4 (Table 3). The mean (SD) change from baseline at Visit 4 was 18.1 (19.63) for 571 patients with values at both visits.

4. Discussion

The VISION study is one of the first 18-month prospective studies to assess and report the clinical characteristics, treatment approaches and patterns, and PROs in patients with T2DM reflecting the real-life treatment of a total of 1192 participants in the MENA region. Overall, the results show that a high number of patients (67.6%) had HbA1c ≥9% (mean HbA1c of 9.9%) at insulin initiation despite 68.3% being on 2 or more OADs and a long duration of diabetes (mean of 8.9 years) before insulin initiation, indicating a significant delay in insulin initiation. According to the literature, clinical inertia, defined as resistance to initiate or intensify treatment in a patient not at the evidence-based HbA1c goal, is conservatively estimated to occur in at least 25% of patients with T2DM. Studies also showed that patient factors associated with more rapid intervention included very poor glycemic control (HbA1c >9%), higher income, medication adherence, recent hospital admission, number of primary care and/or endocrinology visits, and lower complexity of therapy (monotherapy versus combination therapy) [14]. In our study, it seems that even that threshold did not trigger enough treatment intensification, so more studies are needed to identify factors affecting clinical inertia that may help to inform initiatives to address this important and widespread problem. The high HbA1c levels of patients despite being on OADs seen in our study is comparable to the results of the FINE study (9.8%) conducted in 11 Asian countries [15]. Slightly lower values were shown in the TREAT study enrolling patients from Greece, Portugal, Romania, Sweden, and Turkey (9.6%) [16],

Table 3 – Patient-reported outcomes.

Variable	Region MENA (N = 1192)	Algeria (N = 181)	Egypt (N = 645)	Saudi Arabia (N = 288)	UAE (N = 78)
Patients completely satisfied with diabetes medication, n (%)					
Baseline[1]	66 (6.2)	20 (11.4)	13 (2.1)	25 (14.6)	8 (10.3)
After 18 months[2]	168 (29.1)	42 (33.9)	113 (27.8)	7 (28.0)	6 (26.1)
Patients somewhat satisfied with diabetes medication, n (%)					
Baseline[1]	145 (13.7)	25 (14.2)	53 (8.4)	43 (25.1)	24 (30.8)
After 18 months[2]	257 (44.5)	51 (41.1)	186 (45.8)	9 (36.0)	11 (47.8)
EITQ (mean score [SD])[3]					
Baseline	44.1 (8.4)	48.5 (6.8)	43.0 (9.1)	43.2 (7.2)	46.8 (6.8)
PITQ (score)[4]					
After 18 months	49.4 (8.9)	54.4 (8.4)	47.9 (9.2)	49.6 (4.4)	47.7 (9.1)
Δ PITQ (score) after 18 months[5]	4.9 (10.5)	5.9 (10.2)	5.1 (11.2)	3.6 (8.3)	2.6 (8.4)
EQ-VAS, mean (SD)					
Baseline[6]	61.1 (18.4)	58.0 (19.1)	58.2 (16.7)	67.2 (19.5)	66.3 (17.6)
After 18 months[7]	77.5 (13.4)	78.2 (13.6)	74.6 (12.5)	88.3 (11.0)	75.5 (12.0)
Δ EQ-VAS after 18 months, mean (SD)[8]	18.1 (19.6)	19.0 (22.6)	17.2 (18.0)	22.2 (21.5)	8.8 (15.3)

Abbreviations: EITQ = Expectations about Insulin Therapy Questionnaire; EQ-VAS = EQ Visual Analog Scale; MENA = Middle East and North Africa; N = total population size; n = number of patients; PITQ = Perception about Insulin Therapy Questionnaire; UAE = United Arab Emirates.
Calculated based on the following number of participants:
[1] Region MENA (N = 1059); Algeria (N = 176); Egypt (N = 634); Saudi Arabia (N = 171); UAE (N = 78).
[2] Region MENA (N = 578); Algeria (N = 124); Egypt (N = 406); Saudi Arabia (N = 25); UAE (N = 23).
[3] Region MENA (N = 1183); Algeria (N = 176); Egypt (N = 644); Saudi Arabia (N = 285); UAE (N = 78).
[4] Region MENA (N = 651); Algeria (N = 125); Egypt (N = 407); Saudi Arabia (N = 93); UAE (N = 26).
[5] Region MENA (N = 650); Algeria (N = 125); Egypt (N = 407); Saudi Arabia (N = 92); UAE (N = 26).
[6] Region MENA (N = 1045); Algeria (N = 174); Egypt (N = 523); Saudi Arabia (N = 275); UAE (N = 73).
[7] Region MENA (N = 596); Algeria (N = 125); Egypt (N = 352); Saudi Arabia (N = 93); UAE (N = 26).
[8] Region MENA (N = 571); Algeria (N = 124); Egypt (N = 339); Saudi Arabia (N = 87); UAE (N = 21).

and even lower levels were measured in the INSTIGATE study conducted in Germany, Greece, and Spain (9.4%) [17], stressing the high burden of uncontrolled T2DM in the MENA region. The A1chieve study was carried out in 28 countries across Asia, Africa, Latin America, and Europe; insulin-naïve patients had an HbA1c of 9.5% at baseline [8]. These high levels indicate a delayed start of the insulin therapy across the world, caused by either resistance of the patient and/or the physician to initiate insulin therapy [18].

During the course of study, the mean HbA1c decreased from 9.9% to 7.3%, and the mean change from baseline to Visit 4 was −2.4%. These levels are somewhat similar to other studies in literature of 24 months [16,17], ranging from 7.2% in one to 7.6% in another. However, these levels are higher to the recommended guidelines, suggesting a need for more intensification of the insulin therapy. The higher percentage of patients who were initiated on premixed insulin reached HbA1c <7.5% after 18 months of treatment compared with patients who were initiated on basal insulin. This may be due to lack of intensification of basal insulin regimen to basal-plus or basal-bolus regimen due to clinical inertia. Most diabetes guidelines recommend not using sulfonylureas in combination with premixed insulin as this increases the risk of hypoglycemia. Despite this, around 33.4% of patients who started on premixed insulin continued sulfonylureas throughout the study. The finding that the majority of Egyptian diabetic patients were initiated on premixed insulin and were using sulfonylureas is explained by the fact that these drugs are offered free by the governmental insurance system while the cost of other drugs and basal insulin analog are relatively expensive.

Most treatment modifications took place during the first 6 months, reflected by a pronounced drop in HbA1c levels at Visit 2. These data show that in clinical practice, most modifications in insulin therapy take place during the first 6 months, but further intensification eventually is necessary to achieve HbA1c target levels. The pronounced drop in HbA1c during the first 6 months is also reflected in the frequency of hypoglycemia, which was most common during the same interval. Patients with treatment modifications experienced more hypoglycemia compared with those without any modification. It is possible that fear of this hypoglycemia led to reducing the tendency for intensification of the treatment for better A1c target. Hypoglycemic events were reported less commonly in those who were initiated on premixed insulin compared with those who were initiated on basal insulin. One possible explanation might be inappropriate titration of basal insulin after reaching target fasting blood glucose. Education regarding preventing hypoglycemia may potentially help in a proper and timely intensification of treatments. Improvement in treatment satisfaction score and other PROs suggests that in most patients, insulin treatment does improve QOL.

Data on PROs in patients with T2DM in the MENA region are scarce. Although less than 40% of patients reached an HbA1c of <7.5%, the percentage of patients who were "completely satisfied" or "somewhat satisfied" with their diabetes medication increased continuously from approximately 20%

to almost 75% of patients by the end of the study. In the FINE study, patients were asked to rate the satisfaction with their diabetes treatment after 6 months as either "not good," "moderate," "good," or "very good;" and 41.3% chose "good" and 35.6% "very good" [15], consistent with our results. The satisfaction of patients with their diabetes treatment is also reflected in the results of the EQ-VAS score, a score measuring the health status not restricted to diabetes, which improved over the course of the study.

The novel treatments such as, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have not been studied in the VISION study, as most of the participating countries did not have these agents freely available or reimbursed during the time the study was conducted. Further, this study had several limitations common to observational studies, for example, no blinding, randomization, or standardization of the treatment was enforced. The drop-out rate was high compared to similar studies from Asia [15], Europe [16,17], and globally [8], and the heterogeneity of customs, health care systems, and guidelines in the different countries of the MENA region may also limit the interpretation of the results.

A particular strength of this study was the non-interventional observation of real-world diabetes treatment across multiple countries of one region. Also, a variety of medical specialists with different levels of expertise were involved to reflect the routine clinical practice.

5. Conclusion

The results of the VISION study unveil the issue of clinical inertia in countries of the MENA region in diabetes management and the importance of not only an early insulin initiation but a timely intensification as well. This conclusion is supported by the high HbA1c levels at the time of insulin initiation and a low number of patients managing to achieve HbA1c of even <7.5% despite insulin treatment and intensification over the 18 months of study period. However, increase in satisfaction with diabetes therapy and QoL measures indicate that the patients are satisfied with their insulin therapy.

Declaration of funding

Eli Lilly and Company, the manufacturer/licensee of Humalog® and Humulin®, sponsored this observational study.

Declaration of financial/other relationships

IB, CS, TT, and ES are employees of Eli Lilly and company. AJ is a former employee of Eli Lilly and Company. KA reports to receive honoraria for lectures and advisory boards with Eli Lilly and company, Novartis, AstraZeneca, GlaxoSmithKline, Novo Nordisk, Servier Laboratories, Boehringer Ingelheim, Pfizer, Merck Serono, Merck Sharp & Dohme Corp., Sanofi Aventis, Amgen and Abbott Laboratories. AH discloses to have served in the Advisory Boards for Merck Sharp & Dohme Corp., AstraZeneca, Merck, Boehringer Ingelheim, Novo Nordisk, Eli Lilly and company, and Algorithme Pharma. RM reports to receive Fees as Speaker and Ad Board from Novo Nordisk, Eli Lilly and company and Sanofi.

Author contributions

AJ, TT and IB were involved in the development of the study concept and design. ES performed statistical analyses. AJ, RM, CS, ES, TT and IB interpreted the data. KA and AH were involved in the data acquisition. All authors critically revised the manuscript for important intellectual content. All authors have approved the final manuscript and agree to be accountable for all aspects of the work.

Acknowledgement

The authors thank all study participants and the 26 investigators who enrolled patients. Doris Hummel and Richi Taneja, Eli Lilly and Company provided medical writing assistance.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.017.

REFERENCES

[1] IDF DIABETES ATLAS. International Diabetes Federation; 2017.
[2] Majeed A, El-Sayed AA, Khoja T, Alshamsan R, Millett C, Rawaf S. Diabetes in the Middle-East and North Africa: an update. Diabetes Res Clin Pract 2014;103:218–22.
[3] Alhyas L, McKay A, Balasanthiran A, Majeed A. Prevalences of overweight, obesity, hyperglycaemia, hypertension and dyslipidaemia in the Gulf: systematic review. JRSM Short Rep 2011;2:55.
[4] Lind M, Oden A, Fahlen M, Eliasson B. The true value of HbA1c as a predictor of diabetic complications: simulations of HbA1c variables. PLoS ONE 2009;4:e4412.
[5] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–9.
[6] Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 2013;36:3411–7.
[7] Asche CV, Bode B, Busk AK, Nair SR. The economic and clinical benefits of adequate insulin initiation and intensification in people with type 2 diabetes mellitus. Diabetes Obes Metab 2012;14:47–57.
[8] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the A1chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[9] Polinski JM, Kim SC, Jiang D, Hassoun A, Shrank WH, Cos X, et al. Geographic patterns in patient demographics and insulin use in 18 countries, a global perspective from the multinational observational study assessing insulin use:

understanding the challenges associated with progression of therapy (MOSAIc). BMC Endocr Disord 2015;15:46.
[10] Jabbar A, Mohamed W, Ozaki R, Mirasol R, Treuer T, Lew T, et al. Patterns and trends in insulin initiation and intensification among patients with type 2 diabetes mellitus in the Western Pacific region. Curr Med Res Opin 2018:1–10.
[11] Hayes RP, Naegeli AN. The contribution of pretreatment expectations and expectation-perception difference to change in treatment satisfaction and end point treatment satisfaction in the context of initiation of inhaled insulin therapy in patients with type 2 diabetes. Diabetes Technol Ther 2010;12:447–53.
[12] Hayes RP, Curtis B, Ilag L, Nelson DR, Wong M, Funnell M. Expectations about insulin therapy, perceived insulin-delivery system social acceptability, and insulin treatment satisfaction contribute to decreases in insulin therapy self-efficacy in patients with type 2 diabetes after 36 weeks insulin therapy. J Diabetes 2013;5:358–67.
[13] Aschner P. IDF clinical practice recommendations for managing Type 2 diabetes. Prim Care 2017.
[14] Bailey CJ. Under-treatment of type 2 diabetes: causes and outcomes of clinical inertia. Int J Clin Pract 2016;70:988–95.
[15] Tsai ST, Pathan F, Ji L, Yeung VT, Chadha M, Suastika K, et al. First insulinization with basal insulin in patients with Type 2 diabetes in a real-world setting in Asia. J Diabetes 2011;3:208–16.
[16] Oguz A, Benroubi M, Brismar K, Melo P, Morar C, Cleall SP, et al. Clinical outcomes after 24 months of insulin therapy in patients with type 2 diabetes in five countries: results from the TREAT study. Curr Med Res Opin 2013;29:911–20.
[17] Liebl A, Jones S, Goday A, Benroubi M, Castell C, Haupt A, et al. Clinical outcomes after insulin initiation in patients with Type 2 diabetes: 24-month results from INSTIGATE. Diabetes Ther 2012;3:9.
[18] Reach G, Pechtner V, Gentilella R, Corcos A, Ceriello A. Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. Diabetes Metab 2017;43:501–11.