DISEASE REGISTRY REPORT

Compound(s): Not applicable

Multinational, cross-sectional, observational study to describe glycemic control and quality of life for type 1 diabetic adult patients

Registry number: OBS15151

Registry name: SAGE (Study of Adults' GlycEmia in T1DM)

Registry initiation date [date first patient in (FPI)]: 22-Jan-2018

Registry completion date [last patient completed/last patient out (LPO)]: 03-Dec-2018

Registry design: Multinational, multicenter, single visit, cross-sectional, observational study.

Report date: 23-Jul-2019

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

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SYNOPSIS

Title of the registry:	Multinational, cross-sectional, observational study to describe glycemic control and quality of life for type 1 diabetic adult patients. (Study name: SAGE)
Design:	Multinational, multicenter, non-interventional, cross-sectional, observational study. At the single study visit (V1) and after signing the informed consent, eligible patients were included. The Physician collected data from the patient's existing medical records and the patient's interview in an electronic case report form (eCRF). Patient perspective was collected using patient-reported outcomes (PRO) questionnaires. Values of glycated hemoglobin (HbA1c) were obtained from medical records, being measured locally in routine practice using standard method at the laboratory of the respective site. No investigations for the purpose of the study were performed.
Objectives:	**Primary objective** To describe the glycemic control in terms of the percentage of patients with Type 1 diabetes mellitus (T1DM) who were at general target of HbA1c <7% in different predefined age groups (26-44 years; 45-64 years; ≥65 years) **Secondary objectives** To evaluate in T1DM adult patients, in the different predefined age groups: • Psychosocial/PRO - Hypoglycemia fear. - Emotional status. - Treatment satisfaction. - Health-related quality of life (HRQL). • Clinical - Glycated hemoglobin levels, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG). - Percentage of patients who were at individualized target HbA1c levels, as established by the physician. - Association between each group of selected factors (socio-demographics, patient's diabetes complications and comorbidities, treatment for T1DM, structure and process of medical care) and the HbA1c target, both general (HbA1c <7%) and individualized achievement. - Association between psychosocial scores and HbA1c target achievement. - Frequency of hypoglycemic episodes during the last 3 months (for severe hypoglycemia – during the last 6 months). - Therapeutic management (eg, use of insulins by type and frequency; glucose self-monitoring method, device used and frequency; method to measure food intake). • Technology usage - Usage of technology by type (eg, blood glucose monitoring [BMG], continuous glucose monitoring [CGM], pump, diet, and carb counting applications).

Participants planned:	SAGE study was planned to involve a minimum of approximately 2000 and up to approximately 3000 T1DM patients in approximately 15 countries and 200 sites in Europe, Latin America, Africa and Asia during a recruitment period of 12 months. Endocrinologists, general practitioners, and other physicians who were familiar with the management of T1DM patients participated in the study. Selection criteria of the study population were the following: **Inclusion criteria** I 01. Male or female. I 02. Age ≥26 years old. I 03. Clinical diagnosis of presumed autoimmune T1DM treated by insulin. I 04. Diagnosis of T1DM ≥1 year. I 05. Glycated hemoglobin value available within 30 days preceding the study visit or planned to be obtained in routine practice within 7 days after the study visit. I 06. Signed written informed consent. **Exclusion criteria** E 01. Diabetes other than type-1 diabetes (eg, type-2 diabetes, secondary diabetes mellitus [pancreatic history, drug- or chemical-induced diabetes], genetic defects in β-cell function or insulin action). E 02. Patients unable to understand the nature and scope of the study, unable to read and write or unlikely to comply with the protocol, eg, inability and unwillingness to complete the PRO questionnaires. E 03. Change from pump regimen to multiple insulin injections regimen, or switch from multiple dose injections to pump regimen within the last 3 months preceding study visit. E 04. Treatment with oral antidiabetic drugs: thiazolidinedione, sulfonylurea, dipeptidyl peptidase-4 inhibitors – at any time from the diagnosis of T1DM. E 05. Treatment with any investigational drug within the last 3 months.
Scientific committee and members:	Not applicable.
Publications (reference):	Not applicable.
Introduction - Background/rationale:	**Background** The incidence of T1DM is increasing among all age groups, while older individuals represent the fastest growing group of people worldwide. There are strong indications of geographic differences in trends but the overall annual increase is estimated to be around 3% based on the report of International diabetes federation Atlas 7th edition (1). T1DM confers the risk of an array of vascular and nerve complications. Poor glycemic control in T1DM is related to long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Prevalence of complications is related to the duration of diabetes (2). Median survival age for adults with diabetes is estimated to be 10.5 years shorter than that when diabetes is absent (3). The main objective parameter for the assessment of glycemic control is the HbA1c.

	As a chronic disease T1DM impacts the overall health status of the patients and increases the psychosocial burden. The burden also increases with the development of chronic complications. Decisions concerning optimal glycemic control in frail older patients with diabetes are often difficult. It is uncertain whether strict glycemic control results in benefit or harm in this population. Older age was not an exclusion criterion in most clinical trials, but the mean age of included patients frequently is lower than 65 years old. According to the American Diabetes Association (ADA) and the European Association for the Study of Diabetes consensus recommendations, less stringent HbA1c goals are recommended for frail and older adults when the risk of hypoglycemia is high, diabetes is long-standing, or life expectancy is limited (4). Previous studies (6), (7), (8) demonstrated that good long term glycemic control is associated with a lower risk of microvascular complications. Improved glycemic control delays and slows the progression of diabetes related-complications and has an impact on quality of life (QoL) as a modifiable factor. **Rationale** SAGE study was an international, observational, cross-sectional study focusing on T1DM patients aged 26 years or older. The aim of this study was to describe the glycemic control and QoL of T1DM patients in age groups older than 25 years. Data concerning glycemic control and HbA1c levels in adults with T1DM and, in particular, in those aged 65 years or older would allow to understand better how T1DM impacts this patient population across their whole life span. The aim of this study was to assess how many patients had achieved the HbA1c target <7% specified by the international recommendations in 3 predefined age groups: 26-44 years, 45-64 years, and ≥65 years. Proportions of 40%, 40%, and 20% of study patients to be enrolled in each predefined age groups (26-44 years, 45-64 years, and ≥65 years, respectively) were estimated according to general demographic distribution in the population. Evaluation of the emotional status, treatment satisfaction, fear of hypoglycemia, and HRQL of patients were also assessed in the different age groups. This study identified factors associated with glycemic control and QoL among patient's social and demographic characteristics, treatment regimen, structure, and process of medical care. Patients were seen at a single visit at the Physician office during which data were collected, including: demography, diabetes history, treatments, HbA1c value, and specific PRO questionnaires on HRQL, emotional status, treatment satisfaction, and fear of hypoglycemia. Patients were managed as usual according to local practices and data was collected as assessed in daily routine. The patient's HbA1c level, measured locally at the Physician site using the standard method of the respective laboratory within 1 month prior to the study visit, was taken from patient's health records. According to ADA guidelines the availability of HbA1c value at the time of visit had been reported to result in increased intensification of therapy and improvement in glycemic control (5). This study included up to 3903 patients from 17 countries worldwide. Data are used to identify the most important barriers to glycemic control and to provide caregivers and patients with information and solutions to improve the management of T1DM in adult patients.
Methodology:	**(a) Site and patient selection**

	The study was conducted among 3 predefined age groups (26-44 years; 45-64 years and ≥65 years) of T1DM patients recruited in selected sites in each participating country. Selected sites were expected to see, wherever possible, at least 100 T1DM patients per year on a regular basis (defined as at least 1 visit per year for each patient). Endocrinologists, general practitioners, and other physicians who are familiar with the management of T1DM patients participated in the study. In each country, physicians were selected independently and randomly from the pre-established country specific lists of potential sites. Physicians were asked to recruit TD1M patients aged ≥26 years old who fulfilled the inclusion and exclusion criteria. In order to limit potential biases of patients' selection and ensure the representativeness of study population, eligible patients were recruited in each site according to a defined process (inclusion of consecutive patients during ≤2 months' period after initiation visit) at the single study visit (V1) and after signing the informed consent. However, at country level a ratio of 40%, 40%, and 20% in the different predefined age groups of 26-44 years, 45-64 years, and ≥65 years old, respectively, was to be respected. These ratios were chosen in order to ensure a well-balanced distribution of patients in the 3 age groups in each participating country. **(b) Data collection** Once the informed consent signed, the physician asked the patient to fill in specific paper PRO questionnaires on the own and collected data from patient's file and patient's interview to enter them in the eCRF at the beginning of the visit. Also information on structure (current medical setting of consultation, type of caregivers in charge of the patient, involvement of a diabetes care team; recent [in the previous 6 months] hospitalization) and process (current educational training, self-monitoring of glucose, self-administration of insulin, involvement of proxies [guardians, other relatives, diabetes support groups, other]) of medical care, and data on technology usage (questionnaire) were collected. No investigations for the purpose of the study were performed. **(c) Safety data collection** In this observational study, there was no product exposure studied, and therefore no systematic collection of safety data applied. Adverse drug reactions (ADRs) to any Sanofi product detected during the single study visit (V1) were to be recorded on the ADR specific form and transmitted to the Sponsor within 24 hours (for example: ADRs that were discovered at the time of a clinical research associate monitoring visit or telephone communication with the site). **(d) Data management, review and validation** Data was entered into the eCRF at the study sites. The principal investigator or sub-investigators entered the data in the eCRF in accordance with the data entry manual, for which the principal investigator was responsible. Data entered into the eCRF was promptly stored in the central database. The history of changes was managed with audit trails. After the entry, the data was confirmed, edited as necessary, and then locked in accordance with the specific process so that the data was not further edited. The principal investigator was notified for electronic signature to the eCRF.

	The methodology of data quality control (QC) (site monitoring and/or phone QC) and appropriate consecutive corrective actions are detailed in the Monitoring Plan. The computerized handling of the data by the Sponsor could generate additional requests to which the participating investigator was obliged to respond by confirming or modifying the data questioned. The requests with their responses were appended to the e-CRFs held by the physician and the Sponsor. Data collection and validation procedures were detailed in appropriate operational documents. The database was locked on 06 February 2019. **(e) Statistical considerations** For detailed statistical considerations, please refer to Appendix III, Section 3.2. – Statistical Analysis Plan (SAP). Analyses were conducted on the all eligible patients for the predefined age groups and all age groups. Descriptive analyses were performed overall, for each region and for countries with at least 500 eligible patients (i.e. Italy, Japan and Ukraine). The analyses regarding the association between glycemic control (based on general HbA1c target or individualized HbA1c target) and each group of factors (including socio-demographics, patient's diabetes complications, treatment for T1DM, structure and process of medical care), or PROs were done for eligible population (not for each region/country). **Variables and evaluation criteria:** Main evaluation criteria: • Patients achieving HbA1c target of <7%. Secondary evaluation criteria: • Clinical endpoints *Laboratory endpoints*: - HbA1c (in % and mmol/mol), achievement of individualized HbA1c targeted, as established by the physician. - FPG and PPG (in mg/dL and mmol/L). *Diabetes history, complications and comorbidities*: - Documented symptomatic hypoglycemia within the last 3 months; - Severe hypoglycemia within the last 6 months; - Severe hyperglycemia leading to ketoacidosis within the last 6 months; - Other diabetes complications and comorbidities. *Therapeutic management of T1DM patients:* - Treatment for T1DM: Use of insulins by type and frequency: self-glucose monitoring method, device used and frequency; compliance to diet and lifestyle counseling. - Structure of medical care: Current medical setting of consultation, type of caregivers in charge of the patient, involvement of a diabetes care team; recent (in the previous 6 months) hospitalization and emergency room visit.

	- Process of medical care: Current educational training, self-monitoring of glucose, self-administration of insulin, involvement of proxies (guardians, other relatives, diabetes support groups, other). • Psychosocial/PRO endpoints - Hypoglycemia fear using the Hypoglycemia Fear Survey (HFS II) questionnaire and focusing on the worry domain. - Emotional status using the Problem Areas in Diabetes (PAID) questionnaire. - Patient satisfaction with treatment using the Insulin Treatment Satisfaction Questionnaire (ITSQ). - HRQL using the Audit of Diabetes Dependent Quality of Life (ADDQoL) questionnaire. • Technology usage endpoints: Questionnaire on the usage of blood glucose monitoring (BGM), continuous glucose monitoring (CGM), pump, diet, and carb counting applications (about use of the tools, frequency and difficulty). **Data analyses:** Continuous data was summarized using the number of non-missing / missing data, standard deviation (SD), median, and minimum, quartiles (Q1, Q3), and maximum. If pertinent, 95% confidence interval (CI) of the mean. Categorical and ordinal data were summarized using the number of non-missing/missing data, counts and percentage. If pertinent, 95% CI was also provided. Missing data or unknown responses were not included in the percentages, unless specified. There was no imputation for any missing data and the variables were analyzed as recorded in the database unless otherwise specified in the PROs scoring methods. Statistical analyses were performed at the 5% significance level using 2-sided tests or 2-sided confidence intervals (CIs). Due to the exploratory nature of this study, p-values were provided for descriptive purpose only, and no adjustments for multiple comparisons were performed. *Primary analysis* The primary analysis was to estimate the percentage of eligible patients achieving the general HbA1c target <7% (glycemic control). It was provided with corresponding 2-sided 95% CI for each predefined age group and all age groups by using the binomial-based 'Exact' – Clopper-Pearson method. Descriptive statistics were performed for predefined age group and all age groups for: • HbA1c, (%) in classes: - <7% (<53 mmol/mol); - ≥7% -<7.5% (≥53 mmol/mol -<58.5 mmol/mol); - ≥7.5% -<8% (≥58.5 mmol/mol -<63.9 mmol/mol); - ≥8% -<9% (≥63.9 mmol/mol -<74.9 mmol/mol); - ≥9% -<10% (≥74.9 mmol/mol -<85.8 mmol/mol); - ≥10% -<11% (≥85.8 mmol/mol -<96.7 mmol/mol); - ≥11% (≥96.7 mmol/mol). *Secondary analyses*

	Descriptive analyses of secondary endpoints were conducted for each predefined age group and all ages pooled on the eligible population. • Descriptive statistics were presented for: - Laboratory endpoints (individualized HbA1c target, FPG and PPG), in continuous and in class. - Hypoglycemia including number of patients with at least one symptomatic hypoglycemia (blood glucose [BG] ≤70 mg/dL, BG <54 mg/dL) within the 3 last months and with at least one severe hypoglycemia, within 6 months, as well as the number of episodes in continuous. - Severe hyperglycemia leading to diabetic ketoacidosis - Therapeutic management (treatment for T1DM, structure of medical care and process of medical care). - PRO scores: - for HFS-II: Total score, Behavior subscale score and Worry subscale score; - for PAID: Total score - for ITSQ: ITSQ overall summary score and each of the 5 subscale score. - for ADDQoL: 2 overview independent item scores, individual domains scores and the average weighted impact (AWI) score (total score). - Technology usage endpoints (questionnaire on the usage of BGM, CGM, pump, diet, and carb counting (applications, frequency and difficulty)). • Relationship between the glycemic control and each group of factors These analyses were performed on the eligible population (and not for each region/country) using a multivariate logistic regression model with glycemic control as dependent variable and with factors as covariate, adjusted on region and predefined age groups (except for "socio-demographics" group of factors where 'predefined age group' is a factor). A model was applied independently for each of the 4 groups of factors (socio demographics, patient's diabetes complication, treatment for T1DM and treatment impacting the glycemia and structure and process of medical care). Firstly an analysis of association was done for glycemic control (Yes/No) and each of the factors from the corresponding group, using a Chi-square test. A graphical representation and the association analysis described (Chi-square test threshold 0.20) above led to the selection of the initial pool of factors to be considered for the multivariate model, after a measurement of collinearity between those selected factors. A stepwise selection of significant factors, with an entry level of 0.20 and a stay level of 0.05 was used for the multivariate model. Odds ratio (OR) and 95% CI were provided for each factor of the final multivariate model. For the factors finally kept in the model, interactions with region and age-group were tested and kept in the model only if statistically significant. • Relationship between the glycemic control and each PRO score This analysis was done in the eligible population (not for each region/country) for each score considered independently as detailed below:

- HFS-II Worry subscale score
- PAID Total score
- ITSQ Overall summary score and each of the 5-subscale scores
- ADDQoL 2 overview independent item scores and total AWI score.

Each PROs score detailed above was analyzed using a multivariate logistic regression model with glycemic control (based on general HbA1c target achievement and on individualized HbA1c target achievement) as dependent variable and with each score in continuous taken into account independently, as covariate, adjusted on region and on predefined age groups; interaction score*age group was also included to obtain ORs for each age group. This analysis was repeated for each score. ORs and its 95% CI were provided.

In addition, in order to identify possible confounding factors (socio-demographic factors or other patient characteristics, such as time since diabetes diagnosis, complications, gender, insulin use, education level) in the relationship between glycemic control and each PRO score, a multivariate analysis was conducted.

Sample size calculation:

The sample size justification was based on the fact that the main objective was studied in each country or group of countries separately.

Assuming that HbA1c target would be achieved in 20% to 27% of patients, and that the non-evaluability rate (drop out = patients without full documentation of HbA1c) would be around 5%, the inclusion of 500 to 1000 patients per country/region (eg, group of countries) would allow to calculate 2-sided 95% CI with a precision between 2.5% and 3.9% (all age groups taken into account). With a recruitment ratio of 40%, 40%, and 20% in the different predefined age groups of 26-44 years, 45-64 years and ≥65 years, respectively, the precision would be between 4.0% and 6.3% in the 2 first classes of age and between 5.7% and 9.2% in the last age group ≥65 years.

If the frequency of "glycemic control" was <20%, precision (%) would be higher (Table 1).

Table 1: Sample size

Number of included patients by country (n)	Age group (y)	Number of evaluable patients by age group (n)	Expected proportion of patients at HbA1c target			
			8%	10%	20%	27%
			Precision (%)			
500	26-44	190	3.9	4.3	5.7	6.3
	45-64	190	3.9	4.3	5.7	6.3
	≥65	95	5.6	6.2	8.3	9.2
	All	**475**	**2.4**	**2.6**	**3.5**	**3.9**
1000	26-44	380	2.7	3.0	4.0	4.5
	45-64	380	2.7	3.0	4.0	4.5
	≥65	190	3.9	4.3	5.7	6.3
	All	**950**	**1.7**	**1.9**	**2.5**	**2.8**

HbA1c = glycated hemoglobin; n = number; y = years

Registry period:

This report includes data reported to the SAGE registry from patients included in the study between 22 January 2018 and 03 December 2018. The registry database was locked on 06 February 2019.

RESULTS

The analysis on the eligible population is presented below. The source tables for this analysis are provided in Appendix II. Results of the analysis by region and by country (for Italy, Japan and Ukraine) are presented in Appendix II.

Participant characteristics and primary analyses:

(a) Descriptive data

Participating physicians

A total of 230 participating centers included at least one patient in the study. Median age of participating physicians was 51 (range between 28 and 75) years old, being 56.1% male physicians, 86.1% endocrinologists or diabetologists and 53.9% of the centers were public. Additional details are provided on Appendix II – Table 2.1.1.1.

Overall participation status

The study was conducted in 17 countries, categorized in 5 regions as shown in Table 2.

Table 2: Disposition of patients by age groups, by region and by country – Included population

Country	Included population [a]	Eligible population [b]	26<=Age<45	45<=Age<65	Age>=65
All regions					
All	3903	3858 (98.8%)	1724 (44.7%)	1512 (39.2%)	622 (16.1%)
Asia					
All	784	780 (99.5%)	328 (42.1%)	306 (39.2%)	146 (18.7%)
India	200	200 (100.0%)	83 (41.5%)	77 (38.5%)	40 (20.0%)
Japan	532	528 (99.2%)	208 (39.4%)	217 (41.1%)	103 (19.5%)
Thailand	52	52 (100.0%)	37 (71.2%)	12 (23.1%)	3 (5.8%)
East Europe					
All	1000	996 (99.6%)	418 (42.0%)	391 (39.3%)	187 (18.8%)
Bulgaria	200	200 (100.0%)	81 (40.5%)	83 (41.5%)	36 (18.0%)
Croatia	100	100 (100.0%)	44 (44.0%)	39 (39.0%)	17 (17.0%)
Serbia	199	197 (99.0%)	81 (41.1%)	78 (39.6%)	38 (19.3%)
Ukraine	501	499 (99.6%)	212 (42.5%)	191 (38.3%)	96 (19.2%)
Latin America					
All	492	488 (99.2%)	251 (51.4%)	169 (34.6%)	68 (13.9%)
Argentina	100	99 (99.0%)	40 (40.4%)	39 (39.4%)	20 (20.2%)
Brazil	310	307 (99.0%)	177 (57.7%)	98 (31.9%)	32 (10.4%)
Chile	52	52 (100.0%)	22 (42.3%)	20 (38.5%)	10 (19.2%)
Colombia	30	30 (100.0%)	12 (40.0%)	12 (40.0%)	6 (20.0%)
Middle East					
All	445	444 (99.8%)	187 (42.1%)	192 (43.2%)	65 (14.6%)
Iran	317	317 (100.0%)	128 (40.4%)	128 (40.4%)	61 (19.2%)
Saudi Arabia	128	127 (99.2%)	59 (46.5%)	64 (50.4%)	4 (3.1%)
West Europe					
All	1182	1150 (97.3%)	540 (47.0%)	454 (39.5%)	156 (13.6%)
France	310	296 (95.5%)	119 (40.2%)	120 (40.5%)	57 (19.3%)
Germany	153	152 (99.3%)	61 (40.1%)	63 (41.4%)	28 (18.4%)
Italy	531	523 (98.5%)	281 (53.7%)	197 (37.7%)	45 (8.6%)
United Kingdom	188	179 (95.2%)	79 (44.1%)	74 (41.3%)	26 (14.5%)

Source data: Appendix II – Table 2.1.3.1
[a] Patients who signed the ICF
[b] Included patients ≥26 years old, with T1DM, and insulin treatment who signed informed consent and who had HbA1c evaluation within 45 days preceding the study visit of within 15 days after the study visit.
Note: The percentages were calculated using the number of included patients as the denominator for eligible population for and the eligible population age groups.

A total of 4250 patients were screened in the study. Of them, 345 patients were not enrolled for different reasons including patient's or parent/ guardian's refusal, Investigator's decision or other (additional details on the reasons are provided in Appendix II – Table 2.1.2.1), thus 3905 patients were enrolled in the study and of them 3903 included in the study (2 patients did not sign the informed consent). Finally, a total of 3858 (98.8%) patients were eligible and the reasons for non-eligibility were: no HbA1c available in the time windows (39 patients), age <26 years

or missing (17 patients) and no clinical diagnosis of presumed autoimmune T1DM treated by insulin (3 patients). It should be noted that an individual patient could have several reasons for non-eligibility (Table 3).

Table 3: Disposition of patients by age groups – Included population

	26<=Age<45	45<=Age<65	Age>=65	All
Included population [a]	1738 (100.0%)	1522 (100.0%)	626 (100.0%)	3903 (100.0%)
Eligible population [b]	1724 (99.2%)	1512 (99.3%)	622 (99.4%)	3858 (98.8%)
Reason for not eligible patients [c]				
Age <26 years or missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (0.4%)
No HbA1c available in the time windows	13 (0.7%)	10 (0.7%)	3 (0.5%)	39 (1.0%)
No clinical diagnosis of presumed autoimmune T1DM treated by insulin	1 (0.1%)	0 (0.0%)	1 (0.2%)	3 (0.1%)

Source data: Appendix II – Table 2.1.3.2
a] Patients who signed the ICF – the 17 patients with age <26 years or missing were included in the 3903 patients
[b] Included patients ≥26 years old, with T1DM, and insulin treatment who signed informed consent and who had HbA1c evaluation within 45 days preceding the study visit of within 15 days after the study visit.
[c] A patient could have several reasons for not eligibility
Percentage calculated on the included population

Patients' characteristics

Overall, mean age (SD) of the eligible patients was 47.44 (14.00) years old, and 54.6% of the patients were females. By predefined age groups, the rate of female patients was higher (58.1%) in the youngest group (≥26 - <45 years) than in the rest of the predefined age groups. Similar results for all the predefined age groups were observed for weight and body mass index (Table 4).

Table 4: Demographics by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Age (years)				
Number (%)[a]	1724 (44.7%)	1512 (39.2%)	622 (16.1%)	3858 (100.0%)
Mean (SD)	34.63 (5.44)	52.74 (5.58)	70.04 (4.88)	47.44 (14.00)
Median	34	52	69	46
Min : Max	26:44	45:64	65:90	26:90
Gender				
Number	1724	1512	622	3858
Female	1001 (58.1%)	772 (51.1%)	335 (53.9%)	2108 (54.6%)
Male	723 (41.9%)	740 (48.9%)	287 (46.1%)	1750 (45.4%)
Weight (kg)				
Number	1721	1512	622	3855
Mean (SD)	69.59 (15.11)	72.03 (15.05)	70.46 (15.27)	70.68 (15.15)
Median	68	71	70	69
Min : Max	34:145	38:136	35:130	34:145
Body mass index (kg/m2)				
Number	1720	1509	622	3851
Mean (SD)	24.49 (4.31)	25.62 (4.49)	25.84 (4.64)	25.15 (4.48)
Median	24	25	25	25
Min : Max	16:53	16:45	13:47	13:53
Number	1720	1509	622	3851
<25 kg/m2	1055 (61.3%)	747 (49.5%)	288 (46.3%)	2090 (54.3%)
[25,30] kg/m2	496 (28.8%)	529 (35.1%)	227 (36.5%)	1252 (32.5%)
≥30 kg/m2	169 (9.8%)	233 (15.4%)	107 (17.2%)	509 (13.2%)
Number	1720	1509	622	3851
<27 kg/m2	1330 (77.3%)	1002 (66.4%)	399 (64.1%)	2731 (70.9%)
≥27 kg/m2	390 (22.7%)	507 (33.6%)	223 (35.9%)	1120 (29.1%)

Source data: Appendix II – Table 2.1.5.1.
[a] Number and % of patients for the corresponding age group.

Overall, a total of 44.1% patients had a university/higher level of education. By predefined age groups, these proportions were: 52.6% in the ≥26 - <45 years age group, 39.6% in the ≥45 - <65 years age group and 31.8% in the ≥65 years group. Regarding employment status, 62.8% of the patients were workers (considered when employment status was employee or independent) with 77.3% workers in the ≥26 - <45 years age group, 66.1% in the ≥45 - <65 years age group and 14.3% in the ≥65 years group. Additional details on education and employment by age group are provided in Appendix II – Table 2.1.5.3.

With respect to health insurance, overall, 56.6% of the patients reported to have a public health insurance policy (55.2% in the ≥26 - <45 years age group, 57.0% in the ≥45 - <65 years age group and 59.4% in the ≥65 years group). Additional details on health insurance by age group are provided in Appendix II – Table 2.1.5.4.

Regarding life style conditions, 90.1% of patients reported to live with another adult or in an institution or a community (90.7% in the ≥26 - <45 years age group, 90.2% in the ≥45 - <65 years age group and 88.6% in the ≥65 years group). The percentage of patients who were drivers was 64.5% (70.0% in the ≥26 - <45 years age group, 65.8% in the ≥45 - <65 years age group and 46.0% in the ≥65 years group). The percentage of patients who were compliant with diet, overall, was 71.4% (72.0% in the ≥26 - <45 years age group, 70.9% in the ≥45 - <65 years age group and 70.5% in the ≥65 years group. Additional details on the life style conditions by age group are provided in Appendix II – Table 2.1.6.1.

Details on blood pressure are provided in Appendix II – Table 2.1.5.2.

(b) Primary endpoint: glycemic control (HbA1c <7%)

Overall, 24.3% of patients achieved the general glycemic HbA1c target <7%. In the predefined age groups, the percentage of patients achieving the general HbA1c target was numerically higher in youngest age group than in the two other age groups (27.6% patients in the ≥26 - <45 years group, 21.0% patients in the ≥45 - <65 years group and 22.8% patients in the ≥65 years group). HbA1c depicted in classes is shown in Table 5:

Table 5: Glycemic control (HbA1c <7%) by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Glycemic control n (%) [95% CI] [a]				
Yes (<7%)	476 (27.6%)	318 (21.0%)	142 (22.8%)	936 (24.3%)
[95% CI]	[25.5, 29.8]	[19.0, 23.2]	[19.6, 26.3]	[22.9, 25.6]
No (≥7%)	1248 (72.4%)	1194 (79.0%)	480 (77.2%)	2922 (75.7%)
[95% CI]	[70.2, 74.5]	[76.8, 81.0]	[73.7, 80.4]	[74.4, 77.1]

Source data: Appendix II – Table 2.1.8.1
[a] 2 sided 95% CI – Binomial based exact – Clopper-Pearson method used to obtain the CI.

Additional details are provided in Appendix II – Table 2.1.8.1.

Other analyses:

- Clinical endpoints
  - *Laboratory endpoints*

HbA1c and achievement of individualized HbA1c targeted, as established by the physician

Mean (SD) HbA1c was 7.95% (1.42) [63.44 (15.56) mmol/mol] with comparable results among the predefined age groups but with slightly higher SD in younger patients. That might explain the higher percentage of achieved target <7% was higher in younger patients. It should be noted that at least one third of older age group had an individualized target ≥7.5%. Glycemic control based on individualized target was

achieved by 20.9% of the eligible patients. Higher rate of patients achieving their predefined individualized HbA1c target was observed in patients in the ≥65 years group (26.2%) than in the other two age groups (21.6% in patients in the ≥26 - <45 years group and 17.8% in patients in the ≥45 - <65 years group) (Table 6). The reason why globally the rate of patients achieving their individualized target is lower than the proportion of patients achieving the general target is due to the fact that a more stringent target (<6.5%) than the general one was defined by the physician for some patients in the 2 younger subgroups and this target was not achieved by them. Logically, in the oldest group, the individual target was higher than 7% for some patients and so the rate of patients achieving it was higher than the proportion of patients achieving the general one.

Additional details are provided in Appendix II – Table 2.1.9.1.

Table 6: HbA1c (% and mmol/mol), individualized target value and glycemic control based on individualized target by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
HbA1c (%)				
Number	1724	1512	622	3858
Mean (SD)	7.91 (1.52)	8.02 (1.37)	7.91 (1.24)	7.95 (1.42)
Median	7.70	7.80	7.80	7.79
Min : Max	4.60:17.90	5.00:16.80	4.20:12.60	4.20:17.90
HbA1c (mmol/mol)				
Number	1724	1512	622	3858
Mean (SD)	62.98 (16.66)	64.17 (14.97)	62.96 (13.60)	63.44 (15.56)
Median	60.66	61.75	61.75	61.64
Min : Max	26.78:172.15	31.15:160.12	22.41:114.22	22.41:172.15
Individualized target value (%) as per physician [a]				
Number	1724	1512	622	3858
<6.5% (47.5 mmol/mol)	97 (5.6%)	59 (3.9%)	17 (2.7%)	173 (4.5%)
[6.5%, 7.0%[(47.5,53.0 mmol/mol)	522 (30.3%)	288 (19.0%)	78 (12.5%)	888 (23.0%)
[7%, 7.5%[(53.0,58.5 mmol/mol)	959 (55.6%)	909 (60.1%)	289 (46.5%)	2157 (55.9%)
[7.5%, 8%[(58.5,63.9 mmol/mol)	115 (6.7%)	203 (13.4%)	169 (27.2%)	487 (12.6%)
[8%, 9%[(63.9,74.9 mmol/mol)	27 (1.6%)	50 (3.3%)	65 (10.5%)	142 (3.7%)
≥ 9% (74.9 mmol/mol)	4 (0.2%)	3 (0.2%)	4 (0.6%)	11 (0.3%)
Glycemic control based on individualized target n(%)[95% CI] [b]				
Number	1724	1512	622	3858
Yes (< Individual target)	373 (21.6%)	269 (17.8%)	163 (26.2%)	805 (20.9%)
[95% CI]	[19.7, 23.7]	[15.9, 19.8]	[22.8, 29.8]	[19.6, 22.2]
No (>= Individual target)	1351 (78.4%)	1243 (82.2%)	459 (73.8%)	3053 (79.1%)
[95% CI]	[76.3, 80.3]	[80.2, 84.1]	[70.2, 77.2]	[77.8, 80.4]

Source data: Appendix II – Table 2.1.9.1
[a] Patients with individualized target in each range. If individualized HbA1c target was not defined, general HbA1c target of <7.0% was considered as relevant for the patient.
[b] 2 sided 95% CI for each predefined age group and all age groups. Binomial based exact – Clopper-Pearson method used to obtain the IC.

Fasting plasma glucose (FPG) and postprandial plasma glucose (PPG)

Mean (SD) FPG was 144.8 (62.92) mg/dL, which was also similar among all predefined age groups. Mean (SD) PPG was 171.3 (67.00) mg/dL, also similar among all predefined age groups (Table 7).

Additional details on the FPG and PPG on values on mmol/L and classes are provided in Appendix II – Tables 2.1.9.2 and 2.1.9.3.

Table 7: Fasting plasma glucose by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
FPG (mg/dL)				
Number	1368	1218	510	3096
Mean (SD)	146.3 (66.16)	144.0 (63.15)	142.7 (52.65)	144.8 (62.92)
Median	131	131	133	132
Min : Max	41:607	32:503	31:393	31:607
PPG (mg/dL)				
Number	1172	1047	428	2647
Mean (SD)	170.6 (68.28)	169.9 (65.56)	177.0 (66.85)	171.3 (67.00)
Median	159	163	173	161
Min : Max	42:504	26:546	41:508	26:546

Source data: Appendix II – Table 2.1.9.2 and Table 2.1.9.3
FPG = Fasting plasma glucose

- *Diabetes history, complications and comorbidities*

Diabetes history

Overall, mean (SD) duration of diabetes was 20.73 (12.63) years. Most of the patients (77.8% of the eligible population) had a duration of diabetes ≥10 years (Table 8).

Table 8: Time since diabetes diagnosis by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Time since diabetes diagnosis (years)				
Number	1724	1512	621	3857
Mean (SD)	15.92 (9.05)	22.91 (12.73)	28.79 (15.10)	20.73 (12.63)
Median	16	22	30	19
Min : Max	1:42	1:61	1:68	1:68
Number	1724	1512	621	3857
<10	514 (29.8%)	262 (17.3%)	79 (12.7%)	855 (22.2%)
≥10	1210 (70.2%)	1250 (82.7%)	542 (87.3%)	3002 (77.8%)

Source data: Appendix II – Table 2.1.7.1.

Hypoglycemia

The proportion of patients who reported at least one symptomatic hypoglycemia confirmed by blood glucose ≤ 70 mg/dL within the previous 3 months was 67.7% By predefined age group, these proportions were 69.6% in the ≥26 - <45 years age group, 66.3% in the ≥45 - <65 years age group, and 65.7% in the ≥65 years age group. Median number of symptomatic hypoglycemia events ≤ 70 mg/dL was 4, 3 and 3, respectively.

On the other hand, the proportion of patients who reported at least one symptomatic hypoglycemia with blood glucose <54 mg/dL was 49.9%. By predefined age group, these proportions were slightly higher in the ≥26 - <45 years age group (51.8%) than in the ≥45 - <65 years and the ≥65 years age groups (48.6% and 47.9%, respectively). Median number of symptomatic hypoglycemia events <54 mg/dL was 1, 0 and 0, respectively.

At least one severe hypoglycemia event during the previous 6 months was reported in 11.9% of the eligible patients. By predefined age groups, these proportions were 11.5% in the ≥26 - <45 years group, 12.2% in the ≥45 - <65 years age group and 12.6% in the elderly group.

Hypoglycemia is summarized in Table 9:

Table 9 : Hypoglycemia by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
At least one symptomatic hypoglycemia with blood glucose ≤70 mg/dL within the last 3 months	1183 (69.6%)	991 (66.3%)	402 (65.7%)	2576 (67.7%)
At least one symptomatic hypoglycemia with blood glucose <54 mg/dL within the last 3 months	882 (51.8%)	728 (48.6%)	293 (47.9%)	1903 (49.9%)
At least one severe hypoglycemia within 6 months	197 (11.5%)	185 (12.2%)	78 (12.6%)	460 (11.9%)
Number of symptomatic hypoglycemia with blood glucose ≤70 mg/dL per patient within the last 3 months				
Number	1699	1494	612	3805
Mean (SD)	10.08 (17.77)	9.44 (17.44)	8.74 (17.45)	9.61 (17.59)
Median	4	3	3	3
Q1 : Q3	0:12	0:10	0:10	0:10
Number of symptomatic hypoglycemia with blood glucose <54 mg/dL per patient within the last 3 months				
Number	1701	1496	612	3809
Mean (SD)	3.77 (8.21)	3.35 (8.12)	3.04 (7.78)	3.49 (8.11)
Median	1	0	0	0
Q1 : Q3	0:4	0:3	0:3	0:3
Number of severe hypoglycemia within 6 months per patient				
Number	1720	1511	621	3852
Mean (SD)	0.46 (2.24)	0.45 (2.91)	0.41 (1.62)	0.45 (2.45)
Median	0	0	0	0
Q1 : Q3	0:0	0:0	0:0	0:0
At least one hospitalization/emergency visit within the last 6 months linked to a severe hypoglycemia [b]	49 (24.9%)	47 (25.4%)	25 (32.1%)	121 (26.3%)

Source data: Appendix II – Table 2.1.10.1
[a] Any of documented, probable within 3 months and severe within 6 months.
[b] Percentage is calculated among patients with at least one severe hypoglycemia

Additional details on hypoglycemia are provided in Appendix II – Table 2.1.10.1.

Severe hyperglycemia leading to ketoacidosis

Overall, 162 (4.2%) patients reported at least one severe hyperglycemia leading to diabetic ketoacidosis within the previous 6 months. Higher proportions were observed in the ≥26 - <45 years and in the ≥45 - <65 years age groups (4.8% and 4.0%, respectively) than in the ≥65 years (2.9%) group. The most frequent predisposing factors which led to ketoacidosis were: skip of insulin injections (23.5% of the patients with ketoacidosis), infection (21.6%) and pump malfunctioning (13.6%).

Mean (SD) number of severe hyperglycemia leading to diabetic ketoacidosis per patient within the 6 previous months was 0.11 (0.82) episodes. By predefined age group, mean (SD) episodes of severe hyperglycemia leading to diabetic ketoacidosis within the last 6 months was lower in the ≥65 years age group (0.04 [0.24]) than in the 2 younger groups (0.15 [1.05] in the ≥26 - <45 years age group and 0.10 [0.67] in the ≥45 - <65 years group).

A total of 76 (46.9%) patients had at least one hospitalization/emergency visit within the previous 6 months linked to severe hyperglycemia leading to diabetic ketoacidosis. Comparable results were observed for the ≥26 - <45 years and ≥65

years age groups (50.6% and 55.6%, respectively) and this proportion was lower in the ≥45 - <65 years group (39.3%).

Severe hyperglycemia is summarized in Table 10:

Table 10: Severe hyperglycemia by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Severe hyperglycemia leading to diabetic ketoacidosis				
At least one within 6 months	83 (4.8%)	61 (4.0%)	18 (2.9%)	162 (4.2%)
Number of episodes per patient				
Number	1723	1512	620	3855
Mean (SD)	0.15 (1.05)	0.10 (0.67)	0.04 (0.24)	0.11 (0.82)
Median	0	0	0	0
Q1 : Q3	0:0	0:0	0:0	0:0
If ketoacidosis, predisposing factors within last 6 months [a]				
Infection	19 (22.9%)	12 (19.7%)	4 (22.2%)	35 (21.6%)
Food poisoning	5 (6.0%)	0 (0.0%)	1 (5.6%)	6 (3.7%)
Has not taken insulin	19 (22.9%)	15 (24.6%)	4 (22.2%)	38 (23.5%)
Ketogenic diet	10 (12.0%)	4 (6.6%)	2 (11.1%)	16 (9.9%)
Pump malfunctioning	15 (18.1%)	6 (9.8%)	1 (5.6%)	22 (13.6%)
At least one hospitalization/emergency visit within 6 months linked to severe hyperglycemia leading to diabetic ketoacidosis [a]	42 (50.6%)	24 (39.3%)	10 (55.6%)	76 (46.9%)

Source data: Appendix II – Table 2.1.10.2
[a] Percentage is calculated among patients with at least one severe hyperglycemia leading to diabetic ketoacidosis

Additional details are provided in Appendix II – Table 2.1.10.2.

Other diabetes complications and comorbidities

Overall, regarding other diabetes complications, diabetic retinopathy was reported in 33.2% of the patients; diabetic neuropathy was reported in 32.5% patients (mostly peripheral neuropathy); and renal function impairment related to diabetes was reported in 15.9% of patients.

The most frequent comorbidities reported were hypertension (28.7%) and dyslipidemia (26.5%).

The proportion of patients with at least one microvascular complication (diabetic neuropathy, diabetic retinopathy or renal function impairment related to diabetes) was 46.7%. By predefined age groups, these proportions were 35.9% in the ≥26 - <45 years age group, 52.3% in the ≥45 - <65 years age group and 63.2% in the ≥65 years age group.

On the other hand, the proportion of patients with at least one macrovascular complication (coronary heart disease, acute myocardial infarction, myocardial revascularization procedure, heart failure stroke, transient ischemic attack, peripheral vascular disease, peripheral revascularization procedure, foot ulcer or lower limb amputation for arterial reason) was 14.3%. By predefined age groups, these proportions were 4.8% in the ≥26 - <45 years age group, 17.7% in the ≥45 - <65 years age group and 32.6% in the ≥65 years age group

Additional details on diabetes complications and comorbidities are provided in Appendix II – Table 2.1.11.1; and additional details on microvascular and macrovascular complications by time since diagnosis and age group are provided in Appendix II – Table 2.1.11.2.

- *Therapeutic management of T1DM patients*

Treatment for T1 Diabetes Mellitus

The most frequent insulin administration device used was injections/pens reported in 79.9% of patients, with higher proportions in the elderly group (88.9%) than in the other two predefined age groups, followed by pump reported in 19.9% patients which was reported to be more frequently used in the ≥26 - <45 age group (24.0%) than in the other two predefined groups.

Basal plus short acting insulin was the most frequent insulin regimen reported (68.9% of patients), followed also by pump (20.1% of patients).

Overall, median total insulin daily dose was 46 U/day (0.66 U/Kg). By predefined age groups, median total insulin daily dose was 48 U/day (0.68 U/Kg) in the 26 - <45 years age group, 46 U/day (0.65 U/Kg)) in the ≥45 - <65 years age group and 42 U/day (0.59 U/Kg) in the elderly age group.

Patient-driven titration was reported in more than half of the eligible patients (57.0%).

The proportion of patients who reported titration of basal insulin "every week" was 23.7%, while 22.4% of patients reported titration of basal insulin "more than 1 week (1 to 6 days), with similar results across age groups. On the other hand, 27.5% of patients reported titration of basal insulin "less than every month" from 22.4% in patients ≥65 years old to 30.4% in the 26-<45 years age group.

A summary of the insulin treatment used is summarized in Table 11:

Table 11: Current insulin treatment for T1D by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Insulin device	1724	1512	622	3858
Pump	413 (24.0%)	290 (19.2%)	66 (10.6%)	769 (19.9%)
Injections/pens	1310 (76.0%)	1218 (80.6%)	553 (88.9%)	3081 (79.9%)
Pump and injections/pens	0 (0.0%)	4 (0.3%)	3 (0.5%)	7 (0.2%)
Sometimes pump and sometimes injections/pens	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)
Insulin regimen	1724	1512	622	3858
Pump [a]	414 (24.0%)	294 (19.4%)	69 (11.1%)	777 (20.1%)
Basal + short acting insulin	1151 (66.8%)	1048 (69.3%)	461 (74.1%)	2660 (68.9%)
Premix alone	60 (3.5%)	66 (4.4%)	44 (7.1%)	170 (4.4%)
Premix + other	18 (1.0%)	19 (1.3%)	8 (1.3%)	45 (1.2%)
Basal alone	53 (3.1%)	55 (3.6%)	30 (4.8%)	138 (3.6%)
Short acting insulin alone	28 (1.6%)	30 (2.0%)	10 (1.6%)	68 (1.8%)
Insulin taken				
Pump [b]	413 (24.0%)	290 (19.2%)	66 (10.6%)	769 (19.9%)
Basal*	1213 (70.4%)	1108 (73.3%)	497 (79.9%)	2818 (73.0%)
Intermediate acting NPH	155 (9.0%)	159 (10.5%)	69 (11.1%)	383 (9.9%)
Long acting analogs	1058 (61.4%)	949 (62.8%)	428 (68.8%)	2435 (63.1%)
1st generation	669 (38.8%)	554 (36.6%)	243 (39.1%)	1466 (38.0%)
2nd generation	389 (22.6%)	395 (26.1%)	185 (29.7%)	969 (25.1%)
Premix*	78 (4.5%)	85 (5.6%)	52 (8.4%)	215 (5.6%)
Short acting insulin*	1196 (69.4%)	1100 (72.8%)	480 (77.2%)	2776 (72.0%)
Short acting analogs	1024 (59.4%)	930 (61.5%)	382 (61.4%)	2336 (60.5%)
Regular human insulin	174 (10.1%)	176 (11.6%)	98 (15.8%)	448 (11.6%)
Total insulin daily dose (U/day)				
Number	1681	1472	612	3765
Mean (SD)	50.95 (23.14)	50.43 (25.24)	46.39 (23.74)	50.01 (24.13)
Median	48	46	42	46
Min : Max	8:226	8:277	8:170	8:277
Total insulin daily dose (U/kg/day)				
Number	1678	1472	612	3762
Mean (SD)	0.74 (0.31)	0.70 (0.30)	0.65 (0.28)	0.71 (0.30)
Median	0.68	0.65	0.59	0.66
Min : Max	0.10:3.04	0.08:3.15	0.10:1.92	0.08:3.15
Recommended way of titrations	1699	1498	619	3816
Physician-driven	703 (41.4%)	648 (43.3%)	291 (47.0%)	1642 (43.0%)
Patient-driven	996 (58.6%)	850 (56.7%)	328 (53.0%)	2174 (57.0%)

Frequency of titration of basal insulin				
Number	1156	1044	464	2664
More than 1 week (1 to 6 days)	255 (22.1%)	229 (21.9%)	112 (24.1%)	596 (22.4%)
Every week	263 (22.8%)	255 (24.4%)	114 (24.6%)	632 (23.7%)
Less than every week but more than every 2 weeks	73 (6.3%)	69 (6.6%)	31 (6.7%)	173 (6.5%)
Less than every 2 weeks but more than every month	214 (18.5%)	214 (20.5%)	103 (22.2%)	531 (19.9%)
Less than every month	351 (30.4%)	277 (26.5%)	104 (22.4%)	732 (27.5%)
Frequency of titration of short acting insulin				
Number	1578	1364	533	3475
More than 1 week (1 to 6 days)	906 (57.4%)	731 (53.6%)	263 (49.3%)	1900 (54.7%)
Every week	195 (12.4%)	179 (13.1%)	77 (14.4%)	451 (13.0%)
Less than every week but more than every 2 weeks	50 (3.2%)	46 (3.4%)	22 (4.1%)	118 (3.4%)
Less than every 2 weeks but more than every month	171 (10.8%)	181 (13.3%)	88 (16.5%)	440 (12.7%)
Less than every month	256 (16.2%)	227 (16.6%)	83 (15.6%)	566 (16.3%)

Source data: Appendix II – Table 2.1.12.1
[a] Pump, pump and injections/pens, sometimes pump and sometimes injection
[b] Pump only
* alone or in combinations, including patients with pump and injections/pens, sometimes pump and sometimes injection

Additional details on pump use are provided in Appendix II – Table 2.1.12.2.

The type of insulin in those patients who used injections/pens is provided in Table 12.

Additional details on the therapeutic management for injections/pens: basal insulin + short acting insulin, premix alone, premix and other insulin, basal insulin alone and short acting insulin alone by age groups are provided in Appendix II – Tables 2.1.12.4, 2.1.12.5, 2.1.12.6, 2.1.12.7 and 2.1.12.8, respectively.

Table 12: For injections/pens: type of insulin used by age group – Eligible population

	26<=Age<45 (N=1310)	45<=Age<65 (N=1218)	Age>=65 (N=553)	All (N=3081)
Type of insulin used				
Number	1310	1218	553	3081
Basal + short acting insulin	1151 (87.9%)	1048 (86.0%)	461 (83.4%)	2660 (86.3%)
Premix alone	60 (4.6%)	66 (5.4%)	44 (8.0%)	170 (5.5%)
Premix + other	18 (1.4%)	19 (1.6%)	8 (1.4%)	45 (1.5%)
Basal alone	53 (4.0%)	55 (4.5%)	30 (5.4%)	138 (4.5%)
Short acting insulin alone	28 (2.1%)	30 (2.5%)	10 (1.8%)	68 (2.2%)

Source data: Appendix II – Table 2.1.12.3

With regards to the 2660 patients who used basal insulin + short acting insulin, most of them (82.7%) used a combination of long acting analogues and short acting analogs, being similar in all predefined age groups. Up to 78.8% reported to have 1 basal injection per day mainly in the evening and a mean (SD) of short acting injections per day of 2.97 (0.56).

Overall, mean (SD) total basal daily dose was 0.36 (0.18) U/Kg/day and mean (SD) total short acting daily dose was 0.39 (0.20) U/Kg/day, and mean (SD) ratio of insulin daily dose was 0.48 (0.14) being also similar among all predefined age groups.

Injections in the abdomen were the most frequently reported administration site (50.6% of the patients). Higher proportions in this administration site were observed in the elderly group (58.6%) than in the other two predefined age groups (47.0% and 51.0% in the 26 - <45 years and the ≥45 - <65 years age groups, respectively).

Disposable pens were the most frequent device used reported by 1727 (64.9%) of the 2660 patients using basal insulin + short acting insulin and up to overall 97.5%

	patients reported that insulin was self-administered with comparable results among all predefined age groups. On the other hand, the proportion of patients who reported to have concomitantly taken at least one glucose lowering drug other than insulin was 11.1%. By predefined age groups, these proportions were 8.3% in the ≥26 - <45 years age group, 12.9% in the ≥45 - <65 years age group and 14.6% in the ≥65 years age group. The most frequent glucose lowering drug used was metformin which was reported in 9.3% of patients (6.9% in the ≥26 - <45 years age group, 10.9% in the ≥45 - <65 years age group and 11.7% in the ≥65 years age group). Additional details on the concomitant ongoing therapies for diabetes other than insulin by age group are provided in Appendix II – Table 2.1.12.9. **Non-antidiabetic concomitant treatments impacting glycemia** The proportion of patients who reported to take non-antidiabetic concomitant ongoing medications impacting the glycemia was 25.5%.By predefined age groups, the highest proportion was observed in the elderly group (48.7% of patients) followed by the ≥45 - <65 years age group (30.0% of patients) and the ≥26 - <45 years age group (13.2% of patients). Overall, the most frequent drugs impacting the glycemia reported were beta blockers (9.8% of patients) and diuretics (8.0% of patients). Additional details on the concomitant ongoing medications impacting the glycemia are provided in Appendix II – Table 2.1.12.10. **Structure of medical care** More than half of the eligible population (58.3%) were treated in a hospital setting, followed by clinic setting in 32.9% and private practice was reported in 20.2% of the patients. Of note, a patient could be treated in several structures (hospital, clinic, private practice). Health care professionals managing the patient were mainly physicians specialized in diabetologia (54.6%) and endocrinologists (52.1%). The proportion of patients that had at least one recent (in the previous 6 months) hospitalization/emergency room visit due to reasons different from severe hypoglycemia or severe hyperglycemia leading to diabetic ketoacidosis was 9.6%. Similar results were observed in this type of hospitalization in all predefined age groups. Additional details on the structure of medical care is provided in Appendix II – Table 2.1.12.11. **Process of medical care** Glucagon available at home was reported in 34.4% of patients. Similar results were observed in the ≥26 - <45 years and the ≥45 - <65 years age groups (35.8% and 35.3%, respectively), while a lower proportion was observed in the elderly group (28.5%). The most frequently reported people involved in patient's medical care were "partner or other adults living with the patient" in 78.7% of the eligible patients, being similar among all predefined age groups. Additional details on the process of medical care by age group is provided in Appendix II – Table 2.1.12.12. • Psychosocial/PRO endpoints **Hypoglycemia fear using the Hypoglycemia Fear Survey questionnaire and focusing on the worry domain** Overall, mean (SD) score in the HFS-II worry domain was 20.96 (14.73) meaning a low worry of hypoglycemia. Similar results were observed among the 3 predefined age groups: 21.34 (14.60) in patients included in the ≥26 - <45 years group, 20.98

(14.91) in patients included in the ≥45 - <65 years group, and 19.87 (14.64) in patients included in the ≥65 years group (Table 13).

Additional details on the HFS-II domains are included in Appendix II – Table 2.1.13.1.

Table 13: HFS-II Hypoglycemia fear survey questionnaire by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Total Score				
Number	1716	1507	617	3840
Mean (SD)	38.10 (21.09)	38.68 (22.82)	39.74 (23.13)	38.59 (22.11)
95% CI (mean)	[37.10,39.10]	[37.53,39.84]	[37.92,41.57]	[37.89,39.29]
Worry Subscale				
Number	1718	1503	616	3837
Mean (SD)	21.34 (14.60)	20.98 (14.91)	19.87 (14.64)	20.96 (14.73)
95% CI (mean)	[20.65,22.03]	[20.22,21.73]	[18.71,21.03]	[20.50,21.43]

Source data: Appendix II – Table 2.1.13.1
Note: Each score calculated only if more than 75% of the items have responses
Note: Higher total score reflects greater fear of hypoglycemia (range [0;132]).
A higher score on the Worry subscale indicates more worry concerning episodes of hypoglycemia and its consequences (range [0;72])

Emotional status using the Problem Areas in Diabetes questionnaire

Overall, mean (SD) score in the PAID questionnaire was 32.47 (21.48) meaning a low emotional distress due to diabetes. Similar results were observed for patients in the ≥26 - <45 years group (33.77 [21.45]) and for patients in the ≥45 - <65 years group (32.28 [21.29]). Patients in the ≥65 years group showed the lowest score on emotional distress due to diabetes according to the PAID questionnaire with a mean (SD) score of 29.35 (21.72) (Table 14).

Additional details on the PAID questionnaire are included in Appendix II – Table 2.1.13.2.

Table 14: Problem Areas in Diabetes (PAID) questionnaire by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
PAID Total Score				
Number	1714	1506	618	3838
Mean (SD)	33.77 (21.45)	32.28 (21.29)	29.35 (21.72)	32.47 (21.48)
95% CI (mean)	[32.75,34.79]	[31.20,33.35]	[27.64,31.07]	[31.79,33.15]

Source data: Appendix II – Table 2.1.13.2
Note: PAID Total score considered as missing when ≥5 items not responded
Higher score corresponding to higher emotional distress due to diabetes (range [0-100])

Patient satisfaction with treatment using the Insulin Treatment Satisfaction Questionnaire

Mean (SD) overall ITSQ treatment satisfaction was 69.14 (17.86) which means a rather high level of satisfaction. By predefined age groups a higher overall satisfaction was observed in the ≥65 years age group (72.48 [17.38]) than in the ≥26 - <45 years age group (67.73 [17.65]) and the ≥45 - <65 years age group (69.36 [18.10]).

Regarding the 5 ITSQ domains score, mean (SD) inconvenience domain score was 72.55 (23.71) showing low treatment inconvenience, mean (SD) lifestyle domain score was 61.91 (25.64) meaning not too much burden on lifestyle (lowest level of satisfaction), mean (SD) hypoglycemic control domain score was 67.81 (21.29) meaning rather high satisfaction with hypoglycemic control, mean (SD) glycemic

control domain score was 68.05 (22.90) meaning rather high satisfaction with glycemic control, and mean (SD) delivery system domain score was 75.35 (21.47) meaning rather high satisfaction with delivery system (highest level of satisfaction).

Higher scores were also observed in the elderly age group especially when compared to the ≥26 - <45 years age group (Table 15):

Table 15: Insulin Treatment Satisfaction Questionnaire (ITSQ) by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Overall summary score [a]				
Number	1685	1484	607	3776
Mean (SD)	67.73 (17.65)	69.36 (18.10)	72.48 (17.38)	69.14 (17.86)
95% CI (mean)	[66.89,68.58]	[68.44,70.28]	[71.10,73.87]	[68.57,69.70]
Inconvenience [b]				
Number	1709	1504	619	3832
Mean (SD)	70.47(23.81)	72.87(24.24)	77.55 (21.27)	72.55 (23.71)
95% CI (mean)	[69.34,71.60]	[71.64,74.09]	[75.87,79.23]	[71.80,73.30]
Lifestyle [b]				
Number	1712	1505	618	3835
Mean (SD)	60.87 (25.94)	62.28 (25.52)	63.89 (24.99)	61.91 (25.64)
95% CI (mean)	[59.64,62.10]	[60.99,63.57]	[61.91,65.86]	[61.10,62.72]
Hypoglycemic control [b]				
Number	1713	1504	619	3836
Mean (SD)	67.26 (21.05)	67.64 (21.74)	69.73 (20.76)	67.81 (21.29)
95% CI (mean)	[66.27,68.26]	[66.54,68.74]	[68.10,71.37]	[67.14,68.48]
Glycemic control [b]				
Number	1707	1501	615	3823
Mean (SD)	66.05 (23.56)	68.30 (22.71)	72.97 (20.67)	68.05 (22.90)
95% CI (mean)	[64.93,67.17]	[67.15,69.45]	[71.34,74.61]	[67.32,68.77]
Delivery system [b]				
Number	1702	1496	615	3813
Mean (SD)	74.09 (21.48)	75.59(21.80)	78.27(20.31)	75.35(21.47)
95% CI (mean)	[73.06,75.11]	[74.49,76.70]	[76.66,79.88]	[74.67,76.03]

Source data: Appendix II – Table 2.1.13.3
[a] A total score is only calculated when all five subscales scores are not missing.
[b] If missing data comprise <20% of the items in the subscale, the score is calculated by imputing the missing values based on an average of the non-missing items. Otherwise the subscale was considered as missing. Transformed score= 100*((7-scalemean)/6). Higher scores indicate better treatment satisfaction (range [0-100]).

Additional details are provided in Appendix II – Table 2.1.13.3.

Health-Related Quality of Life using the Audit of Diabetes Dependent Quality of Life questionnaire

Overall, the mean (SD) AWI score was -2.22 (1.78) showing an overall small negative impact of diabetes on QoL. Comparable results were observed in the predefined age groups.

Regarding the item that assessed present quality of life, overall mean (SD) was 0.74 (1.20) indicating the mean response was between 'neither good or bad (0)' and 'good (1)' with similar results in all predefined age groups.

With regards to the item that assessed how their quality of life would be without diabetes, overall mean (SD) was -1.55 (1.06), which was between 'a little bit better (-1)' and 'much better (-2)', with similar results among the predefined age groups.

ADDQoL is summarized in Table 16:

Table 16: Audit of Diabetes Dependent Quality of Life (ADDQoL) questionnaire by age group – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Average weighted impact score				
Number	1712	1504	618	3834

Mean (SD)	-2.20 (1.79)	-2.30 (1.85)	-2.08 (1.56)	-2.22 (1.78)
95% CI (mean)	[-2.28,-2.11]	[-2.39,-2.21]	[-2.21,-1.96]	[-2.28,-2.16]
In general my present quality of life is [a]:				
Number	1715	1507	621	3843
Mean (SD)	0.80 (1.19)	0.72 (1.19)	0.67 (1.21)	0.74 (1.20)
95% CI (mean)	[0.74,0.85]	[0.66,0.78]	[0.57,0.76]	[0.71,0.78]
If I did not have diabetes, my quality of life would be [b]:				
Number	1716	1505	621	3842
Mean (SD)	-1.54 (1.10)	-1.58 (1.05)	-1.51 (0.98)	-1.55 (1.06)
95% CI (mean)	[-1.59,-1.49]	[-1.63,-1.52]	[-1.59,-1.43]	[-1.58,-1.52]

Source data: Appendix II – Table 2.1.13.4
[a] Range from -3 (extremely bad) to 3 (excellent).
[b] Range from -3 (very much better) to 1 (worse).
Weighted impact score = impact rating (-3 [very much greater] to +1 [less impact]) x importance rating (0 [not at all important] to 3 [very important]) = -9 (maximum negative impact of diabetes) to +3 (maximum positive impact of diabetes).
Total score range: -9 (maximum negative impact of diabetes) to +3 (maximum positive impact of diabetes).

Full details on the ADDQoL are provided in Appendix II – Table 2.1.13.4.

- Relationship between the glycemic control (general target) and each group of factors

Relationship between glycemic control and socio-demographic factors

The multivariate analyses (analyses adjusted for regions) showed that socio-demographic factors associated with better glycemic control were a younger age, lower BMI, lower diastolic blood pressure, higher level of education, driver rather than no driver and compliance with diet (Table 17).

Table 17: Logistic Multivariate Analysis for the identification of socio-demographics factors associated with the HbA1c general target achieved – Step-wise selection model adjusted by region

Factor/Levels	Adjusted OR, CI 95%	P-value
Age (years)		
[26-45[years	Reference	**0.049**
[45-65[years	0.82, (0.69,0.98)	0.028
≥65 years	1.03, (0.82,1.31)	0.785
Body Mass Index (Kg/m²)		
<25 kg/m²	Reference	**<0.001**
[25-30[kg/m²	0.75, (0.63,0.90)	0.002
≥30 kg/m²	0.61, (0.46,0.80)	<0.001
Diastolic Blood Pressure (mmHg)		
<80 mmHg	Reference	**<0.001**
[80-90[mmHg	0.68, (0.57,0.81)	<0.001
≥90 mmHg	0.59, (0.43,0.82)	0.001
Diet		
Yes	Reference	**<0.001**
No	0.71, (0.58,0.87)	<0.001
Driver		
Driver	Reference	**0.010**
No driver	0.79, (0.66,0.94)	0.010
Level of education		
University / Higher Education	Reference	**<0.001**
Secondary	0.84, (0.71,1.00)	0.047
Primary	0.40, (0.27,0.60)	<0.001
Illiterate+Unknown+Doesn't want to answer	0.81, (0.51,1.29)	0.379

Source data: Appendix II – Table 2.1.14.12.1
Step-wise selection model with the selected factors. Entry level 0.2 and stay level 0.05
Type III p-value adjusted by the factors kept in the model according to the stepwise specifications.
Logistic Regression Model adjusted by region
Model is based on 3473 observations
Association of Predicted Probabilities and Observed Responses – Area under curve: 0.63
Hosmer and Lemeshow goodness-of-fit test: 0.80

An additional multivariate analysis (adjusted by age group, region, and factors previously identified) including interaction of region with diet showed that in Latin America, diet was not associated with glycemic control (p=0.268), and in Asia, no compliance with diet is associated with better glycemic control (OR [95% CI: 1.65, [1.12, 2.41]; p=0.001). Additional details on these analyses are provided on Appendix II – Table 2.1.14.12.2.

Relationship between glycemic control and patient diabetes complications and comorbidities

The multivariate analyses (analyses adjusted for regions and age group) showed that regarding diabetes history, complications and comorbidities factors, longer time since diagnosis (more than 10 years), severe hyperglycemia leading to ketoacidosis within the last 6 months, microvascular diabetes complications and dyslipidemia were associated with poorer glycemic control. On the other hand, having at least one symptomatic hypoglycemia <54 mg/dL within the last 3 months was associated with better glycemic control (Table 18).

Table 18: Logistic Multivariate Analysis for the identification of patient diabetes complications and comorbidities factors associated with the HbA1c general target achieved – final model adjusted by region and predefined age groups

Factor/Levels	Adjusted OR, CI 95%	P-value
Time since diabetes diagnosis (years)		
<10 years	Reference	**0.046**
≥10 years	0.83, (0.69,1.00)	0.046
At least one symptomatic hypoglycemia blood glucose <54 mg/dL (3.0 mmol/L) within the last 3 months		
No	Reference	**<0.001**
Yes	1.32, (1.13,1.54)	<0.001
At least one severe hyperglycemia leading to diabetic ketoacidosis		
No	Reference	**<0.001**
Yes	0.46, (0.30,0.72)	<0.001
At least one microvascular diabetes complication		
No	Reference	**0.023**
Yes	0.81, (0.68,0.97)	0.023
Dyslipidemia		
No	Reference	**<0.001**
Yes	0.63, (0.51,0.77)	<0.001

Source data: Appendix II – Table 2.1.15.11
Step-wise selection model with the selected factors. Entry level 0.2 and stay level 0.05
Type III p-value adjusted by the factors kept in the model according to the stepwise specifications.
Logistic Regression Model adjusted by region and predefined age groups
Model is based on 3750 observations
Association of Predicted Probabilities and Observed Responses – Area under curve: 0.61
Hosmer and Lemeshow goodness-of-fit test: 0.11

Relationship between glycemic control and treatment for T1DM or treatment impacting the glycemia

The multivariate analyses (analyses adjusted for regions and age group) showed that regarding treatment, a lower total daily dose of insulin was associated with a better glycemic control (OR [95% CI]: 2.37 [1.89, 2.99], p<0.001 for total dose <33 U/day

compared to ≥62 U/day, (OR [95% CI]: 1.47 [1.17, 1.84], p<0.001 for total dose to ≥33 and <46 U/day compared to ≥62 U/day). Taking at least one glucose lowering drug is associated with poorer glycemic control (OR [95% CI]: 0.67 [0.51, 0.90], p=0.007).

Additional details on the relationship between glycemic control and treatment for T1DM or treatment impacting the glycaemia are provided on Appendix II – Table 2.1.16.10).

Relationship between glycemic control and structure and process of medical care

The multivariate analyses (analyses adjusted for regions and age group) showed that regarding structure and process of medical care, being managed by other HCP than diabetologist/endocrinologist as well as having no health insurance was associated with poorer glycemic control (Table 19).

Table 19: Logistic Multivariate Analysis for the identification of structure and process of medical care associated with the HbA1c general target achieved – final model adjusted by region and predefined age groups

Factor/Levels	Adjusted OR, CI 95%	P-value
Health care professional managing the patient		
Diabetologist or Endocrinologist only	Reference	**<0.001**
Diabetologist or Endocrinologist and other HCP	0.71, (0.61,0.84)	<0.001
Other HCP but no Diabetologist/Endocrinologist	0.33, (0.17,0.64)	0.001
Health insurance		
Yes	Reference	**0.017**
No	0.80, (0.66,0.96)	0.017

Source data: Appendix II – Table 2.1.17.4.1
Step-wise selection model with the selected factors. Entry level 0.2 and stay level 0.05
Type III p-value adjusted by the factors kept in the model according to the stepwise specifications.
Logistic Regression Model adjusted by region and predefined age groups
Model is based on 3856 observations
Association of Predicted Probabilities and Observed Responses – Area under curve: 0.59
Hosmer and Lemeshow goodness-of-fit test: 0.15

An additional multivariate analysis (adjusted by age group, region and factors previously identified) including interaction between region and health insurance, showed that in Asia having health insurance was associated with a better glycemic control (OR [95% CI]: 0.37 [0.19, 0.71] for No versus Yes; p=0.003) but no association between health insurance and glycemic control in the other regions was observed. Additional details on these analyses are provided on Appendix II – Table 2.1.17.4.2.

- Relationship between the glycemic control (based on individualized target) and each group of factors

Relationship between glycemic control and socio-demographic factors

The multivariate analyses (analyses adjusted for regions) showed that socio-demographic factors associated with better glycemic control were an older age (OR [95% CI]: 1.56 [1.24, 1.97]; p<0.001, for ≥65 years age group compared to the 26-45 years age group), lower BMI (OR [95% CI]: 0.75 [0.62, 0.90]; p=0.002, for 25-30 Kg/m^2 group and OR [95% CI]: 0.66 [0.50, 0.87]; p=0.004 for ≥30 Kg/m^2 group compared to the BMI<25kg/m^2 group), lower diastolic blood pressure (OR [95% CI]: 0.70 [0.58, 0.84]; p<0.001 for 80-90 mmHg group compared to <80 mmHg) and higher level of education (OR [95% CI]: 0.47 [0.32, 0.68]; p<0.001 for primary group

	and OR [95% CI]: 0.78 [0.65, 0.93]; p=0.006 for the secondary group compared to university/higher education group). Additional details on the relationship between glycemic (based on individualized target) and socio-demographic factors are provided in Appendix II – Table 2.1.18.9. **Relationship between glycemic control and patient diabetes complications and comorbidities** The multivariate analyses (analyses adjusted for regions and age group) showed that regarding complications and comorbidities factors, having at least one symptomatic hypoglycemia <54 mg/dL within the 3 last months (OR [95% CI]: 1.41 [1.20, 1.66]; p<0.001) is associated with better glycemic control. On the other hand, having at least one severe hyperglycemia leading to ketoacidosis within the last 6 months (OR [95% CI]: 0.36 [0.21, 0.61]; p<0.001) is associated with poorer glycemic control, as well as having microvascular diabetes complications and dyslipidemia. Additional details on the relationship between glycemic (based on individualized target) and patient diabetes complications and comorbidities are provided in Appendix II – Table 2.1.19.8. **Relationship between glycemic control and treatment for T1DM or treatment impacting the glycemia** The multivariate analyses (analyses adjusted for regions and age group) showed that regarding treatment, premix insulin (alone or in addition to other) and basal insulin alone or short acting insulin alone were associated to poorer glycemic control compared to the use of pump, as well as a lower total daily dose of insulin (OR [95% CI]: 2.31 [1.80, 2.97] p<0.001 for total dose <33 U/day compared to ≥62 U/day, OR [95% CI]: 1.77 [1.39, 2.25] p<0.001 for total dose to ≥33 and <46 U/day compared to ≥62 U/day; and OR [95% CI]: 1.32 [1.04, 1.69]; p=0.025 for total dose to ≥46 and <62 U/day compared to ≥62 U/day). Additional details on the relationship between glycemic control (based on individualized target) and treatment for T1DM or treatment impacting the glycaemia, are provided in Appendix II – Table 2.1.20.8.1. An additional multivariate analysis (adjusted by age group, region and factors previously identified) including interaction between region and insulin regimen) showed that: • in Latin America and Asia, basal insulin alone or short acting insulin alone compared to the use of a pump was associated with a poorer glycemic control (OR [95% CI]: 0.21 [0.08, 0.56], p=0.002 and 0.10 [0.01, 0.75], p=0.025, respectively). • in Asia, the use of premix (alone or in addition to other insulin) compared to the use of pump was also associated with a poorer glycemic control (OR [95% CI]: 0.38 [0.16, 0.92], p=0.032). Additional details on these analyses are provided on Appendix II – Table 2.1.20.8.2. **Relationship between glycemic control and structure and process of medical care** The multivariate analyses (analyses adjusted for regions and age group) showed that regarding structure and process of medical care, being managed by other HCP than diabetologist/endocrinologist was associated with poorer glycemic control (OR [95% CI]: 0.49 [0.25, 0.93]; p=0.030) as well as having no health insurance (OR [95% CI]: 0.74 [0.61, 0.91]; p=0.004 for no health insurance compared to having one).

	Additional details on the relationship between glycemic control (based on individualized target) and structure and process of medical care are provided in Appendix II – Table 2.1.21.4. • Relationship between the glycemic control and PRO endpoints **Relationship between general glycemic control and PROs** The multivariate analyses (analyses adjusted for regions and age group) showed that regarding PROs, higher scores in the HFS-II worry subscale and in the PAID score were associated with a poorer glycemic control. On the other hand, higher scores in ITSQ (total score and in the inconvenience, hypoglycemic control, glycemic control and delivery system domains) and in ADDQoL (AWI and overview item 1) were associated with a better glycemic control. Additional details on the relationship between general glycemic control and PROs including the association for each age group, are provided in Appendix II – Table 2.1.22.1. An additional multivariate analysis (analyses adjusted for regions, age groups and potential confounders) showed that: - After adjustment on potential confounders (health care professional managing the patient, diet, driver, level of education, time since diabetes diagnosis (years), at least one microvascular diabetes complication and at least one severe hyperglycemia leading to diabetic ketoacidosis), as well as region and age, higher ITSQ total score was associated with better glycemic control (OR [95% CI]: 1.14 [1.09, 1.19], p<0.001 for an increase of 10 points in score). - After adjustment on potential confounders (BMI, health care professional managing the patient, diastolic blood pressure, diet, level of education, time since diabetes diagnosis (years) and at least one microvascular diabetes complication) as well as region and age, higher scores in the ITSQ inconvenience domain were associated with better glycemic control (OR [95% CI]: 1.07 [1.03, 1.11, p<0.001] for an increase of 10 points in score). - After adjustment on potential confounders (diet, driver, level of education, at least one symptomatic hypoglycemia blood glucose <54 mg/dL (3.0 mmol/L) within the last 3 months and at least one severe hyperglycemia leading to diabetic ketoacidosis) as well as region and age, higher scores in the ITSQ hypoglycemic control domain were associated with better glycemic control (OR [95% CI]: 1.06 [1.02, 1.10], p=0.002 for an increase of 10 points in score). - After adjustment on potential confounders (diet and at least one severe hyperglycemia leading to diabetic ketoacidosis) as well as region and age, higher scores in the ITSQ glycemic control domain were associated with better glycemic control (OR [95% CI]: 1.24 [1.19, 1.29], p<0.001 for an increase of 10 points in score). - After adjustment on potential confounders (health care professional managing the patient, diastolic blood pressure, diet, driver, level of education, time since diabetes diagnosis (years), health insurance, at least one symptomatic hypoglycemia blood glucose <54 mg/dL (3.0 mmol/L) within the 3 months and at least one microvascular diabetes complication) as well as region and age, higher scores in the ITSQ delivery system domain were associated with better glycemic control (OR [95% CI]: 1.04 [1.00, 1.09], p=0.037 for an increase of 10 points in score).

- After adjustment on potential confounders (diastolic blood pressure, diet, total insulin daily dose (U/day), driver, level of education, time since diabetes diagnosis (years), health insurance and at least one severe hyperglycemia leading to diabetes ketoacidosis) as well as region and age, higher PAID score was associated with poorer glycemic control (OR [95% CI]: 0.92 [0.88, 0.96], p<0.001 for an increase of 10 points in score).

Additional details on the relationship between glycemic control and PROs scores considering potential confounders are provided in Appendix II – Table 2.1.23. 64.

Relationship between glycemic control (based on individualized target) and PROs

The multivariate analyses (analyses adjusted for regions and age group) showed that regarding PROs, higher scores in the PAID score were associated with a poorer glycemic control. On the other hand, higher scores in ITSQ (total score and in the inconvenience, hypoglycemic control, glycemic control and delivery system domains) were associated with a better glycemic control. No association was found between glycemic control (based on individualized target) and other PROs scores (eg, HFS-II or ADDQoL).

Additional details on the relationship between glycemic control (based on individualized target) and PROs adjusted for regions and age group are provided in Appendix II – Table 2.1.24.1.

An additional multivariate analysis (analyses adjusted for regions, age groups and potential confounders) showed that:

- After adjustment on potential confounders health care professional managing the patient, level of education, insulin regimen, at least one microvascular diabetes complication and at least one severe hyperglycemia leading to diabetic ketoacidosis), as well as region and age, higher ITSQ total score was associated with better glycemic control (OR [95% CI]: 1.10 [1.05, 1.16], p<0.001 for an increase of 10 points in score).
- After adjustment on potential confounders (BMI, health care professional managing the patient, diastolic blood pressure, level of education and at least one microvascular diabetes) as well as region and age, higher scores in the ITSQ inconvenience domain were associated with better glycemic control (OR [95% CI]: 1.05 [1.01, 1.09, p=0.009] for an increase of 10 points in score).
- After adjustment on potential confounders (at least one severe hyperglycemia leading to diabetic ketoacidosis) as well as region and age, higher scores in the ITSQ glycemic control domain were associated with better glycemic control (OR [95% CI]: 1.20 [1.16, 1.25], p<0.001 for an increase of 10 points in score).
- After adjustment on potential confounders (diastolic blood pressure, total insulin daily dose (U/day), level of education, health insurance, insulin regimen and at least one severe hyperglycemia leading to diabetic ketoacidosis) as well as region and age, higher PAID score was associated with poorer glycemic control (OR [95% CI]: 0.94 [0.90, 0.98], p=0.003 for an increase of 10 points in score).

Additional details on the relationship between glycemic control and PROs scores considering potential confounders are provided in Appendix II – Table 2.1.25. 29.

- Technology usage endpoints

The most frequent technology used, according to this diabetes questionnaire, was a finger-stick blood glucose meter which, overall, was reported to be used by 92.0% of the eligible patients, with similar proportions in all the predefined age groups. Of them, 63.0% of the patients found the use of the finger-stick blood glucose meter extremely easy with higher proportions in the ≥26 - <45 years and the ≥45 - <65 years age groups (67.3% and 62.4%, respectively) than in the elderly age group (52.4%).

Continuous glucose meter usage was reported to be used by 23.2% of the eligible patients and of them 73.2% found its use to be extremely easy, with comparable proportions in all predefined age groups.

Higher rates in the use of insulin pump were observed in the ≥26 - <45 years and the ≥45 - <65 years age groups (23.4% and 18.7%, respectively) than in the elderly age group (10.9%). The proportion of patients who found the use of insulin pump extremely easy was higher (61.0%) in the ≥26 - <45 years group compared to patients in the ≤45 - <65 years age and ≥65 years age groups (52.1% and 47.8%), respectively.

Similar proportions were observed in the ≥26 - <45 years and the ≥45 - <65 years age groups in the use of blood ketone meter (11.9% and 11.8%, respectively) with regards to the elderly group (7.2%) and in the proportion of patients who found its use extremely easy (67.3% and 62.4% versus 44.4%, respectively).

The use of applications was low in all predefined age groups although higher proportions in their usage were observed in the youngest age group.

The technology use in diabetes questionnaire is summarized in Table 20. Additional details are provided in Appendix II – Tables 2.1.26.1 to 2.1.26.11.

Table 20: Technology use in diabetes questionnaire – Eligible population

	26<=Age<45 (N=1724)	45<=Age<65 (N=1512)	Age>=65 (N=622)	All (N=3858)
Use of finger-stick blood glucose meter				
Number	1724	1512	622	3858
Yes	1581 (91.7%)	1393 (92.1%)	574 (92.3%)	3548 (92.0%)
Difficulty to use [a]				
Number	1580	1393	574	3547
Extremely easy	1064 (67.3%)	869 (62.4%)	301 (52.4%)	2234 (63.0%)
Use of continuous glucose meter				
Number	1724	1512	622	3858
Yes	421 (24.4%)	348 (23.0%)	125 (20.1%)	894 (23.2%)
Difficulty to use [a]				
Number	421	348	123	892
Extremely easy	315 (74.8%)	246 (70.7%)	92 (74.8%)	653 (73.2%)
Use of insulin pump				
Number	1724	1512	622	3858
Yes	403 (23.4%)	282 (18.7%)	68 (10.9%)	753 (19.5%)
Difficulty to use [a]				
Number	403	282	67	752
Extremely easy	246 (61.0%)	147 (52.1%)	32 (47.8%)	425 (56.5%)
Use of blood ketone meter				
Number	1724	1512	622	3858
Yes	205 (11.9%)	178 (11.8%)	45 (7.2%)	428 (11.1%)
Difficulty to use [a]				
Number	205	178	45	428
Extremely easy	138 (67.3%)	111 (62.4%)	20 (44.4%)	269 (62.9%)
Use of applications to help the patient monitor their diet or count their carbohydrate consumption				
Number	1724	1512	622	3858
Yes	247 (14.3%)	155 (10.3%)	34 (5.5%)	436 (11.3%)
Use of applications to help the patient monitor or improve their exercise level				
Number	1724	1512	622	3858
Yes	173 (10.0%)	103 (6.8%)	20 (3.2%)	296 (7.7%)

	Use of applications to help the patient remember to take their diabetes medication Number 1724 1512 622 3858 Yes 88 (5.1%) 58 (3.8%) 17 (2.7%) 163 (4.2%) **Use of applications to help the patient adjust their diabetes medication correctly** Number 1724 1512 622 3858 Yes 95 (5.5%) 59 (3.9%) 22 (3.5%) 176 (4.6%) **Use of applications to help the patient manage their weight** Number 1724 1512 622 3858 Yes 93 (5.4%) 69 (4.6%) 18 (2.9%) 180 (4.7%) **Use of applications to store personal health information** Number 1724 1512 622 3858 Yes 108 (6.3%) 81 (5.4%) 20 (3.2%) 209 (5.4%) **Use of applications to store health insurance information** Number 1724 1512 622 3858 Yes 67 (3.9%) 58 (3.8%) 18 (2.9%) 143 (3.7%) Source data: Appendix II – Tables 2.1.26.1 to 2.1.26.11
Discussions:	**(a) Key results** The SAGE study included 3858 eligible patients from 17 countries worldwide: 44.7% of the patients in the ≥26 - <45 years age group, 39.2% of the patients in the ≥45 - <65 years age group and 16.1% of the patients in the ≥65 years age group. More than half (53.9%) of the physicians practiced in public centers. **Patients' characteristics** The eligible patients included a good balance between males (45.4%) and females (54.6%), with a higher percentage of females in the ≥26 - <45 years age group (58.1%). Mean (SD) BMI was 25.15 (4.48) Kg/m^2, with comparable results in the predefined age groups. A total of 509 (13.2%) had an abnormal BMI (≥30 Kg/m^2), with a lower percentage (9.8%) in the ≥26 - <45 years age group than in the ≥45 - <65 years age group (15.4%) and the ≥65 years age group (17.2%). Mean (SD) duration of diabetes was 20.73 (12.63) years. The number of patients who had a duration of the diabetes ≥10 years was 3002 (77.8% of the eligible population). **Primary objective** The primary endpoint was to describe the percentage of patients who achieved the general HbA1c target <7% (glycemic control). Overall, this target was achieved by the 24.3% of the eligible population. By predefined age groups a higher percentage (27.6%) was observed for the patients between 26 and 45 years old group, when compared with the ≥45 - <65 years and the ≥65 years age groups (21.0% and 22.8%, respectively). This low percentage in achievement was comparable with results from other studies (6), (7), (8). **Secondary objectives** Individualized HbA1c achievement Individual targets below 7.5% were set by physicians in most of the patients (83.4%). The proportion of patients who achieved the individualized HbA1c target was 20.9%. Lower rate was reported for patients in the ≥45 - <65 years (17.8%) and the highest rate was achieved by patients in the elderly group (26.2%). The reason why globally the rate of patients achieving their individualized target is lower than the proportion of patients achieving the general target is due to the fact that a more stringent target (<6.5%) than the general one was defined by the physician for some patients in the 2 younger subgroups and this target was not achieved by them. Logically, in the oldest group, the individual target was higher than 7% for some patients and so the rate of patients achieving it was higher than the proportion of patients achieving the general one. Laboratory tests

	Similar results were observed among the predefined age groups for the FPG and the PPG. Hypoglycemia Symptomatic hypoglycemia within the previous 3 months was reported in 2893 (75.8%) patients (higher rates in the ≥26 - <45 years age group (78.3%). Documented symptomatic hypoglycemia (blood glucose ≤70 mg/dL and <54 mg/dL) episodes were reported in 2576 (67.7%) and 1903 (49.9%) patients, respectively (also higher rates in the ≥26 - <45 years age group [69.6% and 51.8%, respectively]). Severe hypoglycemia within the previous 6 months was reported in 460 (11.9%) patients, with comparable results in the predefined age groups. Hyperglycemia Severe hyperglycemia leading to diabetic ketoacidosis in the previous 6 months was reported in 162 (4.2%) patients (lower rates in the elderly group (2.9%), with patients not taking insulin (23.5%) as the most frequent predisposing factor leading to diabetic ketoacidosis, followed by infection (21.6%). Other diabetic complications and comorbidities Among the most frequent reported complications were: diabetic retinopathy (33.2%) and diabetic neuropathy (32.5%). Renal function impairment due to diabetes was reported in 15.9% of the patients. The proportion of patients who reported at least one microvascular diabetes complication was 46.7% and the proportion of patients who reported at least one macrovascular comorbidity was 14.3%. The most frequent comorbidities reported were: hypertension (28.7%) and dyslipidemia (26.5%). Therapeutic management The majority of the eligible patients (79.9%) used injection/pens as insulin device (with higher proportions in the elderly group [88.9%]). Median total insulin daily dose was 46 U/day (0.66 U/Kg/day) with similar results among the predefined age groups. Basal plus short acting insulin (68.9%) was the most frequent insulin regimen reported (higher rates also in the elderly group [74.1%]). Basal insulin dose was adjusted less than every week in more than half of the patients. The proportion of patients who used pump was 19.9%. The proportion of patients who reported to have concomitantly taken at least one glucose lowering drug other than insulin was 11.1%. By predefined age groups, these proportions were 8.3% in the ≥26 - <45 years age group, 12.9% in the ≥45 - <65 years age group and 14.6% in the ≥65 years age group. The most frequent glucose lowering drug used was metformin which was reported in 9.3% of patients (6.9% in the ≥26 - <45 years age group, 10.9% in the ≥45 - <65 years age group and 11.7% in the ≥65 years age group). Overall a total of 985 (25.5%) patients reported having taken at least one non-antidiabetic concomitant medication impacting the glycaemia (higher percentages were observed in the ≥65 years age group [48.7%] and in the ≥45 - <65 years age group [30.0%] than in the ≥26 - <45 years age group [13.2%]). The most frequently reported were beta blockers (9.8%) and diuretics (8.0%). Structure and process of medical care More than half (58.3%) of the patients were treated in a hospital setting. Quality of life Overall, according to PRO questionnaires, patients showed low emotional distress due to diabetes and worry of hypoglycemia, moderate to high treatment satisfaction and small negative impact on quality of life related to diabetes.

	Similar results were observed among all the predefined age groups in the HFS-II worry domain and in the ADDQoL. Higher percentages of satisfaction in the ITSQ overall summary score and the 5 domain scores were observed in the elderly group. A lower emotional distress due to diabetes according to the PAID questionnaire was also observed in the elderly group. <u>Relationship between the glycemic control and each group of factors</u> Regarding general HbA1c target the following relationships were observed: • The multivariate analyses adjusted for regions showed that the socio-demographic factors associated with better glycemic control were a younger age, lower BMI, lower diastolic blood pressure, higher level of education, driver rather than no driver and compliance with diet. • The multivariate analyses (analyses adjusted for regions and age group) showed that regarding diabetes history, complications and comorbidities factors, longer time since diagnosis (more than 10 years), severe hyperglycemia leading to ketoacidosis within the last 6 months, microvascular diabetes complications and dyslipidemia were associated with poorer glycemic control. On the other hand, having at least one symptomatic hypoglycemia <54 mg/dL within the last 3 months was associated with better glycemic control • The multivariate analyses adjusted for regions and age group showed that regarding treatment, a lower total daily dose of insulin is associated with a better glycemic control. Taking at least one glucose lowering drug is associated with poorer glycemic control. • The multivariate analyses (analyses adjusted for regions and age group) showed that regarding structure and process of medical care, being managed by other HCP than diabetologist/endocrinologist as well as having no health insurance was associated with poorer glycemic control. Regarding individualized HbA1c target the following relationships were observed: • The multivariate analyses adjusted for regions showed that socio-demographic factors associated with better glycemic control were an older age, lower BMI, lower diastolic blood pressure and higher level of education. • The multivariate analyses adjusted for regions and age group showed that regarding complications and comorbidities factors, having at least one symptomatic hypoglycemia <54 mg/dL within the 3 last months is associated with better glycemic control. On the other hand, having at least one severe hyperglycemia leading to ketoacidosis within the last 6 months is associated with poorer glycemic control, as well as having microvascular diabetes complications or dyslipidemia. • The multivariate analyses adjusted for regions and age group showed that regarding treatment, the use of a pump compared to the use of premix (alone or in addition to other insulin) and to the use of basal alone or short acting alone insulin is associated with a better glycemic control as well as a lower total daily dose of insulin. • The multivariate analyses adjusted for regions and age group showed that regarding structure and process of medical care, being managed by other HCP than diabetologist/endocrinologist was associated with poorer glycemic control and having health insurance is associated with a better glycemic control.

	Relationship between glycemic control and PROs Regarding general HbA1c target the following relationships were observed: • The multivariate analyses (analyses adjusted for regions and age group) showed that regarding PROs, higher worry of hypoglycemia (higher HFS-II worry score) and emotional distress (higher PAID score) were associated with a poorer glycemic control, whereas higher treatment satisfaction (higher ITSQ scores) and smaller impact of diabetes on quality of life (higher ADDQoL scores) were associated with a better glycemic control. Regarding individualized HbA1c target the following relationships were observed: • The multivariate analyses (Analyses adjusted for regions and age group) showed that regarding PROs, higher emotional distress (higher PAID score) was associated with a poorer glycemic control, whereas higher treatment satisfaction (higher ITSQ scores) was associated with a better glycemic control. No association was found between glycemic control (based on individualized target) and other PROs (i.e HFS II or ADDQOL) Technology usage The most frequent technology used was finger-stick blood glucose meter with comparable proportions in all the predefined age groups. More than half (63.0%) of the patients found the use of this technology extremely easy (lower proportions in the elderly group [52.3%]). Continuous glucose meter usage was reported to be used by 23.2% of the eligible patients and of them 73.2% found its use to be extremely easy, with comparable proportions in all predefined age groups. (b) Interpretation The results of this SAGE study are in line with the previous results of other studies conducted separately in the predefined age groups (6), (7) and (8). Overall, the percentage of patients achieving the general HbA1c target <7% (glycemic control) was 24.3% with higher rates in the group of 26-45 years old (27.6%) than in the group of patients between 45 and 65 years old (21.0%) and in the group of patients older than 65 years old (21.0%). There were more variability in younger patients and this may explain why there were more patients with HbA1c <7% in the 26-45 years age group. Regarding individualized HbA1c target which was achieved by 20.9% of the patients, higher rates were observed in the achievement of glycemic control for the elderly age group (26.2%) whose HbA1c target was higher. The reason for this achievement in the elderly group could probably be that the individualized target is less stringent for elderly patients. Relationships between glycemic control and groups of factors (socio-demographics [such as age, BMI, diastolic blood pressure, level of education, driver patients and compliance with diet], patient's diabetes history and complications [such as time since diagnosis, at least one symptomatic hypoglycemia <54 mg/dL], microvascular diabetes complications, dyslipidemia), treatment for T1DM [such as lower insulin daily doses] and structure and process of medical care [being managed by HCP and health insurance]) were observed in this SAGE study that could be of interest for future research. Relationships between glycemic control and PROs were also observed. Higher treatment satisfaction (higher ITSQ scores) was associated with better glycemic control and higher emotional distress (higher PAID score) was associated with poorer glycemic control. The study had some limitations: the SAGE study did not include patients from North America or Africa and may therefore not be fully representative of the global

	population of patients with T1DM, and the cross-sectional design of the study (this study design cannot be used to analyze behavior over a period of time and does not help determine causality). (c) Generalizability The SAGE study has compiled a large experience in the current clinical practice on the management of T1DM from 17 participating countries worldwide, even if North America or Africa are not included. It was expected that the data collected would represent a realistic characterization of clinical outcome measures related to the objectives assessed by the physicians in routine clinical practice. In addition, the study showed limited missing data (usual source of questioned results validity).
Conclusions:	SAGE is a global observational study including a large sample of patients across worldwide countries with a good representation. It confirmed that in real life settings, glycemic control remains sub optimal in T1DM adult patients, with low rates in the achievement of HbA1c targets. The study showed that a better glycemic control achieved was associated with factors such as younger age (only when the glycemic control is based on general target HbA1c <7%, since if the glycemic control is based on individualized HbA1c target, older age is the factor related to a better glycemic control) lower BMI, higher level of educational and having at least one symptomatic hypoglycemia <54 mg/dL within the past 6 months and, on the other hand, having at least one severe hyperglycemia leading to ketoacidosis within the last 6 months, microvascular diabetes complications and dyslipidemia were associated with poorer glycemic control (based on general target). Regarding PROs, higher treatment satisfaction was associated with better glycemic control and higher emotional distress due to diabetes was associated with poorer glycemic control.
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