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A sub-analysis of the SAGE study in Italy indicates good glycemic control in type 1 diabetes

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Abstract *Background and aims:* Intensive glycemic control minimizes the risk of micro- and macrovascular complications in patients with type 1 diabetes (T1D). We report glycemic control in Italian participants (age groups: 26–44, 45–64, and ≥65 years) of the global SAGE study.
Methods and results: The primary endpoint was proportion of participants who achieved an HbA_{1c} <7% in predefined age groups. In the 523 patients with T1D, mean age was 44.6 years and mean body mass index (BMI) was 25 kg/m^2. Mean HbA_{1c} was 7.5% and 29.4% had HbA_{1c} <7.0%, with the highest percentage in those 26–45 years (31.7%) and the lowest in those ≥65 years (20%). Altogether, 22.9% of patients achieved their physician-established individualized HbA_{1c} target. Most patients had ≥1 symptomatic hypoglycemic episode in the previous 3 months (≤70 mg/dL 82.5%; ≤54 mg/dL 61%). Severe hypo- and hyperglycemia were experienced by 16.3% and 12% of patients, of which 7.1 and 9.5%, respectively, required hospitalization/emergency visits. More patients achieved HbA_{1c} <7% with CSII (30%) than with multiple daily insulin injections (27.9%). In multivariate analysis, BMI (OR 0.94, 95% CI 0.89–0.99, p = 0.032) and adherence to diet (OR 0.36, 95% CI 0.18–0.70, p = 0.0028) were significantly associated with HbA_{1c} <7.0%.
Conclusions: Glycemic control can be considered good in the Italian SAGE cohort, especially in younger patients, who more frequently use pumps/continuous glucose monitoring. Greater patient education and use of technology may further support this achievement. Patients should be encouraged to maintain a low BMI and adhere to their diet.

1. Introduction

The achievement of intensive glycemic control is crucial to minimize the risk of micro- and macro-vascular complications in patients with type 1 diabetes (T1D), as demonstrated in the DCCT/EDIC trials (Diabetes Control and Complications trial/Epidemiology of Diabetes Intervention and Complications trial) [1,2]. Specifically, intensive treatment reduced the risk for development of retinopathy by 76%, albuminuria by 54%, neuropathy by 60%, and cardiovascular diseases by 32%. Moreover, in addition to delaying the onset and slowing the progression of disease-related complications, intensive therapy also reduces the costs of diabetes care compared to

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conventional glucose-lowering therapy [3]. As further evidence, in a recent study using 30 years of data from DCCT, excellent glycemic control substantially decreased the rates of complications such as retinopathy requiring laser surgery, comorbidities such as end-stage renal disease, stroke, and neuropathy, as well as death, while overall improving the quality of life [4].

If the benefits of good glycemic control have been apparent for decades, it remains suboptimal worldwide. The last US data from the T1D Exchange Clinic Registry on over 25,000 patients with T1D indicates that the mean HbA_{1c} is around 7.5%–7.9% beyond age 30, and only 21% of adults achieve a target goal of <7.0% [5]. The real-life Study of Adults' GlycEmia in T1DM (SAGE) investigation collected data from January to December 2018 on 3903 participants globally, analyzing glycemic control, hypoglycemia, and diabetes management in T1D [6]. In the entire study population, glycemic control was worrying, with only 24% of participants achieving an HbA_{1c} target <7.0%. The lowest value was recorded in the Middle East and the highest in Eastern and Western Europe. However, the incidence of hypoglycemia and hyperglycemia varied across regions, with both significantly impacting the costs of care. Fear of insulin-related hypoglycemia and unawareness of hypoglycemia represent barriers to adequate treatment for prescribers and patients [7,8]. According to the Italian Annals of AMD (Associazione Medici Diabetologi) database report, based on a total of 34,705 patients with T1D visited during 2018 in 258 centers for diabetes care, the mean level of HbA_{1c} was 7.7% (±1.3), and 30.2% had an $HbA_{1c} \leq 7\%$ [9]. We carried out the present analysis with the aim to evaluate sociodemographics, glycemic control, therapy, and comorbidities, in addition to psychosocial aspects related to the disease in adults with T1DM of different ages of Italian participants of the global SAGE study.

2. Methods

2.1. Study design and participants

The current research is a sub-analysis of the Italian cohort participating in the large, observational, global SAGE study designed to evaluate the glycemic control in adults with T1D in Western and Eastern Europe, Middle East, and Latin America [6]. Full details of the global protocol and analyses have been previously published [6]. Briefly, the study involved endocrinologists, general practitioners, and other physicians routinely managing patients with T1D. Physicians were selected independently and randomly from pre-established specific lists of sites. Inclusion criteria included age ≥26 years with T1D for ≥1 year, insulin treatment, and an HbA_{1c} measurement within 30 days prior to the study visit or planned to be obtained within 7 days after the study visit. The main exclusion criteria were non-T1D, current, or previous (3 months) switch from continuous subcutaneous insulin infusion (CSII) to insulin injection regimen [6].

2.2. Data collection and endpoints

Investigators collected at a single study visit data from the participant's file and interview into an electronic case report form. The parameters of interest were age, sex, body mass index (BMI), class of BMI (normal weight: BMI < 25 kg/m^2; overweight: BMI 25–29 kg/m^2; and obesity: BMI ≥ 30 kg/m^2), disease duration, education level (primary, secondary, university/higher, other), employment status (non-worker, worker), habitation (urban, rural), health insurance (private, public), living (not-alone, alone), adherence (yes/no) to dietary advice (recommendation for carbohydrate intake, a balanced healthy diet with appropriate intake of fat and fiber and other special dietary advice) physical activity [no activity (0 days/week), limited activity (1–3 days/week); sufficient activity (≥4 days/week)], family history of T1D, insulin treatment [injection/pen, continuous subcutaneous insulin infusion (CSII)], total daily insulin dose, recommended insulin dose adjustment (patient-driven or physician driven) and frequency of dose adjustment, insulin injection regimen [MDI (multiple daily insulin injections), long acting or short acting insulin alone, premix + other), insulin type (first and second generation long acting insulin, short acting analog insulin, regular human insulin, premix insulin)] and use of technology (self-monitoring blood glucose, SMBG; continuous glucose monitoring, CGM; CSII), and ketone meters. HbA_{1c} assessment was performed locally in routine practice using the standard methodology at the laboratory of each site. The individualized HbA_{1c} target, as established by the physician, was also recorded. Fasting plasma glucose (FPG), defined as the last available laboratory plasma glucose or last self-monitored fasting blood glucose, was recorded during the investigation visit. No investigations for the purpose of the study were carried out. The study was performed according to local regulatory requirements, including Institutional Review Board and Independent Ethical Committee approval, and conducted in accordance with the Declaration of Helsinki [10]. Data were collected between January 2018 and December 2018.

The primary endpoint was the proportion of participants who achieved an HbA_{1c} <7% in predefined age groups (26–44 years; 45–64 years; ≥65 years). Main secondary clinical endpoints were HbA_{1c}, FPG, achievement of physician-established HbA_{1c} target, documented symptomatic hypoglycemic episodes with blood glucose ≤70 mg/dL [3.9 mmol/mol] or 54 mg/dL [3.0 mmol/mol] in the previous 3 months, severe hypoglycemia defined as an event requiring assistance of another person, and hyperglycemia defined as an event leading to diabetic ketoacidosis (DKA) in the previous 6 months. Other endpoints included self-reported severe hypoglycemia or severe hyperglycemia events leading to hospitalization/emergency in the previous 6 months. In the case of DKA, the predisposing factors, if available, were collected. At the study visit, the investigators also administered questionnaires to evaluate the fear of hypoglycemia (Hypoglycemia fear survey, HFS-II), emotional distress due to diabetes (Problem Areas in Diabetes questionnaire, PAID), and insulin

treatment satisfaction (insulin treatment satisfaction questionnaire, ITSQ).

2.3. Data analysis

All results are presented as mean ± standard deviation (SD), median with interquartile (IQR) range for continuous variables, or frequencies and percentages for categorical variables. The results presented are for participants with data available for each parameter. No imputation for missing data was done, and the variables were analyzed as recorded in the database. Due to the descriptive nature of this study, no inferential test was applied, and p-values were not calculated. All analyses were performed overall and by each group of interest (age classes: 26–45, 45–65, >65 years; insulin dose adjustment approach: patient-driven, physician-driven, CSII, MDI). Univariate logistic regression models were run to estimate the association between patient characteristics (sex, age, BMI, level of education, employment status, adherence to diet, physical activity, and type of technology) and achievement of glycemic control (HbA_{1c} < 7% and physician-established individualized target). In univariate analysis, age and BMI were considered continuous variables. All the variables included in univariate analyses were also considered in a multivariate logistic approach to adjust for possible confounding factors. The results are expressed as odds ratio (OR) with relative 95% confidence intervals (95% CI). All analyses were run with SAS version 9.4.

3. Results

3.1. Patient characteristics

The Italian cohort of SAGE involved 523 patients with T1D distributed in 26 centers, of which 25 were located in public hospitals. The centers and the number of patients were distributed evenly throughout the country [9 in the north (n = 189), 10 in the center (n = 196), and 7 in the south (n = 138)]. Moreover, 20 of the 26 participating centers were specialized in endocrinology or diabetology, and the remaining in internal medicine or another specialty.

Patient characteristics are reported in Table 1. The mean age in the entire cohort was 44.6 years and the mean BMI was 25 kg/m^2. In the entire population, 57.0% had a BMI <25 kg/m^2, while the remainder were overweight (33.3%) and obese (9.8%). The mean duration of diabetes was 21.2 years. About one-fifth of patients had a family history of T1D. Regardless of age group, most participants lived in urban areas (87.8%) and with other adults (90.2%).

Overall, most participants (83%) agreed to dietary advice. Only 24.7% of participants reported sufficient physical activity, with the highest proportion in patients aged ≥45 years.

3.2. HbA_{1c}, hypoglycemia, and hyperglycemia

Overall, the mean HbA_{1c} was 7.5%, with slight differences among the three age groups (Table 2). The proportion of patients achieving HbA_{1c} <7.0% was 29.4%, with the highest percentage in the 26–45 year age category (31.7%) and the lowest in those over 65 years (20%). The physician-established individualized target for HbA_{1c} was achieved in 22.9% of patients. Small differences among age groups were seen (Table 2). Fewer than half of the participants (40.7%) had an individualized target between 6.5 and 7%, and 11.1% had a target of <6.5%.

Most patients had experienced at least one symptomatic hypoglycemic episode in the previous 3 months (≤70 mg/dL 82.5%; ≤54 mg/dL 61%). The proportion was the lowest in patients ≥65 years (73.3%) and the highest in the 26–45 age group (84.3%). The proportion of patients with severe hypo- and hyperglycemia in the previous 6 months was 16.3% and 12%, respectively, with higher rates in the younger age categories. The mean number of severe hypoglycemic events per patient in the previous 6 months was 1 ± 3.9 (Table 2).

Finally, the proportion of patients admitted to the hospital or visited at the emergency room for severe hypoglycemia and DKA was 7.1% and 9.5%, respectively. Most patients with severe hypoglycemia were in the 45–64 year age range, while those with DKA were in the 26–45 year age range. Among patients with DKA, omission of insulin and pump malfunction were the predisposing factors in 27.0% and 25.4% of cases, respectively (Table 2).

3.3. Insulin regimens and technology used

In all, 55.4% of the patients enrolled in the study were injections/pen users, with the highest prevalence in the ≥65 year age group (Table 3). Half of the patients were on MDI, while a very small number were on a basal or short-acting insulin alone or premix insulin regimen. A second-generation long-acting insulin analog was used in 40.5% of patients and a short-acting insulin analog in 53.0% (Table 3). These percentages were even higher among patients using injection or pen (n = 290): second-generation long-acting, 73.1%; short-acting 95.5%.

The mean daily insulin dose per kg of body weight was comparable across age groups. Slightly more than half of the patients were using patient-driven insulin dose adjustment (57%), with no substantial differences among age groups. The frequency of basal and short-acting insulin dose adjustment was similar across age groups. In most cases, this was every week or <1 month for basal insulin instead of less than twice a week for short-acting insulin.

Regarding the use of technology, 44.6% of patients were using CSII and 42.3% were using CGM, with substantially increased rates of adopting booth technologies in the 26–45 age and 45–65 groups compared to older patients. Most patients in the CSII group used CGM (60.6%) versus 29.1% of patients in the MDI group (data not shown). The prevalence of patients with T1D using SMBG, alone or in combination with the sensor, was 95%.

3.4. Endpoints by use of technology and type of titration

More patients achieved an HbA_{1c} <7% (30%) in the CSII group than with MDI (27.9%), and the mean HbA_{1c} was

Table 1 Participant characteristics by age group.

Parameter[a]	All ages	Age group, years		
		≥26 to <45	≥45 to <65	≥65
	N = 523	N = 281	N = 197	N = 45
Proportion of total population, %	100	53.7	37.7	8.6
Age, years, mean ± SD	44.6 ± 12.9	34.5 ± 5.4	53.2 ± 5.5	69.9 ± 4.3
Sex, female, n (%)	253 (48.4)	144 (51.2)	88 (44.7)	21 (46.7)
Body mass index, kg/m^2, mean ± SD	25.0 ± 4.1	24.5 ± 3.7	25.6 ± 4.5	25.8 ± 4.3
Body mass index, n (%)				
<25 kg/m^2	298 (57.0)	173 (61.6)	101 (51.3)	24 (53.3)
25–30 kg/m^2	174 (33.3)	90 (32.0)	69 (35.0)	15 (33.3)
≥30 kg/m^2	51 (9.8)	18 (6.4)	27 (13.7)	6 (13.3)
Duration of diabetes, years, mean ± sd	21.2 ± 12.1	17.4 ± 8.8	24.8 ± 12.4	28.9 ± 18.4
Duration of diabetes, n (%)				
<10 years, n (%)	97 (18.5)	63 (22.4)	24 (12.2)	10 (22.2)
≥10 years, n (%)	426 (81.5)	218 (77.6)	173 (87.8)	35 (77.8)
Education level, n (%)				
Primary	70 (13.4)	23 (8.2)	39 (19.8)	8 (17.8)
Secondary	283 (54.1)	156 (55.5)	107 (54.3)	20 (44.4)
University/higher	144 (27.5)	90 (32.0)	40 (20.3)	14 (31.1)
Other	26 (5.0)	12 (4.3)	11 (5.6)	3 (6.7)
Employment status, n (%)				
Non-worker	149 (28.5)	56 (19.9)	56 (28.4)	37 (82.2)
Worker	374 (71.5)	225 (80.1)	141 (71.6)	8 (17.8)
Habitation, n (%)				
Urban	459 (87.8)	247 (87.9)	171 (86.8)	41 (91.1)
Rural	64 (12.2)	34 (12.1)	26 (13.2)	4 (8.9)
Health insurance, n (%)				
Private	11 (2.9)	8 (4.1)	3 (2.0)	0 (0.0)
Public	369 (97.1)	185 (95.9)	150 (98.0)	34 (100.0)
Living, n (%)				
Not alone	472 (90.2)	251 (89.3)	182 (92.4)	39 (86.7)
Alone	51 (9.8)	30 (10.7)	15 (7.6)	6 (13.3)
Adherence to diet, n (%)	434 (83.0)	228 (81.1)	168 (85.3)	38 (84.4)
Physical activity, n (%)				
None (0 days/week)	161 (30.8)	98 (34.9)	52 (26.4)	11 (24.4)
Limited (1–3 days/week)	233 (44.6)	124 (44.1)	89 (45.2)	20 (44.4)
Sufficient (≥4 days/week)	129 (24.7)	59 (21.0)	56 (28.4)	14 (31.1)
Family history of T1DM, n (%)	115 (22.6)	60 (21.9)	44 (23.0)	11 (25.6)

SD, standard deviation; T1DM1, type 1 diabetes.
[a] The results presented are for participants with data available for each parameter.

slightly lower with CSII (7.4%) compared to MDI (7.6%) (Table S1). The proportion of patients with symptomatic hypoglycemic events ≤54 mg/dL in the previous 3 months was higher with CSII than MDI (69.9 vs. 55.8%) as well as with severe events in the previous 6 months (22.7 vs. 10.7%; Table S1). HbA_{1c} levels by type of titration are shown in Table 4. Slightly more participants using patient-driven titration of insulin had an HbA_{1c} <7.0% (32.2% vs. 25.8%). Mean HbA_{1c} was somewhat higher in those using physician-driven titration, as was mean FPG.

3.5. Patient-reported outcomes

Table 5 shows the patient-related outcomes (PROs) by age group. There were only very slight differences in HFS-II and PAID scores across age groups. The differences tended to be lower in older patients. Similarly, ITSQ scores tended to be higher in older patients, which corresponded to better treatment satisfaction.

3.6. Univariate analysis

In univariate analysis, only BMI, education, and adherence to diet were significantly correlated with HbA_{1c} <7.0% (Table S2). In particular, the higher the BMI, the lower the glycemic control, as did people with primary education, compared with those with higher education and those who did not adhere to their dietary plan. In univariate analysis, adherence to diet and sufficient physical activity were significantly associated with the individualized HbA_{1c} target (Table S3).

3.7. Multivariate analysis

All the variables included in Tables S2 and S3 were considered in multivariate analyses. Among these, only BMI (OR 0.94, 95% CI 0.89–0.99, p = 0.032) and adherence to diet (OR 0.36, 95% CI 0.18–0.70, p = 0.0028) were significantly associated with HbA_{1c} <7.0%. In multivariate

Table 2 Endpoints by age group.

Parameter[c]	All ages	Age groups, years		
		≥26 to <45	≥45 to <65	≥65
	N = 523	N = 281	N = 197	N = 45
HbA_{1c}				
HbA_{1c} <7%, n (%)	154 (29.4)	89 (31.7)	56 (28.4)	9 (20.0)
Mean ± SD HbA_{1c} (%)	7.5 ± 1.1	7.5 ± 1.1	7.6 ± 1.1	7.7 ± 1.1
Mean ± SD HbA_{1c} mmol/mol	58.7 ± 11.8	58.1 ± 11.8	59.2 ± 11.7	60.7 ± 12.1
Individualized HbA_{1c} target value, n (%)				
<6.5% (<47.5 mmol/mol)	58 (11.1)	32 (11.4)	24 (12.2)	2 (4.4)
6.5–7.0% (47.5–53.0 mmol/mol)	213 (40.7)	121 (43.1)	80 (40.6)	12 (26.7)
7.0–7.5% (53.0–58.5 mmol/mol)	211 (40.3)	114 (40.6)	79 (40.1)	18 (40.0)
7.5–8% (58.5–63.9 mmol/mol)	33 (6.3)	12 (4.3)	12 (6.1)	9 (20.0)
8.0–9% (63.9–74.9 mmol/mol)	8 (1.5)	2 (0.7)	2 (1.0)	4 (8.9)
≥9% (≥74.9 mmol/mol)	–	–	–	–
Achieved individualized HbA_{1c} target, n (%)	120 (22.9)	65 (23.1)	44 (22.3)	11 (24.4)
FPG				
Mean ± SD FPG (mmol/L)	8.0 ± 3.3	8.1 ± 3.2	7.9 ± 3.4	8.5 ± 3.5
Mean ± SD FPG (mg/dL)	144.9 ± 59.8	145.0 ± 58.1	142.5 ± 61.3	153.5 ± 63.1
Hypoglycemia and hyperglycemia				
≥1 symptomatic hypoglycemia with BG ≤ 3.9 mmol/L (≤70 mg/dL) in the previous 3 months, n (%)	430 (82.5)	236 (84.3)	161 (82.1)	33 (73.3)
≥1 symptomatic hypoglycemia with BG < 3.0 mmol/L (<54 mg/dL) in the previous 3 months, n (%)	318 (61.0)	178 (63.3)	114 (58.5)	26 (57.8)
Severe hypoglycemia in the previous 6 months, n (%)	85 (16.3)	48 (17.1)	33 (16.8)	4 (8.9)
Mean ± SD number of events/participant	1.0 ± 3.9	1.1 ± 4.2	1.0 ± 3.8	0.1 ± 0.5
Median (min, max)	0.0 (0.0–36.0)	0.0 (0.0–36.0)	0.0 (0.0–30.0)	0.0 (0.0–2.0)
≥1 hospitalization/emergency visit linked to severe hypoglycemia in the previous 6 months, n (%)[a]	6 (7.1)	2 (4.2)	4 (12.1)	0 (0.0)
Severe hyperglycemia in the previous 6 months, n (%)	63 (12.0)	32 (11.4)	28 (14.2)	3 (6.7)
Events/participant, median (min, max)	0.0 (0.0–23.0)	0.0 (0.0–23.0)	0.0 (0.0–10.0)	0.0 (0.0–3.0)
≥1 hospitalization/emergency visit within 6 months linked to severe hyperglycemia leading to DKA, n (%)[b]	6 (9.5)	5 (15.6)	1 (3.6)	0 (0.0)
If ketoacidosis, predisposing factors, n (%)				
Poisoning	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ketogenic diet	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	6 (9.5)	5 (15.6)	1 (3.6)	0 (0.0)
Has not taken insulin	17 (27.0)	8 (25.0)	8 (28.6)	1 (33.3)
Pump malfunctioning	16 (25.4)	9 (28.1)	6 (21.4)	1 (33.3)

SD, standard deviation; FPG, fasting plasma glucose; DKA, diabetic ketoacidosis.
[a] Calculated on total number of patients with severe hypoglycaemia in the previous 6 months.
[b] Calculated on total number of patients with severe hyperglycaemia in the previous 6 months.
[c] Presented results are for participants with data available for each given parameter.

analysis, the individualized HbA_{1c} target was significantly associated only with adherence to diet (OR 0.41, 95% CI 0.20–0.87, p = 0.0199).

4. Discussion

The present sub-analysis of the Italian cohort of the global SAGE study allows for several insights into the glycemic control of patients with T1D in Italy. Participants were equally distributed among the north, middle, and south of Italy, while there was a definite predominance of care in public hospitals. The first finding is that the glycemic control, defined as the percentage of patients with HbA_{1c} <7%, in the Italian cohort (29.4%) is substantially higher than that observed in the global SAGE population (24.3%) [6]. It is also slightly higher than the mean proportion of patients achieving glycemic control in Western Europe (27%). The difference between the Italian cohort and the overall global SAGE cohort also persists comparing patients according to age. As in the SAGE study, a higher proportion of younger patients achieved glycemic control compared to older patients [6]. The prevalence of patients with $HbA_{1c} \leq 7\%$ in our analysis is comparable to that reported in the Italian Annals of AMD published in 2020 and 2021 (≈30%, from two cohorts over 30,000 patients with T1D), thus suggesting that the overall results from the Italian cohort of SAGE might be related to the population of patients with T1D in Italy [9].

The second finding is that the physician-established HbA_{1c} target of <6.5% and 6.5–7% was defined in a higher percentage of patients in the Italian cohort (11% and 41%) compared to the global SAGE cohort (4% and 23%) and the Western Europe cohort (6.7% and 32.5%). The finding is mainly driven by patients less than 65 years old. However, this is not surprising because it is likely that the individualized target range is higher in older patients. Regarding

Table 3 Type of insulin regimens and device used.

Parameter[a]	All ages	Age groups, years		
		≥26 to <45	≥45 to <65	≥65
	N = 523	N = 281	N = 197	N = 45
Insulin treatment				
Device, n (%)				
Injections/pens	290 (55.4)	141 (50.2)	114 (57.9)	35 (77.8)
CSII	233 (44.6)	140 (49.8)	83 (42.1)	10 (22.2)
Insulin regimen, n (%)				
Basal + short acting insulin (MDI)	262 (50.1)	120 (42.7)	108 (54.8)	34 (75.6)
CSII	233 (44.6)	140 (49.8)	83 (42.1)	10 (22.2)
Basal alone	9 (1.7)	8 (2.8)	0 (0.0)	1 (2.2)
Premix + other	3 (0.6)	3 (1.1)	0 (0.0)	0 (0.0)
Short acting insulin alone	16 (3.1)	10 (3.6)	6 (3.0)	0 (0.0)
Insulin type, n (%)				
Basal[b]	274 (52.4)	131 (46.6)	108 (54.8)	35 (77.8)
Long-acting analogs	274 (52.4)	131 (46.6)	108 (54.8)	35 (77.8)
1st generation	62 (11.9)	29 (10.3)	29 (14.7)	4 (8.9)
2nd generation	212 (40.5)	102 (36.3)	79 (40.1)	31 (68.9)
Short acting insulin[b]	281 (53.7)	133 (47.3)	114 (57.9)	34 (75.6)
Short acting analogs	277 (53.0)	132 (47.0)	111 (56.3)	34 (75.6)
Regular human insulin	4 (0.8)	1 (0.4)	3 (1.5)	0 (0.0)
Mean ± SD total insulin daily dose				
U/kg/day	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
U/day	42.7 ± 19.3	42.6 ± 18.1	43.1 ± 20.4	41.1 ± 21.2
Recommended insulin dose adjustment approach, n (%)				
Patient-driven	298 (57.0)	164 (58.4)	108 (54.8)	26 (57.8)
Physician-driven	225 (43.0)	117 (41.6)	89 (45.2)	19 (42.2)
Basal insulin dose adjustment frequency, n (%)				
More than 1 week (1–6 days)	45 (22.2)	21 (21.9)	17 (22.1)	7 (23.3)
Every week	83 (40.9)	36 (37.5)	33 (42.9)	14 (46.7)
Less than every month	75 (36.9)	39 (40.6)	27 (35.1)	9 (30.0)
Short-acting insulin dose adjustment frequency, n (%)				
More than 1 week (1–6 days)	299 (67.6)	159 (66.8)	113 (67.7)	27 (73.0)
Every week	77 (17.4)	51 (21.4)	22 (13.2)	4 (10.8)
Less than every month	66 (14.9)	28 (11.8)	32 (19.2)	6 (16.2)
Technology use, n (%)				
SMBG	497 (95.0)	266 (94.7)	189 (95.9)	42 (93.3)
CGM	221 (42.3)	120 (42.7)	86 (43.7)	15 (33.3)
Pump	233 (44.6)	140 (49.8)	83 (42.1)	10 (22.2)
Ketone	63 (12.0)	38 (13.5)	24 (12.2)	1 (2.2)

SD, standard deviation.
[a] Presented results are for participants with data available for each given parameter.
[b] Alone or in combination.

these results, we can comment that a large proportion of patients were using second-generation long-acting insulin (40.5%) and CSII (44.6%) compared to the overall SAGE cohort. Indeed, in this latter cohort, only 25% used second-generation long-acting insulin, and 20% an insulin pump. The prevalence of CSII in the Italian cohort is higher than what is seen in real-life in Italy [9], especially in younger patients. Nonetheless, it is consistent with what was observed in the Western Europe participants of the SAGE cohort, wherein 42.3% used an insulin pump. Such a high proportion of patients on CSII can be explained by the fact that the Italian cohort primarily involved centers that are specialized in the treatment of T1D. Notwithstanding, it is clear that the use of second-generation long-acting insulins and insulin pumps for diabetes care is becoming increasingly common, at least in developed countries [11]. Moreover, new drugs and devices can benefit most patients with T1D and help them to achieve their treatment goals [12,13]. Indeed, as seen in the supplementary data, patients on CSII have a glycemic control that is numerically better than those on MDI (HbA_{1c} CSII 7.4%, MDI 7.6%), again confirming the data reported in the latest Italian Annals of AMD HbA_{1c} CSII 7.5%, MDI 7.8).

However, older patients who may not be familiar with new devices may be disfavored in this regard. Indeed, in the present analysis, fewer older patients were using CSII. We can also argue that more stringent targets are pursued and obtained in Italy even compared with Western countries. The goal is likely due to a more appropriate lifestyle, as attested by the lower percentage of obese subjects (Italy, 9.8%; overall SAGE, 13.2%; Western Europe, 14.6%).

The secondary endpoints of the study were the frequency of symptomatic and severe hypoglycemic episodes and the number of hospitalizations or visits to the emergency room due to severe hypoglycemia and hyperglycemia. The number of hypoglycemic episodes, symptomatic

Table 4 Endpoints by type of titration.

Parameter[a]	Type of titration	
	Patient-driven	Physician-driven
	N = 298	N = 225
HbA_{1c} <7%, n (%)	96 (32.2)	58 (25.8)
Mean ± SD HbA_{1c} (%)	7.5 ± 1.0	7.6 ± 1.1
Mean ± SD HbA_{1c} (mmol/mol)	58.0 ± 11.4	59.7 ± 12.2
Mean ± SD FPG (mmol/L)	7.9 ± 3.2	8.2 ± 3.4
Mean ± SD FPG (mg/dL)	143.1 ± 58.0	147.2 ± 62.1

SD, standard deviation; FPG, fasting plasma glucose.
[a] The results presented are for participants with data available for each parameter.

and severe, in the Italian cohort is higher than the overall SAGE population, which is in line with the better glycemic control observed. Indeed, the rate of symptomatic hypoglycemia (at least one event in the previous 3 months) was 84% in the Italian cohort in the 26–44 age group compared to 70% in the same global age group, with a higher percentage of those achieving HbA_{1c} <7% (32% vs 28%). The number of severe hypoglycemia episodes was also higher in the Italian cohort (16.3% vs 11.9%) compared to the overall global SAGE population, as well as the number of episodes per person during the previous 6 months, even if not clinically relevant (1 per person/6 months vs. 0.5). In particular, the proportion of patients with severe hypoglycemia was higher in CSII users vs. non-users (22.7 vs. 10.7%), the former with lower HbA_{1c}. It is possible that these patients had CSII with no automation and/or continuous glucose monitoring systems with no alarms.

Conversely, the proportion of severe hypoglycemic events requiring hospital intervention was very low in Italy with respect to global SAGE data (7.1% vs. 26.3%) and also slightly less than Western Europe (9%), suggesting a high level of patient education in managing hypoglycemia.

Despite the encouraging results we obtained from the sub-analyses, an important fraction of patients still do not reach their individualized target. Univariate and multivariate analyses identified low adherence to diet and BMI as factors contributing to the loss of good glycemic control, although the use of technology was not associated with achieving the glycemic target. This is an important result, suggesting that an appropriate diet to maintain or reach an adequate BMI should be advised and adherence verified during office visits. The study was not aimed to collect specific data about composition of the diet or eating habits. The question raised by the investigators during the study concerned the adherence to diet, lifestyle, and carbohydrates counting as proposed by the diabetes team care and following national guidelines [14]. The latest Italian guidelines, drawn up following GRADE methodology, report that a low glycemic index diet does not seem to be effective to achieve good glycemic control and body weight [15]. The increased prevalence of obesity and overweight among patients with type 1 diabetes is worrying. While a variety of diets have been proposed for type 2 diabetes, adequate research on type 1 diabetes is lacking [16]. However, despite this, comprehensive lifestyle intervention, including physical activity and a Mediterranean diet, represents the desired approach for T1D [17]. Therefore, there is still ample room for improvement that can be obtained by increasing strategies for self-management. The use of newer insulins such as second-generation long-acting insulins, CGM, or newer technologies such as automated insulin delivery systems may further help to achieve individual glycemic targets reducing hypoglycemia [12,18].

Finally, the data on PROs agrees with the global SAGE study [19], although Italian patients appear to have less

Table 5 PROS by age group.

Parameter[a]	All ages	Age groups, years		
		≥26 to <45	≥45 to <65	≥65
	N = 523	N = 281	N = 197	N = 45
HFS-II				
Total score, median [IQR]	32.0 (21.0–46.0)	31.0 (22.0–46.0)	33.0 (21.0–45.0)	29.5 (19.5–45.5)
Behavior subscale, median [IQR]	15.0 (10.0–21.0)	15.0 (10.0–21.0)	15.0 (11.0–21.0)	17.0 (10.0–21.0)
Worry subscale, median [IQR]	16.0 (9.0–27.0)	17.0 (9.0–27.0)	16.0 (9.0–26.0)	14.0 (8.0–21.0)
PAID total score, median [IQR]	26.3 (12.5–43.8)	26.3 (15.0–42.5)	28.8 (12.5–45.0)	17.5 (10.0–32.5)
ITSQ score				
Overall summary score, median [IQR]	71.0 (59.4–81.8)	70.2 (59.9–80.2)	70.4 (58.0–81.6)	82.0 (69.1–87.7)
Inconvenience, median [IQR]	80.0 (60.0–90.0)	76.7 (60.0–90.0)	76.7 (53.3–90.0)	90.0 (80.0–100.0)
Lifestyle, median [IQR]	66.7 (44.4–83.3)	66.7 (44.4–83.3)	66.7 (44.4–83.3)	83.3 (55.6–88.9)
Hypoglycemic control, median [IQR]	66.7 (53.3–80.0)	66.7 (53.3–80.0)	66.7 (53.3–80.0)	73.3 (60.0–85.0)
Glycemic control, median [IQR]	66.7 (50.0–83.3)	66.7 (50.0–77.8)	66.7 (50.0–83.3)	77.8 (66.7–88.9)
Delivery system, median [IQR]	86.1 (69.4–94.4)	84.7 (69.4–94.4)	83.3 (69.4–94.4)	91.7 (80.6–100.0)

IQR, interquartile range.
HFS-II: Higher total score reflects greater fear of hypoglycemia (RANGE [0; 132]). A higher score on Behavior subscale reflects a greater tendency to avoid hypoglycemia and/or its negatives consequences. (RANGE [0; 60]). A higher score on the Worry subscale indicates more worry concerning episodes of hypoglycemia and its consequences (RANGE [0; 72]). **PAID Total score:** Higher score corresponding to higher emotional distress due to diabetes (range [0–100]) **ITSQ score**: Higher scores indicate better treatment satisfaction (range [0–100]).
[a] The results presented are for participants with data available for each parameter.

fear of hypoglycemia, less diabetes distress, and greater treatment satisfaction. The questionnaire administered to patients did not reveal any difference among age groups regarding the fear of hypoglycemia and emotional distress. Conversely, older patients showed better treatment satisfaction than other age groups, possibly because a higher proportion reached their individualized HbA_{1c} target compared to different age groups.

Among the strengths of the study is its real-world nature, the large number of patients studied, and the homogeneous geographical distribution of participating centers. However, the study sites were all highly specialized and may not necessarily be representative of general diabetes care. The descriptive nature of the study and the lack of additional information about the kind of technologies used also limit more detailed interpretation of the hypoglycemic data.

In conclusion, the present sub-analysis of the SAGE study on the Italian cohort showed that glycemic control can be regarded as good, particularly in relatively young patients who more frequently use pumps/CGM. Thus, it is possible that greater patient education and the use of technology such as CGM can help support patients in achieving glycemic targets. Notwithstanding, overall, glycemic control is still suboptimal. Our analysis suggests that the greater use of technology and newer analogs may be, at least in part, related to the more favorable glycemic control in Italian patients with T1D. Our study also indicates that patients should be actively encouraged to maintain a low BMI and adhere to their dietary plan, which can help achieve HbA_{1c} targets and reduce the risk of complications. Thus, an increased understanding of glycemic control and the reasons for inadequate control can help to optimize therapy and improve outcomes.

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Declaration of competing interest

DB has provided advisory board services for served as a consultant or speaker for Abbott, AstraZeneca, Sanofi and has received speaker fees for Abbott, Eli Lilly, Novo Nordisk, Roche Diagnostics and Sanofi. CI has provided advisory board services for Novo Nordisk, Lilly, Abbott, Menarini, Roche Diabetes Care, and Ascensia, and has received speaker fees for Novo Nordisk, Abbott, Senseonics, Lilly, and Boehringer Ingelheim Pharmaceuticals. GP has provided advisory board services for Dompè, speaker fees for Eli Lilly, Grant Recipient for Amgen Inc, Sanofi, Dompè, Abbott, Novo Nordisk, consulting fee from AstraZeneca, Sanofi, Eli Lilly, Enthera.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2022.11.008.

Appendix

List of Italian centers participating in the SAGE Study.

3800001 Roberto Anichini, Alice Magiar, Pistoia;
3800002 Cristiana Maria Baggiore, Firenze;
3800003 Olga Disoteo, Antonella Porcu, Milano;
3800004 Enzo Bonora, Maddalena Trombetta, Verona;
3800006 Daniela Bruttomesso, Federico Boscari, Padova;
3800007 Mario Carrano, Salerno;
3800008 Maria Gisella Cavallo, Marco Giorgio Baroni, Roma;
3800012 Alberto Di Carlo, Ilaria Casadidio, Lucca;
3800013 Maurizio Di Mauro, Catania;
3800014 Angelo Foglia Anna De Simone Napoli;
3800015 Lucia Frittitta, Catania;
3800016 Gabriella Garrapa, Fano (Pesaro Urbino);
3800017 Bruno Giorda, Elisa Nada Chieri, Torino;
3800018 Giuseppina Guarino, Sandro Gentile, Napoli;
3800019 Concetta Irace, Serena Catalano, Catanzaro;
3800020 Davide Lauro, Roma;
3800021 Davide Maggi, Eleonora Ambrosetti, Genova;
3800022 Marianna Maranghi, Daniela Pergolini, Roma;
3800023 Maria Letizia Petroni, Francesca Marchignoli, Bologna;
3800025 Emanuela Orsi, Alessia Gaglio, Milano;
3800026 Piermarco Piatti, Lucilla Monti, Milano;
3800027 Paolo Pozzilli, Silvia Pieralice, Roma;
3800028 Filippo Privitera, Catania;
3800031 Roberto Trevisan, Mascia Albizzi, Bergamo;
3800032 Raffaella Buzzetti, Angela Carlone, Roma;
3800033 Dario Pitocco, Linda Tartaglione, Roma.

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