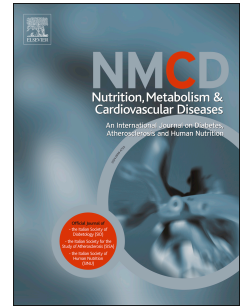


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Metabolic control and complications in Italian people with diabetes treated with continuous subcutaneous insulin infusion

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Abstract

Background and Aims: The objective of this cross-sectional study was to evaluate degree of glycemic control and frequency of diabetic complications in Italian people with diabetes treated with continuous subcutaneous insulin infusion (CSII).

Methods and Results: Questionnaires investigating the organization of diabetes care centres, individuals' clinical and metabolic features and pump technology and management were sent to adult and paediatric diabetes centres using CSII in Italy. Standard clinical variables, demographic data and acute and chronic diabetes complications were derived from local clinical management systems. A total of 6,623 people with diabetes from 93 centers formed the sample; 98.8% had type 1 diabetes mellitus, 57.2% were female, 64% wore a conventional pump and 36% wore a sensor-augmented pump. The median glycated haemoglobin (HbA_{1c}) level was 60 mmol/mol (7.6%). The HbA_{1c} target (i.e. <58 mmol/mol under <18 years and <53 mmol/mol for over that age) was achieved by 43.4% of paediatric and 23% of adult participants. Advanced pump functions, higher rate of sensor use, pregnancy in the year prior to the study and longer duration of diabetes were associated with lower HbA_{1c} levels.

Most frequent chronic complications related to diabetes were retinopathy, microalbuminuria and hypertension. In the year preceding the study, 5% of participants reported ≥ 1 episode of severe hypoglycaemia and 2.6% reported ≥ 1 episode of ketoacidosis.

Conclusions: Advanced personal skills and sensor use are associated with better metabolic control outcomes in Italian people on CSII. The scarcity of severe hypoglycaemic episodes confirms the positive effect of CSII on that complication.

Clinical trial registration number: ClinicalTrials.gov NCT 02620917

Key words: continuous subcutaneous insulin infusion (CSII); metabolic control; acute and chronic complications; diabetes mellitus

Introduction

During the past 25 years CSII has become a viable alternative to multiple daily insulin injections (MDI) in people with type 1 diabetes mellitus (T1DM). Meta-analyses of both randomised controlled trials (RCTs) and observational studies have found lower HbA_{1c}, less severe hypoglycaemic (SH) episodes and a better quality of life in people on CSII compared to those on MDI (1-3). A limitation of such reviews, however, has been the inclusion of MDI-treated individuals not using basal insulin analogue or CSII-treated individuals using regular insulin. Recent studies comparing CSII and MDI with analogue insulin showed less evident benefits for CSII (4, 5).

Sensor-augmented insulin pump (SAP) combine an insulin pump with continuous glucose monitoring (CGM). RCTs have shown that SAPs improve metabolic control without increasing SH episodes in individuals with T1DM with elevated HbA_{1c} levels and reduce the frequency and duration of hypoglycaemic events in individuals with satisfactory glucose control (6-8). Recent studies have also suggested an advantage for CSII on protection against chronic diabetic complications and cardiovascular mortality (9 - 13).

In 2013, we performed a survey on CSII in Italy addressing the organization of diabetes centres and care recipients and device characteristics (14). Quality of glycemic control, chronic complications and acute metabolic complications were not considered. We report here a new survey to investigate metabolic control and diabetes complications in CSII-treated individuals in Italy.

Methods

Study design

In this multicentre cross-sectional study, data were collected with questionnaire sent by e-mail to the heads of adult and paediatric diabetes care centres where CSII is used. Centres were identified from previous surveys and information from companies selling CSII devices. Incomplete data were integrated by phone or e-mail.

Participants

Subjects treated with CSII for at least 1 year were consecutively enrolled among people who attended diabetes outpatient clinics between September 2015 and October 2016. Exclusion criteria were previous diagnosis of dementia or psychosis and pregnancy in progress. Prior to enrolment, informed consent was obtained from each participant. The study was approved by the Ethical Committee of each centre and registered on ClinicalTrials.gov (NCT 02620917). Procedures complied with the ethical standards of the institutional and national committees on human experimentation and with the Helsinki Declaration of 1975.

Measures

Standard clinical variables (i.e. serum HbA_{1c}, total cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, and creatinine), demographic data (i.e. age, gender, type of diabetes, diabetes and CSII duration and body mass index), and presence of hypertension and chronic diabetes complications (i.e. retinopathy, nephropathy, and cerebral, cardiac and peripheral vasculopathy), were derived from local files. The mean HbA_{1c} level of participants from the year prior to the study was calculated. Information about pump characteristics, use of advanced pump functions (i.e. different bolus types, bolus calculator and temporary basal rates), days of sensor use and frequency of the self-monitoring of blood glucose were downloaded from insulin pumps or glucometers or recovered from CGM devices and were reported in the questionnaire.

Participants were asked to record the number of SH episodes experienced during the year preceding enrolment in the study, and the frequency of episodes was expressed as cumulative number of SH episodes per participant. For adult participants, an SH episode was defined as an event requiring assistance and the administration of carbohydrates or glucagon (15). For paediatric participants SH referred to an event associated with coma, seizures or neurological symptoms requiring parenteral treatment. The number of diabetic ketoacidoses (DKA), defined as acidosis and hyperglycaemia, and the number of visits to the emergency room for acute metabolic complications of diabetes were collected from medical records. Information about the organisation of each centre included the number of people with T1DM, start of CSII treatment, team composition (physicians, nurses, dieticians and psychologists) and around-the-clock availability.

Statistical analysis

Continuous data were expressed as median and interquartile ranges (IQR). Categorical data were compared between groups using a chi-square test, whereas groups of continuous data were compared with the Mann-Whitney or Kruskal-Wallis test. All tests were two-sided and a p-value less than 0.05 was considered to be significant. A linear mixed-effect regression model was used to identify the predictors of HbA_{1c} among clinically relevant variables (i.e. age, duration of diabetes, duration of CSII, type of device, sensor use, CHO-counting and use of advanced pump functions), accounting for the centre-effects. The centre was included in the model as a random effect, because participant outcomes were expected to differ from centre to centre, possibly due to differences among centres instead of differences among participants who present at different centres. Statistical analysis was performed using R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria)

(16)

Results

Study Participants and Centers

Italy has 272 diabetes care centres that use CSII. Of them, 93 were included in the study,—21 offering paediatric care and 72 offering adult care,—caring for 6,623 subjects.

In 41% of the adult care centres, the caring team was composed of physician, dietician and nurse, whereas 71% of the pediatric centres had a team including physician, nurse, dietician and psychologist. Among the centres, 71% offering adult care and 86% offering paediatric care were available around-the-clock.

Demographic and clinical data appear in Table 1. Most participants who received CSII treatment had T1DM (98.8%) and were older than 18 years. Compared to paediatric participants adults had longer CSII use and were more frequently female, likely for pump use during pregnancy. Adults checked their blood glucose less often than paediatric participants (median 5.0 (IQR 4.0-5.0) vs. 6.1 (IQR 6.0-7.0) blood glucose tests per day, $p<0.05$).

Chronic complications of diabetes (i.e. retinopathy and microalbuminuria) and hypertension were more prevalent among adult participants (Supplementary Table 1). Total cholesterol, HDL-cholesterol, triglycerides and creatinine were in the normal range across the different age groups (Supplementary Table 2).

Use of devices

Irrespective of age, 4,263 (64.3%) participants used a conventional pump and 2,360 (35.7%) used a pump with an associated or integrated CGM system (SAP).

Among participants who used a SAP, a glucose sensor was used 15 (I7-24) days per month; 785 participants (33.2%) used the sensor less than 10 days per month, 739 (31.3%) 10-19 days per month and 836 (35.5%) 20 or more days per month. The rate of sensor use was higher in subjects

less than 18 years of age (Table 1), with the highest rate among participants 0-5 years old (median 30 days per month [IQR 25.0-30.0]).

Most participants, whether paediatric or adult, took advantage of advanced pump features : 81.2% of participants used temporary basal, 82.2% bolus options, 56.5% the bolus calculator and 75.9% CHO counting. The prevalence was greater among participants who used SAPs than among ones who used a conventional pump (temporary basal 84.2% vs. 79.1%, $p<0.0001$; bolus options 89.2% vs. 77.8%, $p<0.0001$; bolus calculator 72.5% vs. 64.3%, $p<0.0001$; CHO counting 81.8% vs. 72.2%, $p<0.0001$).

Metabolic control.

Median HbA_{1c} during the year before enrolment in the study was 60.0 mmol/mol (7.6%) and tended to be lower in participants aged 6-12 years (Supplementary Table 2). Male participants had lower HbA_{1c} (58.5 [IQR 53.0-67.0] mmol/mol or 7.5% [IQR 7.1-8.3] % vs. 60.0 [IQR 54.0-68.0] mmol/mol or 7.6% [IQR 7.1-8.4]%; $p<0.05$).

The median HbA_{1c} level was less than 53.0 mmol/mol (7.0%) in 23.0% of participants and less than 58.0 mmol/mol (7.5%) in 42.0% (Figure 1). Considering that the target HbA_{1c} level varies between children and adults, HbA_{1c} lower than 58.0 mmol/mol (7.5%) was achieved by 43.4% of participants under 18 years of age, whereas only 23.0% of adults met the HbA_{1c} goal of <53.0 mmol/mol (7%).

Yearly levels of HbA_{1c} were lower in 217 women who became pregnant in the year prior to data collection than of the other 3,610 female participants (51.0 [IQR 45.0-51.0]mmol/mol or 6.8[IQR 6.3-6.8]% vs. 60.0 [IQR 54.0-68.0] mmol/mol or 7.6[IQR 7.1-8.4]%; $p<0.0001$).

CHO counting and use of advanced pump functions were associated with lower HbA_{1c} levels (Figure 2). Participants who used SAP had lower HbA_{1c} (58.0 [IQR 52.0-66.0] mmol/mol or 7.5 [IQR 6.9-8.2] % vs 60.0 [IQR 54.0-67.0] mmol/mol or 7.6 [IQR 7.1-8.3]%, $p<0.0001$). In addition, participants who used a sensor more than 20 days per month had lower HbA_{1c} than those who used

it fewer than 20 days per month: 58.0 (IQR 51.0-65.0) mmol/l or 7.5 (IQR 6.8-8.1)% vs. 59.0 (IQR 53.0-66.0) mmol/mol or 7.6 (IQR 7.0-8.2)%; $p=0.0008$).

HbA_{1c} was lower in adult and paediatric participants who were monitored by a team composed of physician, nurse, dietician and psychologist than in those monitored by an incomplete team: 58.5 (IQR 53.0-66.0) mmol/l or 7.5 (IQR 7.0-8.2)% vs. 60.0 (IQR 54.0-68.5) mmol/mol or 7.6 (IQR 7.1-8.4)%, $p<0.0001$).

The results of the multivariable analysis (Table 2) revealed that a longer duration of diabetes (β -0.04, 95% C.I. -0.09 to -0.01), SAP use (β -1.47, 95% C.I. -2.43 to -0.51), sensor use (β -0.09, 95% C.I. -0.13 to -0.04), bolus option (β -1.76, 95% C.I. -2.90 to -0.63) and CHO counting (β -2.66, 95% C.I. -3.83 to -1.49) were associated with lower HbA_{1c} levels. The effect of using a bolus calculator on HbA_{1c} was nearly statistically significant (β -1.02, 95% C.I. -2.09 to 0.06).

Acute complications

Concerning metabolic emergencies in the previous year, 5.0% of participants reported at least one episode of SH, 2.6% an episode of ketoacidosis and 3.5% a visit to the emergency room for either reason.

Episodes of SH occurred in 52 out of 533 participants with cardiovascular disease and in 243 out of 5,471 participants without cardiovascular disease (9.8% vs. 4.4%, $p<0.0001$).

They also occurred more frequently in adults (5.6% vs. 2.1% in participants aged less than 18 years, $p<0.0001$), especially among those more than 50 years old (6.1%). Most participants who reported episodes of SH (200 of 337, 59.3%) reported experiencing one episode per year, although 63 participants (18.7% among participants with SH and 0.9% overall) reported experiencing three or more episodes per year.

Adult participants with HbA_{1c} levels less than 48.0 mmol/mol (6.5%) had significantly more SH episodes per year than ones with HbA_{1c} levels ≥ 48.0 mmol/mol (6.5%): 0.17 versus 0.10,

respectively ($p < 0.05$). No such difference emerged among paediatric participants. SH episodes were more frequent in participants who used CGM (7.3% vs 3.9%, $p < 0.0001$).

Occurrence of ketoacidosis differed across age groups: 12.1% among participants 0–5 years old, 2.0% among 6–12 years old, 4.1% among 13–17 years old, 2.6% among 18–50 years old and 1.8% among older than 50 years ($p = 0.0003$). HbA_{1c} level was 64.0 (IQR 57.0-75.0) mmol/mol or 8.0 (IQR 7.4-9.0)% among participants who experienced episodes of ketoacidosis and 60.0 (IQR 53.0-67.0) mmol/mol or 7.6 (IQR 7.0-8.4)% among those who did not ($p < 0.0001$).

Discussion

We analysed metabolic control and acute and late complications of diabetes in a cohort of Italian paediatric and adult individuals with diabetes mellitus treated with CSII. Participants came from 16 of the 19 regions of Italy.

We found that 43% of paediatric and 23% of adult individuals achieved age-specific HbA_{1c} targets. Concerning adults, our data agree with the U.S. T1D Exchange clinical registry, but considering the pediatric population the fraction on target in Italy is almost twofold that in the United States (17). The difference between adults and youngsters could have different explanations. Adults could have started CSII with higher HbA_{1c} with respect to paediatric individuals, who began CSII mostly to improve their quality of life. Alternatively, paediatric individuals could have benefitted from a more complete caring time or a better use of new technologies.

CGM use in Italy covers only 16 days per month, and our questionnaire did not specifically investigate the reasons for suboptimal CGM. We speculate that the limited coverage may stem from the fact that the national healthcare system does not completely cover sensor costs.

Moreover, since CGM technology is relatively novel, training in its use could be insufficient.

Interestingly, in contrast to other studies addressing CGM, the rate of sensor use in our population was greater in the pediatric section, especially under the age 12, a finding likely due to parents'

motivation and active role diabetes management. Conversely, the rate of sensor use among participants aged 12-17 years was very low (15 days per month). In any case, our data indicate that CGM use is associated with a significantly lower HbA_{1c} level and confirm existing evidence that the benefit of CGM relates to the frequency of its use (18).

In this study SH episodes (0.1 episodes per participant per year) were few compared to both real-world data and data from RCTs (17, 19-21). In our sample, the frequency of SH episodes was greater among participants using a glucose sensor. A possible explanation is that CGM is recommended for persons with disabling hypoglycaemia despite optimal CSII use. Pumps with a low glucose suspend (LGS) or predictive low glucose suspend (PLGS) system can be expected to reduce further the risk of SH. However, though 35.9% of participants used SAP therapy, we do not know which type of instrument they use (i.e. with or without an LGS or PLGS function), and thus cannot speculate further about this point.

Adults with HbA_{1c} levels less than 48.0 mmol/mol (6.5%) exhibited significantly more SH episodes than ones with HbA_{1c} levels \geq 48.0 mmol/mol, which confirms that tight glycaemic control increases the risk of hypoglycaemia. Among paediatric participants, no correlation emerged between SH and HbA_{1c} levels, which confirms the results of a recent Italian multicentre study (22). Participants who experienced episodes of SH had had diabetes for longer than those who had not (20 years [IQR 13-28] vs. 15 years [IQR 9-25], respectively; $p < 0.0001$). An increase in the frequency of SH episodes with increased age and duration of diabetes was also observed in the U.S. T1D Exchange clinical registry (17). Greater hypoglycemia unawareness or greater glucose variability could explain that finding.

Participants with cardiovascular disease had significantly more episodes of hypoglycaemia than participants without. A possible explanation is that participants with cardiovascular complications were older (57 years [IQR 48-65] vs. 35 years [IQR 22-46], respectively; $p < 0.0001$) and had had diabetes for longer (31 years [IQR 20-40] vs. 15 years [IQR 9-24], $p < 0.0001$), which confirms the

idea that individuals with diabetes and cardiovascular disease represent a particularly fragile subgroup with a greater propensity to exhibit metabolic derangement.

We found that DKA is a problem for some participants. Since the risk of DKA was greater in participants with HbA_{1c} levels greater than 64.0 mmol/mol (8.0%), poor compliance with diabetes treatment could have contributed to their increased risk of DKA.

HbA_{1c} was lower in participants monitored by a team with physician, nurse, dietician and psychologist than those monitored by a less complete team. The difference, albeit statistically significant, might not be clinically relevant, however. Complete diabetes care teams are associated with a superior use of technology, fewer dropouts, increased CGM and advanced bolus use (14), but many centres, especially the smallest ones, have a lack of personnel. In most adult care centres, teams have no psychologist, although psychological support is an important part of regular follow-up.

Our study had several limitations. First, only approximately 30.0% of the Italian diabetes care centres using CSII participated. Our results, however, appear to be representative of the situation across the country since centre and patient characteristics were similar to those of a previous survey that reported data of 79.8% of Italian people with diabetes treated with CSII (14).

We did not have a reference group of individuals treated with MDI; nevertheless, a partial comparison is possible with AMD Annals (23) which have reported routine clinical data of a network of diabetes clinics. In the last report concerning 28,000 individuals with T1DM (84.5% treated with MDI), the mean HbA_{1c} level was 65.0±16.0 mmol/mol (8.1±1.5%). Only 22.3% of MDI-treated individuals obtained the HbA_{1c} target of less than 53.0 mmol/mol (7.0%), whereas 44.5% showed HbA_{1c} levels greater than 64.0 mmol/mol (8.0%), compared to 29.8% in our study.

Another major limitation of the study is that the number of SH episodes experienced during the year preceding enrolment was based on recall which obviously implies inaccuracies although most people with type 1 diabetes have a good recall of SH over a 1-year period (24)

Lastly, because the study was cross-sectional, no conclusions can be drawn about the effect of CSII on chronic diabetes complications (25).

Conclusions

We provide a picture of the metabolic control and frequency of acute complications of diabetes in Italian individuals treated with CSII. Mean HbA_{1c} levels were satisfactory, but only 43% of children and 23% of adults achieved their age-specific HbA_{1c} target levels. Better metabolic control was associated with CHO counting, use of advanced pump functions, compliance with sensor use, pregnancy in the year prior to the study and longer duration of diabetes. The low frequency of SH episodes confirms the positive effect of CSII on that complication.

Highlights

- The study marks the largest Italian study on glucose control in CSII-treated people
- The median HbA_{1c} level among all participants was 60.0 mmol/mol (7.6%)
- User skills with sensors is associated with lower HbA_{1c} levels
- The frequency of severe hypoglycaemia and ketoacidosis episodes was very low

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CONFLICT OF INTEREST

GL acted as advisory board member for Eli Lilly, Boheringer Ingelheim and Merck Sharp & Dohme, received speaker honorary from Novo Nordisk, Sanofi Aventis and Astrazeneca

RB acted as advisory board member for Lifescan, Novo Nordisk, Roche, Eli Lilly and received speaker honoraria from Eli Lilly, Abbott, Sanofi Aventis, Theras, Medtronic, Ypsomed

LB none

VDB none

AG none

GG acted as advisory board member for Johnson & Johnson and Novo Nordisk, received speaker honoraria from Novo Nordisk, Medtronic, Pharmextracta

DI none

LL has received speaker fees from Astra Zeneca, Eli Lilly, Medtronic, Menarini, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi Aventis, Takeda, and has provided advisory services to Astra Zeneca, Eli Lilly, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi Aventis, Takeda

IR acted as advisory board member for Roche Diagnostics, received speaker honoraria from Eli Lilly, Roche Diagnostics, Menarini

RS acted as advisory board member for Abbott and Eli Lilly and received speaker honoraria from Roche Diagnostics, Sanofi Aventis and Medtronic

DB acted as advisory board member for Abbott and Novo Nordisk, received speaker honoraria from Eli Lilly, Lifescan, Roche Diagnostics, Sanofi Aventis.

CONTRIBUTOR STATEMENT

All authors contributed substantially to the study design, data collection, data analysis and interpretation, and the writing or revision of the manuscript. All authors approved the publication of the final version of the manuscript. No author received any specific grant from funding agencies in the public, commercial or non-profit sectors for the research.

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Appendix. Members of the Italian Study Group on Diffusion of CSII

All the following primary investigators and clinical centers, listed by region or city (affiliation), participated in this study:

Calabria

Locri , F. Mammì and M. Bruzzese.

Campania

Caserta, M.Schettino and M.G. Nuzzo; Cava dè Tirreni, V. Di Blasi, R. Fresa and C. Lambiase; Napoli, D. Iafusco, A. Zanfardino and S. Confetto; Napoli, L. Bozzetto, G. Annuzzi A. Alderisio and G.Riccardi; Napoli, S.Gentile, G.Marino and G.Guarino.,

Emilia Romagna

Bologna, S. Zucchini and G. Maltoni; Cesena - Ravenna, T. Suprani and V. Graziani; Forlì, M. Nizzoli and S. Acquati; Modena: R.Cavani and S.Romano; Montecchio Emilia, M. Michelini and E. Manicardi; Parma, R. Bonadonna and A. Dei Cas; Parma, E. Dall'aglio and M. Papi; Piacenza, S. Riboni; Reggio Emilia, V. Manicardi and E. Manicardi; Reggio Emilia, E. Manicardi and V. Pagni; Reggio Emilia: A. Lasagni and M.E. Street; Scandiano, U. Pagliani and C. Rossi.

Friuli Venezia Giulia

Monfalcone, R. Assaloni, B. Brunato and C. Tortul; Pordenone, G. Zanette and P. Li Volsi; Udine, M. Zanatta; Udine, L. Tonutti, S. Agus and M.A. Pellegrini.

Lazio

Ceccano, P. Pozzilli and G. Beretta Anguissola; Latina, R. Buzzetti, C. Moretti C and G. Leto; Roma, P. Pozzilli, S. Manfrini and A.R. Maurizi; Roma, S. Leotta, M. Altomare, S. Abbruzzese, S. Carletti and C. Suraci; Roma, S. Filetti; Roma, M.L. Manca Bitti and S. Arcano; Roma, M.G. Cavallo and M. De Bernardinis; Roma, D. Pitocco, S. Caputo, A. Rizzi and A. Manto; Roma, R. Schiaffini, M. Cappa and D. Benevento; Roma, S. Frontoni and I. Malandrucchio; Roma, S. Morano and T. Filardi; Roma, D. Lauro. M.A. Marini, E. Castaldo and D. Sabato; Terracina, F. Tuccinardi and E. Forte; Viterbo, C. Arnaldi.

Liguria

Genova, N. Minuto and G. d'Annunzio.

Lombardia

Bergamo, A. Corsi, R. Rota, C. Scaranna and R. Trevisan; Brescia, U. Valentini, A. Girelli, S. Bonfadini and E. Zarra; Brescia, A. Plebani, E. Prandi and B. Felappi; Cinisello Balsamo, A. Rocca, E. Meneghini and P. Galli; Cremona, P. Ruggeri and E. Carrai; Lodi, L. Fugazza, V. Baggi and D. Conti; Milano, E. Bosi, A. Laurenzi, A. Caretto and C. Molinari; Milano, E. Orsi, V. Grancini and V. Resi; Milano, R. Bonfanti, V. Favalli, C. Bonura and A. Rigamonti; Milano, M. Bonomo, F. Bertuzzi, B. Pintaudi and O. Disoteco; Monza, G. Perseghin and S. Perra; Pavia, L. Chiovato, P. De Cata and F. Zerbini; Pavia, E. Lovati and M. Laneri; Tradate, L. Guerraggio; Treviglio-Romano di Lombardia, A.C. Bossi and V. De Mori.

Marche

San Benedetto del Tronto, M. Galetta and I. Meloncelli

Molise

Campobasso, A. Aiello A and S. Di Vincenzo.

Piemonte

Alba e Bra, A. Nuzzi and E. Fraticelli; Alessandria, E. Ansaldi, M. Battezzati, M. Lombardi and M. Balbo; Alessandria, R. Lera and A. Secco; Cuneo, V. De Donno; Novara, F. Cadario and S.

Savastio; Novara, C. Ponzani and G. Aimaretti; Torino, I. Rabbone, G. Ignaccolo, D. Tinti and F. Cerutti.

Puglia

Bari, F. Giorgino, F. Ortolani, E. Piccinno and O. Zecchino, Foggia, M. Cignarelli, O. Lamacchia and G. Picca; San Giovanni Rotondo, S. De Cosmo and A. Rauso.

Sicilia

Catania, L. Tomaselli, A. Tumminia and C. Egiziano; Marsala, A.M. Scarpitta and F. Maggio; Palermo, F. Cardella and R. Roppolo; Partinico, V. Provenzano, M. Fleres and A. Scorsone.

Toscana

Arezzo, A. Scatena; Carrara, G. Gregori; Livorno, S. Lucchesi and F. Gadducci; Livorno, S. Di Cianni Lucchesi and S. Pancani; Pisa, S. Del Prato, M. Aragona, I. Crisci and A. Calianno.

Trentino Alto Adige

Bolzano, B. Fattor and D. Crazzolarà; Bolzano, P. Reinstadler and S. Longhi; Merano, G. Incelli and S. Rauch; Trento, T. Romanelli, M. Orrasch, V. Cauvin and R. Franceschi.

Umbria

Spoletto, C. Lalli.

Veneto

Bassano del Grappa, A. Pianta and A. Marangoni; Belluno, C.N. Aricò; Castelfranco, N. Marin; Chioggia, N. Nogara; Cittadella, N. Simioni and A. Filippi; Conegliano, G.L. Gidoni Guarneri; Dolo-Mirano: M.L. Contin M.L. and A.P. Decata; Legnago, L. Bondesan; Montebelluna: L. Confortin and A. Coracina; Montecchio Maggiore, S. Lombardi and S. Costa; Padova, E. Cipponeri, R. Scotton, S. Galasso and F. Boscari; Portogruaro, M.S. Zanon and C. Vinci; Rovigo, G. Lisato; Venezia, L. Gottardo; Verona, E. Bonora, M. Trombetta, C. Negri and C. Brangani; Verona, C. Maffei, A. Sabbion and M. Marigliano.

TABLES

Table 1. Clinical characteristics of study participants.

Variable	Total	<18 years	≥18 years
Number of participants	6,623	1,025	5,598
Type of diabetes:			
type 1	6,543 (98.8)	1,025 (100)	5,518 (98.6)
type 2	80 (1.2)	0 (0)	80 (1.4)
Age, years ^a	37 (22-49)	14 (11-16)	41 (29-51)
Sex:			
Male	2,796 (42.2)	497 (48.5)	2,299 (41.1)*
Female	3,827 (57.8)	528 (51.5)	3,299 (58.9)
Duration of diabetes, years ^a	16 (9-26)	5 (3-8)	19 (12-28)*
Duration of diabetes at CSII start, years ^a	10 (4-19)	2 (1-4)	12 (6-21)*
Duration of CSII, years ^a	5 (2-8)	2 (1-4)	5 (3-8)*
Blood glucose tests, n/day ^a	5.2 (4.0-6.0)	6.1 (6.0-7.0)	5.0 (4.0-6.0)**
Type of device: ^b			
CSII	4,206 (64.1)	606 (59.1)	3,600 (65.0)***
SAP	2,360 (35.9)	419 (40.9)	1,941 (35.0)
SAP: sensor use, days/month ^{a c}	15 (7-24)	21 (10-30)	15 (7-21)*

Data are presented as n (%) or ^a median (IQR), where appropriate.

Data not available in ^b57 patients and ^c84 patients.

* p<0.0001 vs <18 years

**p<0.05 vs <18 years

***p<0.0005 vs <18 years

Table 2. Multivariable analysis of HbA_{1c}

	Regression coefficient () with 95% C.I.	p-value
Age, years	-0.01 (-0.05 to 0.02)	0.33
Duration of diabetes, years	-0.05 (-0.09 to -0.01)	0.03
Duration of CSII, years	0.06 (-0.03 to 0.16)	0.19
Type of device: SAP vs. CSII	-1.47 (-2.43 to -0.51)	0.003
Sensor use, days/month	-0.09 (-0.13 to -0.04)	0.0001
Temporary basal: yes vs. no	-0.74 (-1.78 to 0.31)	0.17
Bolus options: yes vs. no	-1.76 (-2.90 to -0.63)	0.002
CHO counting: yes vs. no	-2.66 (-3.83 to -1.49)	<0.0001
Bolus calculator: yes vs. no	-1.02 (-2.09 to 0.06)	0.06

The regression coefficients represent i) the change in HbA_{1c} according to a change in 1 unit of the continuous predictor or ii) the change in HbA_{1c} that is associated with the first category with respect to the second category of the binary predictor.

Figure 1. Distribution of mean glycated haemoglobin levels during the year prior to the study among 6,623 Italian individuals treated with continuous subcutaneous insulin infusion.

Figure 2 Median glycated haemoglobin levels during the year prior to the study according to the use of advanced pump functions and CHO counting (* $p < 0.0001$).

Non-users of the bolus calculator include only participants who count carbohydrates.

Fig.1

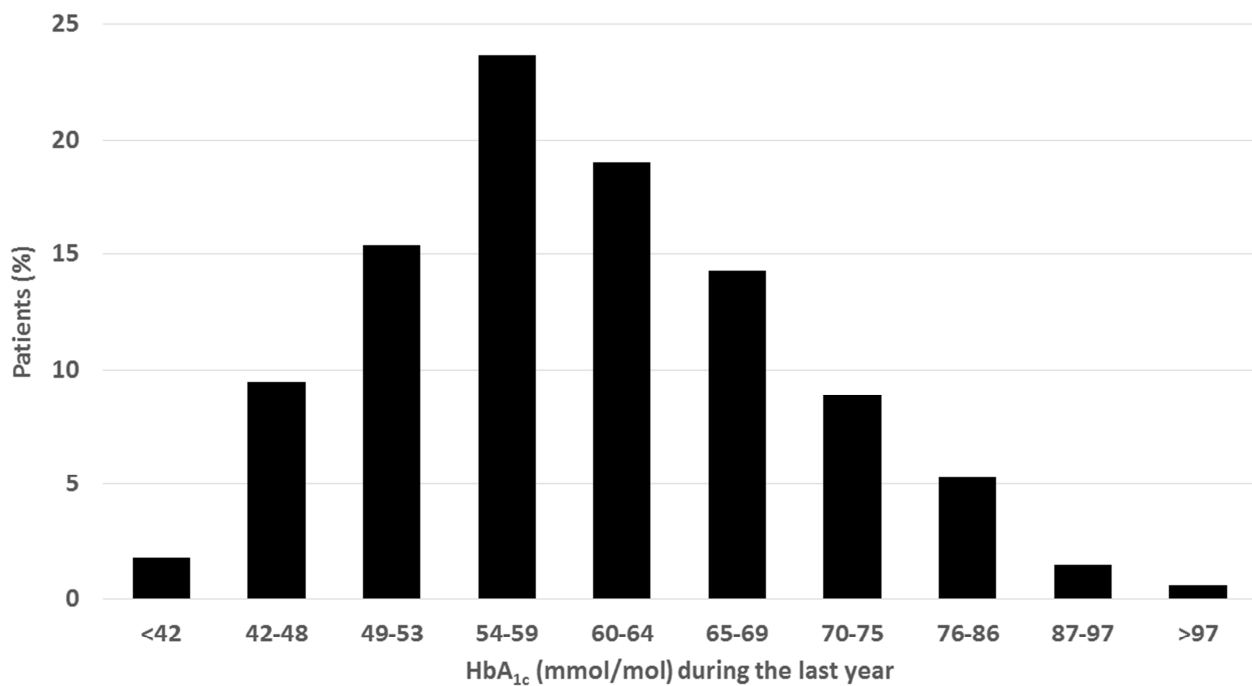
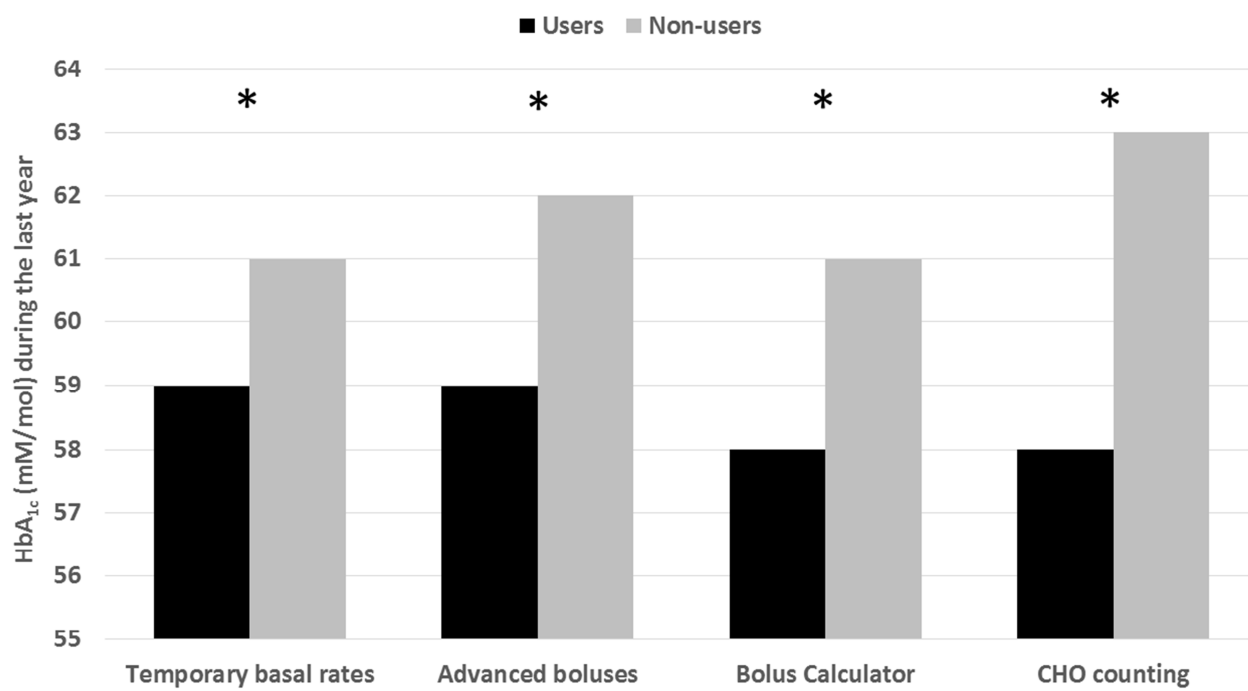


Fig.2



SUPPLEMENTARY TABLES

Supplementary Table 1. Prevalence of chronic complications of diabetes at the time of enrollment

	All participants	<18 years	≥18 years	p-value
Number of participants	6,623	1,025	5,598	-
HYPERTENSION (miss=163)	875 (13.5)	1 (0.1)	874 (16.0)	<0.0001
RETINOPATHY (miss=178):				<0.0001
Absent	4,994 (77.5)	1,005 (99.6)	3,989 (73.4)	
Background	776 (12.0)	2 (0.2)	774 (14.2)	
Proliferative	119 (1.8)	0	119 (2.2)	
Maculopathy	48 (0.7)	0	48 (0.9)	
Laser-treated	508 (7.9)	2 (0.2)	506 (9.3)	
NEFROPATHY (miss=177):				<0.0001
Absent	5,815 (90.2)	999 (98.9)	4,816 (88.6)	
Microalbuminuria	355 (5.5)	4 (0.4)	351 (6.5)	
Macroalbuminuria	119 (1.8)	0	119 (2.2)	
Previous microalbuminuria	127 (2.0)	7 (0.7)	120 (2.2)	
Hemodialysis-Renal transplant	30 (0.5)	0	30 (0.5)	
Cerebral vasculopathy (miss=166):				<0.0001
1 yes	286 (4.4)	0	286 (5.3)	
2 no	5,972 (92.5)	1,010 (99.9)	4,962 (91.1)	
3 n.a.	199 (3.1)	1 (0.1)	198 (3.6)	
Cardiac vasculopathy (miss=166):				<0.0001
1 yes	181 (2.8)	0	181 (3.3)	
2 no	6,201 (96.0)	1010 (100)	5,191 (95.3)	
3 n.a.	75 (1.2)	0	75 (1.4)	
Peripheral vasculopathy (miss=166):				<0.0001
1 yes	236 (3.7)	0	236 (4.3)	
2 no	6,082 (93.6)	1,010 (99.9)	5,036 (92.5)	
3 n.a.	175 (2.7)	1 (0.1)	174 (3.2)	

Data are expressed as n (%).

Supplementary Table 2. Metabolic parameters of 6,623 Italian individuals treated with continuous subcutaneous insulin infusion.

	Total	0-5 years	6-12 years	13-17 years	18-50 years	>50 years	p-value
Number of individuals	6,623	34	356	635	4,190	1,408	-
HbA _{1c} , mmol/mol ^{a b}	60 (53-67)	62 (54 - 74)	58 (53-65)	60 (53-66)	60 (53-67)	60 (54-67)	0.12
Creatinine, mg/dl ^{a c}	0.7 (0.1-0.9)	0.3 (0.2-0.4)	0.4 (0.4-0.5)	0.6 (0.5-0.7)	0.7 (0.6-0.9)	0.8 (0.7-0.9)	<0.0001
Cholesterol, mg/dl ^{a d}	176 (155-196)	145 (129-172)	163 (144-177)	163 (145-181)	176 (156-197)	181 (160-203)	<0.0001
HDL Cholesterol, mg/dl ^{a e}	60 (50-71)	41 (32-52)	62 (51-72)	62 (53-72)	60 (50-71)	61 (49-74)	<0.0001
Triglycerides, mg/dl ^{a f}	66 (51-89)	74 (52-104)	52 (42-66)	57 (45-74)	66 (5-89)	76 (58-105)	<0.0001

Data are expressed as n (%) or ^amedian (IQR).

Data not available in ^b139, ^c686, ^d502, ^e582 and ^f528 patients.