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HbA1c Variability in Adults With Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion (CSII) Therapy Compared To Multiple Daily Injection (MDI) Treatment.

Type 1 Diabetes Insulin Delivery Mode and Glycaemic Variability

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ABSTRACT

Objective: To determine if continuous subcutaneous insulin infusion (CSII) therapy is associated with lower HbA1c variability (long-term glycaemic variability GV) relative to multiple daily injection (MDI) treatment in adults with Type 1 diabetes (T1DM).

Design: Retrospective audit

Setting and participants: Clinic records from 506 adults with T1DM from two tertiary Australian hospitals.

Outcome measures: Long-term GV was assessed by HbA1c standard deviation (SD) and coefficient of variation (CV) in adults on established MDI or CSII therapy, and in a subset changing from MDI to CSII.

Results: Adults (n = 506, (164 CSII), 50% women, mean ± SD age 38.0 ± 15.3 yrs, 17.0 ± 13.7yrs diabetes, mean HbA1c 7.8 ± 1.2% [62 ± 13 mmol/mol] on CSII, 8.0 ± 1.5% [64 ± 16 mmol/mol] on MDI) were followed for 4.1 ± 3.6 yrs. CSII use was associated with lower GV (HbA1c SD: CSII vs. MDI 0.5 ± 0.41% [6 ± 6 mmol/mol] vs. 0.7 ± 0.7% [9 ± 8 mmol/mol] and CV: CSII vs. MDI 6.7 ± 4.6% [10 ± 10 mmol/mol] vs. 9.3 ± 7.3% [14 ± 13 mmol/mol], both P<0.001. Fifty-six adults (73% female, age 36 ± 13 yrs, 16 ± 13 yrs diabetes, HbA1c 7.8 ± 0.8% [62 ± 9 mmol/mol] transitioned from MDI to CSII. Mean HbA1c fell by 0.4%. GV from one-year post-CSII commencement decreased significantly, HbA1c SD pre vs. post-CSII 0.7 ± 0.5% [8 ± 5 mmol/mol] vs. 0.4 ± 0.4% [5 ± 4 mmol/mol]; P<0.001, and HbA1c CV 9.2 ± 5.5% [13 ± 8 mmol/mol] vs. 6.1 ± 3.9% [9 ± 5 mmol/mol]; P<0.001.

Conclusions: In clinical practice with T1DM adults relative to MDI, CSII therapy is associated with lower HbA1c GV. Relationships between HbA1c GV and chronic complications are of interest.

Strengths and limitations of this study

- A relatively large real-world observational study across a wide age and socioeconomic status from two tertiary hospitals allows for generalisability of results
- HbA1c GV, a simple low-cost mathematical measure, assessed using two formulae, with similar results, and in venous blood in accredited laboratories
- Analysis in those on established MDI or CSII therapy and in a subset who changed modalities, and a control group of MDI users who remained on MDI.
- Not a randomised study therefore not able to completely adjust for possible behavioural differences
- Complements and extends a prior publication by the group in which short-term GV based on interstitial fluid Continuous Glucose Monitoring (CGM) measures did not differ by insulin delivery modality.

Keywords: Glycaemic variability, Type 1 diabetes, Continuous subcutaneous insulin infusion, Multiple daily injection.

INTRODUCTION

Type 1 diabetes (T1DM) is characterised by day-to-day glucose fluctuations, much more so than in Type 2 diabetes (T2DM). The Diabetes Control and Complications Trial (DCCT) established that near normal glycaemic control, reflected by HbA1c levels, substantially reduces the risk of long-term vascular and neurologic complications,(1). Short-term GV can be assessed by analysing multiple daily capillary blood glucose levels, or by continuous (interstitial fluid) glucose monitoring

(CGM), and at cellular level has been demonstrated,(2, 3), to increase oxidative stress, inflammation and epigenetic changes,(4). Longer term GV can be assessed by analysing variation in HbA1c levels over time, usually reported as HbA1c standard deviation (SD) and /or coefficient of variation (CV), and has been implicated as an independent risk factor for the development of chronic complications in people with both T1DM and T2DM,(4-7). Short and long term GV do not always correlate.

In people with T1DM, insulin can be delivered by either multiple daily injections (MDI) or by continuous subcutaneous insulin infusion (CSII). There is emerging epidemiologic evidence that CSII use (independent of HbA1c levels) is associated with a reduction in chronic complications in both adult and paediatric age groups and with reduced cardiovascular mortality in adults with T1DM,(5, 8). Although CSII use is generally associated with lower HbA1c levels compared to MDI,(9), there are no consistent reported associations in the literature between short-term and long-term GV and insulin delivery mode. CSII without frequent real-time continuous glucose monitoring (RT-CGM) is usually associated with similar short-term GV as MDI,(10-12), including in our previous study in T1DM adults in the same setting as herein. With regard to long-term GV, there is only one published study, and that is in a paediatric setting, which demonstrated long-term GV benefit of CSII compared to MDI over a three year period,(13).

The primary aim of the present study was to examine HbA1c GV in adults with T1DM treated by CSII and MDI therapies predominantly without RT-CGM use in the real-world setting, not in a clinical trial. Hence, we compared HbA1c SD and CV over years in adults with T1DM treated by CSII, to those of adults treated by MDI, and also in

those changing from MDI to CSII therapy. Results were analysed with and without adjustment for mean HbA1c levels. As glycaemic benefit of technology may differ by user age group,(14) we also compared results in emerging adults (aged 18-26 years) and more mature adults (≥ 26 years).

MATERIALS AND METHODS

Subjects

We undertook a retrospective audit of clinical records of adults with T1DM attending outpatient diabetes clinics at two independent tertiary referral hospitals (Royal North Shore Hospital (RNSH), Sydney and St Vincent's Hospital (SVH), Melbourne, Australia). Data from 1995-2018 were collected. Participants were excluded if they were less than 18 years old, pregnant or breast-feeding, had less than two HbA1c results on record, or had less than one year of CSII therapy. The insulin pumps were not used with continuous real-time CGM (RT-CGM). Flash glucose monitoring became available in Australia in late 2016 and was not subsidised, and RT-CGM only became subsidised for those under 21 years of age in 2017, therefore these modalities were rarely used in our public hospital settings during the study period. The study was approved by the Human Research Ethics Committees of the Northern Sydney Local Health District and St Vincent's Hospital Melbourne. As this was a retrospective audit, it was not appropriate or possible to directly involve patients or public in this work.

Data collection.

All HbA1c results were obtained from laboratories accredited with the National Association of Testing (NATA) and the Royal College of Pathologists of Australasia

(RCPA). All NATA accredited laboratories are required to participate in a standardisation program and to standardise HbA1c measurements to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) guidelines. Patients usually had their laboratory tests performed by the same pathology provider. Demographic and clinical parameters (including insulin treatment modality, chronic complication status, incidence of severe hypoglycaemia (defined as any episode of hypoglycaemia requiring assistance from another person for recovery) were obtained from the medical records. Socioeconomic status was estimated via the subject's home address postcode (zip code) via the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA), 2011,(15).

Glycaemic variability

HbA1c GV was assessed through the mean within-individual SD and CV ((SD HbA1c / mean HbA1c) x 100) of available HbA1c levels. If individuals had changed treatment modality from MDI to CSII, the initial 12 months of HbA1c assessments post-CSII initiation were excluded, (as HbA1c usually decreases significantly during this time),(16, 17).

Statistical analyses

Data were stored in EXCEL (2010) and IBM SPSS Statistics (version 22) and Graph Pad Prism (version 6.0) were used for data analyses, including descriptive statistics, paired and independent T-tests, Chi-square tests and Pearson correlation coefficients. Statistical significance was taken at $P < 0.05$. Results were analysed as a whole and with subgroup analyses by age (18 - < 26 years and ≥ 26 years) and by gender. Participants on established insulin therapies (MDI or CSII) were analysed, as were a

group of individuals analysed pre- and post-insulin modality change (MDI to CSII). The participants who changed from MDI to CSII were matched (by age, baseline HbA1c and years of follow up) to a subgroup of adults who remained on MDI. GV was compared pre- and after 1-year post-modality change in the MDI to CSII group, and pre- and post a matched duration of follow-up in the group who remained on MDI. Where applicable, results were analysed with adjustment by least squares method for hospital location, gender, vascular complications, severe hypoglycaemia, age, diabetes duration, mean HbA1c levels, number of included HbA1c measurements, time between HbA1c measurements, years of follow-up, average decile of socioeconomic advantage and disadvantage and decile of education and occupation.

RESULTS

Subject demographics.

Baseline clinical characteristics of 506 adults with T1DM studied over time whilst on a single insulin delivery modality are shown in Table 1, with participants from both hospitals merged. The group is also described based on insulin delivery mode. SVH participants (n = 112) were more likely to be treated by CSII compared to the RNSH participants (66 (59 %) vs. 98 (25 %); P < 0.001) as SVH was an earlier adopter of CSII into their clinical practice. SVH subjects were more likely to be female, had fewer vascular complications, lower socioeconomic status, longer years of HbA1c follow-up and more available HbA1c measurements compared to the RNSH participants (Supplementary Table 1). The (merged sites, Table 1) CSII users were younger, more likely to be female (in keeping with a noted national trend,(18), and less likely to have vascular complications or a previous documented episode of severe hypoglycaemia and had a significantly lower socioeconomic status relative to the MDI group. There

were no significant differences in the years of follow-up between the CSII and MDI groups, nor the number of HbA1c measurements included in the study. CSII users had a slightly shorter mean ± SD time between HbA1c measurements compared to MDI users (213 ± 173 vs. 249 ± 203) days respectively; P = 0.047). There were no significant differences in mean (SD) HbA1c levels nor the number of measures evaluated over the study period between the CSII and MDI groups (7.8 ± 1.2 % [62 ± 13] mmol/mol (n = 8 HbA1c measures) CSII and 8.0 ± 1.5 % [64 ± 16] mmol/mol (n = 8 HbA1c measures) MDI; P = 0.13).

Table 1 Clinical characteristics of adults with Type 1 diabetes.

	CSII	**MDI**	**P value**
N	164	342	
Age (years)	34±13.4	39±15.8	**< 0.001**
Women (n (%))	106 (65)	148 (43)	**< 0.001**
Years of diabetes	17±12.5	18±14.3	0.55
Years CSII therapy	6.0±3.6	N/A	-
Vascular complications (n (%))*	49 (30)	143 (42)	**0.008**
Severe hypoglycaemia (n (%))†	14 (14)	70 (21)	**0.045**
Socioeconomic status (decile): Advantage / Disadvantage Education& occupation	 8±2.3 8±2.4	 9±1.9 9±1.9	 **0.005** **< 0.001**
Years follow-up	4.1±2.74	4.1±3.97	0.90
HbA1c measures (n)	8±7.3	8±8.2	0.96
Time between HbA1c (days)	213±173.1	249±202.8	**0.047**
Mean HbA1c % [mmol/mol]	 7.8±1.20 [62±13]	 8.0±1.5 [64±16]	 0.13

Data are mean ± standard deviation, or n (percentage). * Microvascular and/or macrovascular complications. † Any episode of severe hypoglycaemia recorded in the medical record.

Lower HbA1c GV in CSII users.

CSII-users had significantly lower long-term variability in HbA1c as reflected by both HbA1c SD and CV measures (Fig. 1). The difference remains statistically significant after adjustment (least squares) for gender, hospital location, chronic complication status, severe hypoglycaemia, baseline HbA1c levels, years of follow-up, number of HbA1c measures, time between HbA1c tests, diabetes duration, socioeconomic status and age (both P = 0.003). In order to account for possible differences in glycaemic control by hospital location, insulin modality treatments were compared separately at the two sites and similar significantly lower GV was observed in CSII (vs. MDI) users (Supplemental Figure 1). GV was also analysed by gender, and similarly lower HbA1c SD and CV was observed in CSII compared to MDI participants in both men and women. HbA1c SD in women ((0.6 ± 0.5 % [7 ± 6] mmol/mol) CSII, (0.8 ± 0.7 % [9 ± 8] mmol/mol) MDI, P = 0.005) and in men ((0.4 ± 0.3 % [5 ± 3] mmol/mol) CSII, (0.8 ± 0.7 % [9 ± 8] mmol/mol) MDI, P = 0.002). HbA1c CV in women ((7 ± 5 % [11 ± 12] mmol/mol) CSII, (9 ± 8 % [14 ± 12] mmol/mol) MDI, P = 0.02) and in men ((6 ± 3 % [8 ± 4] mmol/mol) CSII, (9 ± 7 % [15 ± 13] mmol/mol) MDI, P = 0.002).

Similar pattern of HbA1c variability in adults with T1DM by age group and insulin treatment modality.

Analysis by pre-determined age-subgroups (18 - < 26 years and ≥ 26 years) demonstrated that mean HbA1c was lower in the older CSII vs. older MDI users: (7.6 ± 1.1 % [59 ± 12] mmol/mol) CSII and 7.9 ± 1.4 % [62 ± 16] mmol/mol) MDI; P = 0.034), although there was no statistically significant difference in the 18 - < 26 year old group: (CSII vs. MDI; 8.3 ± 1.3 % [66 ± 14] mmol/mol) vs. 8.5 ± 1.6 % [68 ± 18] mmol/mol) (Supplementary Table 2). Furthermore, there were significantly lower HbA1c SD and

CV over follow-up amongst both age groups treated with CSII versus those treated with MDI (Figure 2).

Lower HbA1c GV in adults changing from MDI to CSII.

Fifty-six adults chose to change their insulin delivery modality from MDI to CSII. These individuals had a mean ± SD age of 36 ± 14 years (35 ± 12 for women and 40 ± 17 for men), diabetes duration of 16 ± 13 years and 73% were female. The observation period included 4.3 ± 3.5 years on MDI and 4.6 ± 4.7 years on CSII after excluding the initial 12 months on CSII (P = 0.56), during which the mean HbA1c fell significantly. There was a similar, significantly greater number of HbA1c measurements used to determine GV whilst on CSII compared to MDI; mean ± SD (n = 10 ± 8 and n = 9 ± 7 respectively; P = 0.002), and a shorter duration between HbA1c measurements whilst on CSII compared to MDI (215 ± 158 and 336 ± 501 days respectively; P < 0.001). HbA1c levels significantly decreased following the switch to CSII, including after excluding the first 12 months of HbA1c following modality change, mean ± SD (7.8 ± 0.8 % [62 ± 9] mmol/mol) MDI vs. (7.4 ± 0.9 % [57 ± 10] mmol/mol) CSII; P < 0.001) (Fig. 3 a). In addition, CSII use lowered HbA1c variability, with CSII commencement decreasing both HbA1c SD (0.7 ± 0.5 % [8 ± 5] mmol/mol) MDI vs. 0.4 ± 0.4 % [5 ± 4] mmol/mol) CSII; P < 0.001) and HbA1c CV (9.2 ± 5.5 % [13 ± 8] mmol/mol) MDI vs. (6.1 ± 3.9 % [9 ± 5] mmol/mol) CSII; P = 0.004) (Fig. 3 b, c). There were no statistically significant correlations between the improvement in HbA1c SD or CV with baseline variables such as age and diabetes duration (data not shown). The change in HbA1c, HbA1c SD and CV was analysed by gender and there were similar improvements in both men and women (Supplementary Table 3)

The 56 adults who changed from MDI to CSII were matched (by age, baseline HbA1c and duration of follow-up) to 56 adults who remained on MDI. There were no statistically significant differences in baseline HbA1c, age, years of follow-up nor time between HbA1c measurements between these groups (Table 2). Individuals who changed to CSII had more HbA1c values whilst on CSII (n= 10 ± 8 vs. 8 ± 6; P = 0.048). In contrast to the adults who changed from MDI to CSII, the adults who remained on MDI did not significantly improve mean, standard deviation or coefficient of variation HbA1c.

Table 2. Glycaemic variability in individuals changing from MDI to CSII compared to matched individuals remaining on MDI

	MDI to CSII			**Remained on MDI**			
	Pre	**Post**	**P value ***	**Pre**	**Post**	**P value ***	**P value ****
N	56			56			
Age (years)	36±13.5			38±15.7			0.58
Baseline HbA1c % [mmol/mol]	7.9±1.4 [63±15.7]			7.9±1.5 [63±16.3]			0.90
Study follow-up (years)	10.0±5.9			9.4±6.5			0.61
HbA1c measurements (n)	9±6.8	10±7.8[A]	**0.002**	8±7.5	8±6.4[A]	1.00	
Time between HbA1c (days)	336±501.1	215±157.8	**<0.001**	281±205.5	238±166.2	0.18	
Mean HbA1c % [mmol/mol]	7.8±0.81 [62±8.7)]	7.4±0.91 [57±9.9]	**<0.001**	7.7±1.09 [61±12.0]	7.7±1.18 61±12.9]	0.64	
HbA1c SD % [mmol/mol]	0.7±0.51 [8±4.8]	0.4±0.40 [5±3.7]	**<0.001**	0.6±0.45 [7±4.8]	0.50±0.30) [5±3.3]	0.10	
HbA1c CV% %			**0.004**		6.4±3.54	0.12	

[mmol/mol]	9.2±5.54 [13±7.6]	6.1±3.89 [9±5.37]	7.8±5.21 [11±6.9]	[9±4.9]

Data are mean ± standard deviation. *Pre- vs. Post- values MDI to CSII and Remains on MDI group. **Values MDI to CSII vs. Remains on CSII. [A] P<0.05 post-value MDI to CSII vs. Remains on CSII group.

DISCUSSION

In this retrospective audit of 506 adults with T1DM from two independent Australian tertiary referral diabetes centres, we report the novel finding that CSII therapy was associated with lower long-term (HbA1c) glycaemic variability than MDI therapy, despite similar mean HbA1c levels across the two modalities. Participants treated by CSII (without regular RT-CGM, low glucose suspend, predictive low glucose suspend or closed loop functions and without regular flash glucose monitoring) had significantly lower HbA1c variability reflected by both SD and CV measures. GV amongst CSII users remained significantly lower after adjustment for age, gender, diabetes duration, hospital location, socioeconomic status, chronic complication status, severe hypoglycaemia, baseline HbA1c levels, years of follow up, number of HbA1c measures and time between HbA1c measures. The groups of emerging and more mature adults showed similar HbA1c GV responses, as did males and females. Similar statistically significant reductions in both measures of HbA1c GV were seen with 56 patients who changed from MDI to CSII therapy, whilst MDI users who remained on MDI for a similar follow-up time did not significantly change their HbA1c GV.

Glycaemic variability has been identified as an independent risk factor for the chronic complications of diabetes,(6, 7) and in a large Swedish diabetes registry based epidemiologic study CSII use was independently associated with a significantly lower risk of cardiovascular complications and death,(5). This finding may at least partly relate to GV, and fluctuations between hyper- and hypoglycaemia inducing inflammation and oxidative stress and epigenetic changes,(2, 4). We speculate that lower HbA1c variability, as associated with CSII use in our study, may underpin or at least contribute to the observed reduced chronic complication and death rates amongst CSII users,(5, 6, 8, 19). There may be divergent effects of insulin treatment modality on measures of short-term (blood or interstitial fluid glucose level based) and long-term (HbA1c) glucose variability. We have previously demonstrated in 119 adult individuals with T1D (77 MDI and 42 CSII users) no statistically significant difference in any of 12 accepted measures of short-term glucose variability over 48 hours when analysed by masked CGM,(20). Unfortunately, due to the costly nature of CGM in Australia at the time of the study, when it was predominantly self-funded, , only a very small subset of patients used episodic RT-CGM and usually less than the 70% of time described as needed to improve glycaemia(21). These negative results are comparable to other studies assessing short-term (CGM) glucose variability in CSII users,(8, 12, 22). Even in studies in which HbA1c levels were significantly improved by CSII or CSII with RT-CGM, short-term GV did not improve in all participants,(14, 23). More recent studies, including those achieving tight glycaemic control,(24), or using RT-CGM and insulin pumps with low-glucose suspend functions,(25), overnight closed loop insulin delivery,(26) or hybrid closed loop CSII,(27) have demonstrated improved short-term glucose variability. These studies have not reported HbA1c GV change. We anticipate that technological advances in pumps, sensors and control

algorithms will continue to reduce short-term GV, and also long-term GV, in both adults and children with T1DM. It is important to consider whether study participants are in clinical trials, with their inherent selection biases and often additional participant support, or in clinical practice (as herein).

Strengths and limitations. This is a real-world study, rather than a clinical trial with potential for selection bias and the Hawthorne (observer) effect,(28). We assessed relatively large numbers of adults with T1DM from two independent tertiary hospitals and did so over a relatively long follow-up period with good numbers of HbA1c measures from accredited pathology services in both CSII and MDI users, and fortunately with similar mean HbA1c in both groups. We report both HbA1c CV and SD and not unexpectedly (given the mathematical derivation of SD from CV), find similar results with both measures. The study is strengthened by the analysis of GV over a wide adult age range, as well as by pre-established age groups and by consideration of gender. As well as a longitudinal observational study there was also an observation of a group changing from MDI to CSII therapy, and comparison to a matched group who remained on MDI. There was a similar number of HbA1c measurements included in the MDI and CSII groups over a long period of follow up (four years in established users, and 10 years in those who changed from MDI to CSII). HbA1c GV is a low cost measure that could be calculated from routine clinical care data (of HbA1c levels), hence is readily applicable to clinical practice (particularly in the era of electronic medical records), and clinical trials. Study limitations are that this clinical audit does not include many patients attending private practices, except for a small subset of the SVH patients who attended a bulk-billing (no cost to patients) private practice on the public hospital grounds, though in Australia CSII therapy is

more commonly provided in public hospitals than in private practice and in order to obtain their insulin pump most CSII users have private health insurance,(29). We acknowledge that there may be treatment differences between the two hospital sites and the bias toward CSII use in the SVH site (due to their interest in and early provision of CSII services in Australia) may impact results. We addressed this by analysing CSII and MDI users by hospital location and found similarly lower GV in the CSII groups. HbA1c measures were performed in different laboratories and likely by different methodologies, though all laboratories were NATA accredited and participants usually attended the same pathology provider. Given the observational nature of the study, we are unable to account for all differences between the MDI and CSII groups, including treatment adherence, motivation and health literacy. We note that the time interval between HbA1c measures is shorter for CSII than MDI, and this may reflect behavioural differences. However, time interval and number of HbA1c measures were statistically adjusted for in the data analyses. We did not record patient diabetes education provided to both groups, however all individuals attended clinics with access to diabetes educators, dieticians and clinicians, that were free of charge to them and usually at the same clinic visit. We acknowledge that more time may have been spent with CSII users for initial CSII education,(18), however the initial 12 months of HbA1c data following CSII commencement, when greater education time was likely provided, was excluded from the study. Therefore, the observed prolonged benefit on glycaemic variability is less likely to be due to initial education. In addition, other groups have demonstrated a benefit in glycaemic control with CSII therapy compared to MDI even when equal education time was provided,(16). We acknowledge that figures related to severe hypoglycaemia event rates, retrieved from medical records, may not be accurate.

Future research directions include confirmatory studies in both adult and paediatric groups with T1DM, linkage of both short and long-term measures of glucose variability to hard clinical events and the effects of pumps with RT-CGM, closed loop insulin delivery systems, bihormonal pumps and insulin adjunct therapies (such as SGLT2 inhibitors, metformin and incretin modulating drugs) on glycaemic variability. Mechanistic studies exploring the clinical, cellular and molecular effects of glycaemic variability are also of relevance. It is imperative that further research addresses the cost benefits of CSII therapy and of RT-CGM therapy to facilitate equitable technology access. Analyses of long-term outcome data to determine recommended HbA1c GV targets are also desirable.

In summary, this study has shown that CSII use is associated with lower HbA1c glycaemic variability in adults with T1DM. HbA1c variability, a simple and low cost measure, thought to modulate chronic diabetes complication risk, should be a routine tool to assess glycaemic control in clinical practice and in clinical research and trials.

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AUTHOR CONTRIBUTIONS

ES researched the RNS data, analysed the data and wrote the manuscript. RM contributed to RNS data collection and reviewed the manuscript. ASJ facilitated SVH data collection and reviewed the manuscript. DC contributed to SVH data collection.

AH reviewed the manuscript. DNO contributed to data generation and collection at SVH and reviewed the manuscript. GF contributed to data generation and collection at RNSH and reviewed the manuscript. AJJ contributed to study design, data generation and collection at SVH and contributed to writing of the manuscript. All authors contributed to data interpretation. AJJ is the guarantor.

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DATA SHARING

This study was a retrospective audit of two tertiary hospital medical records. We do not have ethics approval to share this data.

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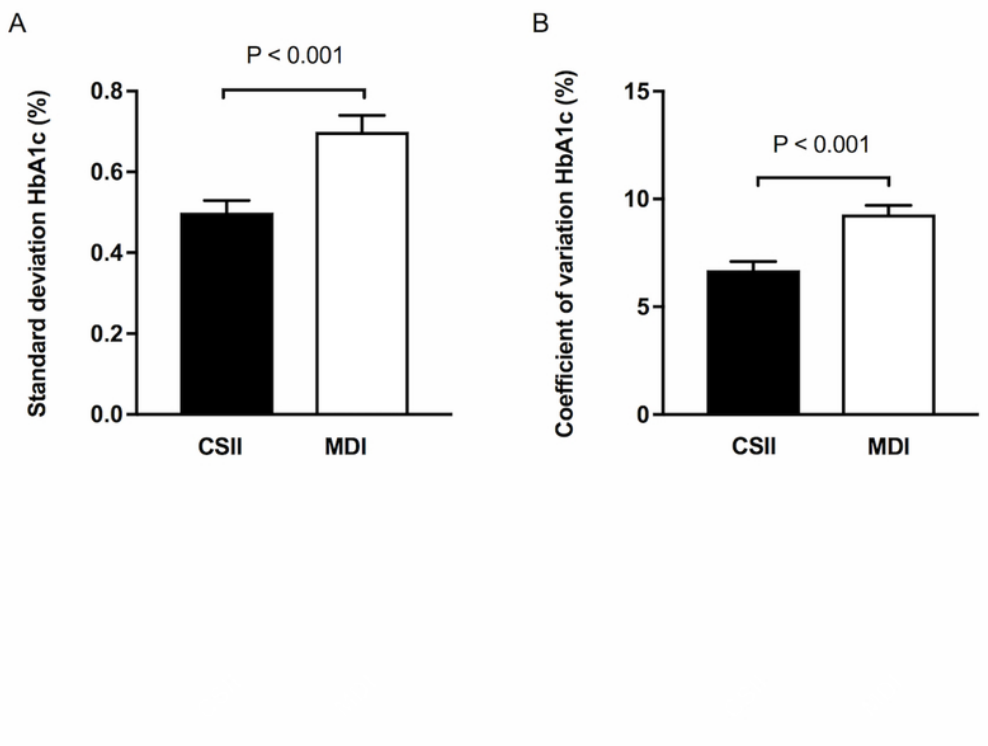
FIGURE LEGENDS

Figure 1. Long-term glycaemic (HbA1c) variability in 164 CSII and 342 MDI participants. Standard deviation of HbA1c over follow-up (0.5 ± 0.4 % [6 ± 6] mmol/mol) CSII, (0.7 ± 0.7 % [9 ± 8] mmol/mol) MDI) (A) and coefficient of variation (CV) of HbA1c over follow-up (6.7 ± 4.6 % [10 ± 10] mmol/mol) CSII, (9.3 ± 7.3 % [14 ± 13] mmol/mol) MDI) (B). Black bars = CSII; white bars = MDI. Graphed values are Mean +/- SEM. P < 0.001.

Figure 2. Long-term glycaemic variability by pre-defined age groups. Adults aged 18 - 26 y (n = 54 on CSII, n = 69 on MDI) standard deviation of HbA1c (0.6 ± 0.4 % [7 ± 8] mmol/mol) CSII, 0.9 ± 0.6 % [11 ± 7] mmol/mol) MDI; P = 0.001) (A) and coefficient of variation HbA1c over follow-up (7.3 ± 5.5 % [12 ± 16] mmol/mol) CSII, 10.5 ± 5.9 % [16 ± 12] mmol/mol) MDI ; P = 0.002) (B). Adults aged ≥ 26 y (110 CSII, 273 MDI) standard deviation of HbA1c (0.5 ± 0.4 % [5 ± 4] mmol/mol) CSII, 0.7 ± 0.7 % [9 ± 8] mmol/mol) MDI; P < 0.001) (C) and coefficient of variation over follow-up (6.3 ± 4.2 % [9 ± 5] mmol/mol) CSII, 8.9 ± 7.6 % [14 ± 13] mmol/mol MDI; P < 0.001**)** (D). Black bars = CSII; white bars = MDI. Graphed values are mean +/- SEM.

Figure 3. Long-term glycaemic variability in individuals changing from MDI to CSII therapy. Fifty-six adults changed from MDI to CSII therapy over the study. Mean HbA1c over follow-up (P < 0.001) (A), standard deviation of HbA1c (P < 0.001) (B) and coefficient of variation of HbA1c over follow-up (P = 0.004) (C). Black circles = MDI; white squares = CSII. Graphed values are mean pre- and post-therapy change.



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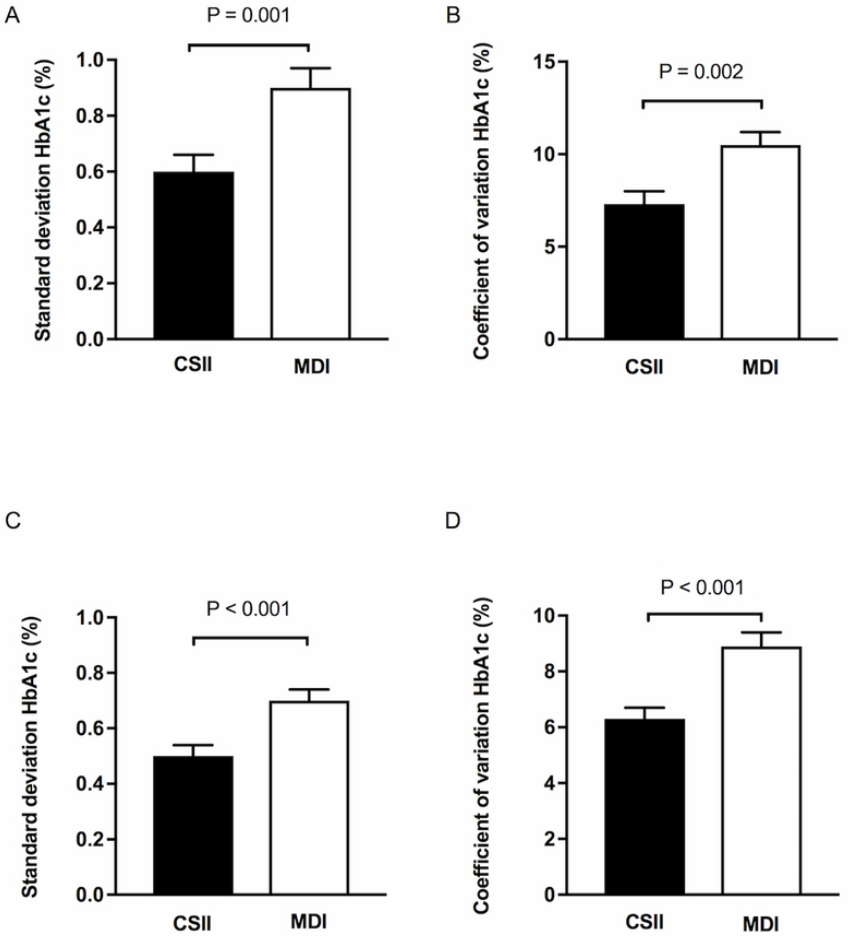

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66x93mm (300 x 300 DPI)

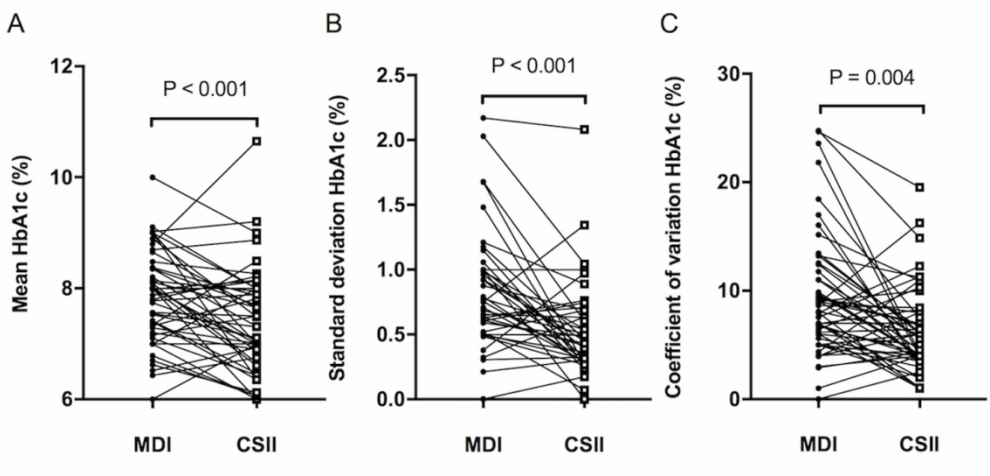


Figure 3. Long-term glycaemic variability in individuals changing from MDI to CSII therapy. Fifty-six adults changed from MDI to CSII therapy over the study. Mean HbA1c over follow-up ($P < 0.001$) (A), standard deviation of HbA1c ($P < 0.001$) (B) and coefficient of variation of HbA1c over follow-up ($P = 0.004$) (C). Black circles = MDI; white squares = CSII. Graphed values are mean pre- and post-therapy change.

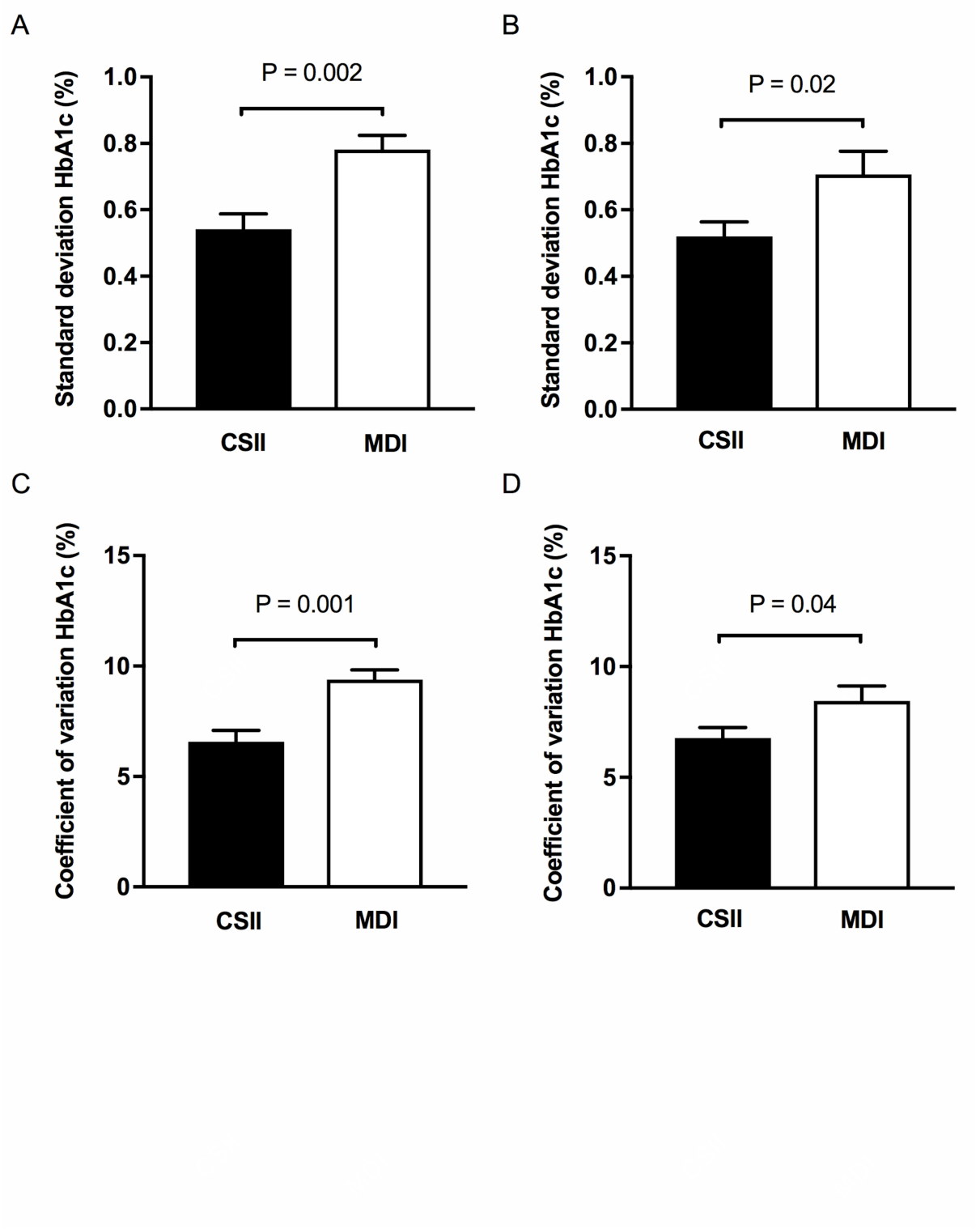
125x59mm (300 x 300 DPI)

Supplementary Table 1.! "#$%&'#!&('')'&*+)$,*&,!-.!'/0#*,!1$*(!234+!5!/$'6+*+,!63!#-&'*$-%7!

Location!	Royal North Shore Hospital!	St Vincent's Hospital	P value !
8!	9:;!	55<!	
"=»!?%!?@AA!	:B!?<;7:A!	CC!?DB7:A!	**<0.001**
EF+!?3+'),A!	9B±5C!	9C±5<!	G7<9!
H-I+%!?%!?@AA!	5B:!?C<A!	CD!?DBA!	**0.049**!
J+'),!-.!/$'6+*+,!	5K±5;!	5B±59!	G7;K!
J+'),!"=»!*(+)'43!	D±;!	K±9!	**0.026**!
L',&0#')!&-I4#$&'*$-%,!?%!?@AAM!	5C5!?;5A!	95!?9GA!	**0.04**!
=+N+)+!(34-F#3&'+I$'!?%!?@AAO!	B;!?<<A!	P!	-
=-&$-+&-%-I$&!,*'*0,!?/+&$#+AQ!	!	!	
E/N'%*'F+!R!S$,'/N'%*'F+!	!	!	
T/0&'*$-%!U!-&&04'*$-%!	:±<!	K±<!	**< 0.001**!
	:±<!	K±9!	**< 0.001**!
J+'),!.-##-1P04!!	97G±57:!	K7G±D7:!	**< 0.001**!!
V6E5&!I+',0)+,!?%A!	K±;!	5D±59!	**< 0.001**!
2$I+!6+*1++%!V6E5&!?/'3,A!	<9B±5:K!	<9K±5BD!	G7:B!
W+'%!V6E5&!!	!	!	
@!!	B7G±57D!!	K7K±57D!!	G7GC
XII-#RI-#Y!	XC;±5CY!	XCG±5<Y!	

S'*'! ')+! I+'%! ±! ,*'%/')/! /+N$'*$-%Z! -)! %! ?4+)&+%*'F+A7! ! M! W$&)-N',&0#')! '%/! I'&)-N',&0#')!&-I4#$&'*$-%,7!!O!E%3!+4$,-/+!-.!,+N+)+!(34-F#3&+'I$'!)+&-)/+/!$%!*(+!I+/$&'#!)+&-)/7!

!



Supplementary Figure 1. [-%FP*+)ı! F#3&'+ı$&! N')$'6$#$*3! $%! "=»! '%/! WS›!

4')*$&$4'%*,!63!(-,4$*'#!#-&'*$-%7!!=*'%/')/!/+N$'*$-%!-.!V6E5&!-N+)!.-##-1P04!?G7D!±!

G7D!@!XC!±!KY!ıı-#Rı-#A!"=»Z!?G7B!±!G7K!@!X:!±!BY!ıı-#Rı-#A!WS›Z!\-3'#!8-)*(!=(-)+!

V-,4$*'#!?EA!'%/!,*'%/')/!/+N$'*$-%!-.!V6E5&!?G7D!±!G7;!@!XC ±!;Y!ıı-#Rı-#A!"=»Z!

?G7K!±!G7D!@!X55!±!:Y!ǁ-#RǁA!WS>Z!=*!L$%&+%*],!V-,4$*'#!?^A7!!"-+..$&$+%*!-.!N')$'*$-%!-.!V6E5&!-N+)!.-##-1P04!?C7C!±!D75!@!X5G!±!5<Y!ǁ-#RǁA!"=>>Z!?:7;!!±!K7K!@!X59!±!55Y!ǁ-#RǁA!WS>Z!\-3'#!8-)*(!=(-)+!V-,4$*'#!?"A!'%/!&-+..$&$+%*!-.!N')$'*$-%!-.!V6E5&!?C7B!±!97B!@!X:!±!DY!ǁ-#RǁA!"=>>!'%/!?B7;±!;7C!@!X<5!±!<GY!ǁ-#RǁA!WS>Z!=*!L$%&+%*],!V-,4$*'#!?SA7!!^#'&_!6'),!'!"=>>a!1($*+!6'),!'!WS>7!!b)'4(+/!N'#0+,!')+!W+'%!cRP!=TW7!

Supplementary Table 2.!"#$%&'#!&('')'&*+)$,*$&,!-.!'/0#*,!1$*(!234+!5!/$'6+*+,!63!'F+!,06F)-04,!-.!5BP<C!3+'),!'%/!F)+'*+)!*('%!-)!+d0'#!*-!<C!3+'),7!

	18-26 y!			≥ 26 y!		
	CSII !	MDI !	P value !	CSII !	MDI !	P value !
8!	D;!	C:!	!	55G!	<K9!	!
EF+!?3+'),A!	<G±<!	<G±<!	G7DK!	;G±55!	;;±5;!	**0.009!**
H-I+%!?%!?@AA!	9;!?C9A!	9G!?;9A!	**0.03!**	K<!?CDA!	55B!?;9A!	**<0.001!**
J+'),!-.! /$'6+*+,!	:±D!	B±C!	G7;B!	<5±59!	<G±5D!	G7DC!
J+'),!"=»! *(+)'43!	C±9!	8RE!	P!	C±;!	8RE!	P!
L',&0#')! &-I4#$&'*$-%,! ?%!?@AAM!	D!?:A!	5G!?5DA!	G79D!	;;!?;5A!	5<<!?DGA!	G75<!
=+N+)+! (34-F#3&'+I$'! ?%!?@AAO!	;!?5GA!	D!?5GA!	G7:C!	5G!?5BA!	CD!?<KA!	G75K!
=-&$-+&-%-I$&! ,*'*0,!?/+&$#+AQ!	! !	! !	! !	! !	! !	! !
E/N'%*'F+R!	:±<!	:±<!	G75<!	B±9!	:±<!	**<0.001!**
S$,'/N'%*'F+!	!	!	!	!	!	
T/0&'*$-%!U! -&&04'*$-%!	:±<! !	:±<! !	G7;5!	B±9!	:±<!	**<0.001!**
=*0/3!.-##-1P 04!?3+'),A!	9±<7C!	97C±;7G!	G7DG	;7D±<7K!	;7<±;7G!	G7D<!
V6E5&! I+',0)+I+%*,! ?%A!	K±C!	:±5G!	G7;G!!	:±B!	B±B!	G7;9!
2$I+!6+*1++%! V6E5&!?/'3,A!	<<5±<9K!	<GD±5<K!	G7C<! !	<G±595!	<C5±<5C!	**0.019**
W+'%!V6E5&!! @!! XI I-#RI-#Y!	! B79±579! XCC±5;Y!	! B7D±57C! XCB±5BY!	! G7D<!!	! K7C±575! XD:±5<Y!	! K7:±57;! XC<±5CY!!	**0.034**!

S'*'! ')+! I+'%! ±! ,*'%/')/! /+N$'*$-%Z! -)! %! ?4+)&+%*'F+A7! ! M! W$&)-N',&0#')! '%/R-)! I'&)-N',&0#')!&-I4#$&'*$-%,7!!O!E%3!+4$,-/+!-.!,+N+)+!(34-F#3&'+I$'!)+&-)/+/!$%! *(+!I+/$&'#!)+&-)/7!

!

!

Supplementary Table 3.!![- %FP*+) I !F#3& ' + I $&!N ')$ ' 6$#$*3!$%!$% / N / 0 ' # , !& (' %F$%F!.) - I ! WS›!*-! " =››!* (+) ' 43!63!F+% / +)7!!!

Gender!	**Male (n = 15)!** **!**			**Female (n= 41)**		
	MDI (pre)	**CSII (post)**	**P value**	**MDI (pre)**	**CSII (post)**	**P value**
W+ ' %!V6E5&!! @!! X I I -#R I -#Y!	! K7B±G7K!! XC<±BY!	! K7 ; ±G7B! XDK±BY!	! **0.014**	! K7 : ±G7B! XC<± : Y!	! K79±57G! XDK±5GY!	! **0.001**
=S!V6E5&!! @!! X I I -#R I -#Y!	! G7C±G7 ; ! XK± ; Y**!**	! G7 ; ±G7<! X ; ±<Y**!**	! **0.007!**	! G7B±G7D! XB±DY!	! G7D±G7 ; ! XD± ; Y!	! **<0.001**
" L!V6E5&!! @!! X I I -#R I -#Y!	! K7 : ± ; 7D! X55±CY**!**	! D75±97<! XK±DY**!**	**0.013!**	: 7K±D7B! X5 ; ±B!Y	! C7 ; ± ; 75! X : ±CY	**0.001**

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	3
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	6

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-7
Bias	#9	Describe any efforts to address potential sources of bias	7-8
Study size	#10	Explain how the study size was arrived at	n/a
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
Statistical methods	#12c	Explain how missing data were addressed	n/a
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8

Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	8
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9-11
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
Main results	#16b	Report category boundaries when continuous variables were categorized	9-11
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	16
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12-17
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

BMJ Open

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HbA1c Variability in Adults With Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion (CSII) Therapy Compared To Multiple Daily Injection (MDI) Treatment.

Type 1 Diabetes Insulin Delivery Mode and Glycaemic Variability

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ABSTRACT

Objective: To determine if continuous subcutaneous insulin infusion (CSII) therapy is associated with lower HbA1c variability (long-term glycaemic variability GV) relative to multiple daily injection (MDI) treatment in adults with Type 1 diabetes (T1DM).

Design: Retrospective audit

Setting and participants: Clinic records from 506 adults with T1DM from two tertiary Australian hospitals.

Outcome measures: Long-term GV was assessed by HbA1c standard deviation (SD) and coefficient of variation (CV) in adults on established MDI or CSII therapy, and in a subset changing from MDI to CSII.

Results: Adults (n = 506, (164 CSII), 50% women, mean ± SD age 38.0 ± 15.3 yrs, 17.0 ± 13.7yrs diabetes, mean HbA1c 7.8 ± 1.2% [62 ± 13 mmol/mol] on CSII, 8.0 ± 1.5% [64 ± 16 mmol/mol] on MDI) were followed for 4.1 ± 3.6 yrs. CSII use was associated with lower GV (HbA1c SD: CSII vs. MDI 0.5 ± 0.41% [6 ± 6 mmol/mol] vs. 0.7 ± 0.7% [9 ± 8 mmol/mol] and CV: CSII vs. MDI 6.7 ± 4.6% [10 ± 10 mmol/mol] vs. 9.3 ± 7.3% [14 ± 13 mmol/mol], both P<0.001. Fifty-six adults (73% female, age 36 ± 13 yrs, 16 ± 13 yrs diabetes, HbA1c 7.8 ± 0.8% [62 ± 9 mmol/mol] transitioned from MDI to CSII. Mean HbA1c fell by 0.4%. GV from one-year post-CSII commencement decreased significantly, HbA1c SD pre vs. post-CSII 0.7 ± 0.5% [8 ± 5 mmol/mol] vs. 0.4 ± 0.4% [5 ± 4 mmol/mol]; P<0.001, and HbA1c CV 9.2 ± 5.5% [13 ± 8 mmol/mol] vs. 6.1 ± 3.9% [9 ± 5 mmol/mol]; P<0.001.

Conclusions: In clinical practice with T1DM adults relative to MDI, CSII therapy is associated with lower HbA1c GV.

Strengths and limitations of this study

- A relatively large real-world observational study across a wide age and socioeconomic status from two tertiary hospitals allows for generalisability of results
- HbA1c GV, a simple low-cost mathematical measure, assessed using two formulae, with similar results, and in venous blood in accredited laboratories
- Analysis in those on established MDI or CSII therapy and in a subset who changed modalities, and a control group of MDI users who remained on MDI.
- Not a randomised study therefore not able to completely adjust for possible behavioural differences
- Complements and extends a prior publication by the group in which short-term GV based on interstitial fluid Continuous Glucose Monitoring (CGM) measures did not differ by insulin delivery modality.

Keywords: Glycaemic variability, Type 1 diabetes, Continuous subcutaneous insulin infusion, Multiple daily injection.

INTRODUCTION

Type 1 diabetes (T1DM) is characterised by day-to-day glucose fluctuations, much more so than in Type 2 diabetes (T2DM). The Diabetes Control and Complications Trial (DCCT) established that near normal glycaemic control, reflected by HbA1c levels, substantially reduces the risk of long-term vascular and neurologic complications,(1). Short-term GV can be assessed by analysing multiple daily capillary blood glucose levels, or by continuous (interstitial fluid) glucose monitoring (CGM), and at cellular level has been demonstrated,(2, 3), to increase oxidative stress,

inflammation and epigenetic changes,(4). Longer term GV can be assessed by analysing variation in HbA1c levels over time, usually reported as HbA1c standard deviation (SD) and /or coefficient of variation (CV), and has been implicated as an independent risk factor for the development of chronic complications in people with both T1DM and T2DM,(4-7). Short and long term GV do not always correlate.

In people with T1DM, insulin can be delivered by either multiple daily injections (MDI) or by continuous subcutaneous insulin infusion (CSII). There is emerging epidemiologic evidence that CSII use (independent of HbA1c levels) is associated with a reduction in chronic complications in both adult and paediatric age groups and with reduced cardiovascular mortality in adults with T1DM,(5, 8). Although CSII use is generally associated with lower HbA1c levels compared to MDI,(9), there are no consistent reported associations in the literature between short-term and long-term GV and insulin delivery mode. CSII without frequent real-time continuous glucose monitoring (RT-CGM) is usually associated with similar short-term GV as MDI,(10-12), including in our previous study in T1DM adults in the same setting as herein. With regard to long-term GV, there is only one published study, and that is in a paediatric setting, which demonstrated long-term GV benefit of CSII compared to MDI over a three year period,(13).

The primary aim of the present study was to examine HbA1c GV in adults with T1DM treated by CSII and MDI therapies predominantly without RT-CGM use in the real-world setting, not in a clinical trial. Hence, we compared HbA1c SD and CV over years in adults with T1DM treated by CSII, to those of adults treated by MDI, and also in those changing from MDI to CSII therapy. Results were analysed with and without

adjustment for mean HbA1c levels. As glycaemic benefit of technology may differ by user age group,(14) we also compared results in emerging adults (aged 18-26 years) and more mature adults (≥ 26 years).

MATERIALS AND METHODS

Subjects

We undertook a retrospective audit of clinical records of adults with T1DM attending outpatient diabetes clinics at two independent tertiary referral hospitals (Royal North Shore Hospital (RNSH), Sydney and St Vincent's Hospital (SVH), Melbourne, Australia). Data from 1995-2018 were collected. Participants were excluded if they were less than 18 years old, pregnant or breast-feeding, had less than two HbA1c results on record, or had less than one year of CSII therapy. The insulin pumps were not used with continuous real-time CGM (RT-CGM). Flash glucose monitoring became available in Australia in late 2016 and was not subsidised, and RT-CGM only became subsidised for those under 21 years of age in 2017, therefore these modalities were rarely used in our public hospital settings during the study period. The study was approved by the Human Research Ethics Committees of the Northern Sydney Local Health District and St Vincent's Hospital Melbourne.

Patient and Public Involvement.

No patient involved. As this was a retrospective audit, it was not appropriate or possible to directly involve patients or public in this work.

Data collection.

All HbA1c results were obtained from laboratories accredited with the National Association of Testing (NATA) and the Royal College of Pathologists of Australasia (RCPA). All NATA accredited laboratories are required to participate in a standardisation program and to standardise HbA1c measurements to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) guidelines. Patients usually had their laboratory tests performed by the same pathology provider. Demographic and clinical parameters (including insulin treatment modality, chronic complication status, incidence of severe hypoglycaemia (defined as any episode of hypoglycaemia requiring assistance from another person for recovery) were obtained from the medical records. Socioeconomic status was estimated via the subject's home address postcode (zip code) via the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA), 2011,(15).

Glycaemic variability

HbA1c GV was assessed through the mean within-individual SD and CV ((SD HbA1c / mean HbA1c) x 100) of available HbA1c levels. If individuals had changed treatment modality from MDI to CSII, the initial 12 months of HbA1c assessments post-CSII initiation were excluded, (as HbA1c usually decreases significantly during this time),(16, 17).

Statistical analyses

Data were stored in EXCEL (2010) and IBM SPSS Statistics (version 22) and Graph Pad Prism (version 6.0) were used for data analyses, including descriptive statistics, paired and independent T-tests, Chi-square tests and Pearson correlation coefficients. Statistical significance was taken at $P < 0.05$. Results were analysed as a whole and

with subgroup analyses by age (18 - < 26 years and ≥ 26 years) and by gender. A further subgroup analysis assessed the impact of insulin modality on GV across tertiles of mean HbA1c using a general linear model. Participants on established insulin therapies (MDI or CSII) were analysed, as were a group of individuals analysed pre- and post-insulin modality change (MDI to CSII). The participants who changed from MDI to CSII were matched (by age, baseline HbA1c and years of follow up) to a subgroup of adults who remained on MDI. GV was compared pre- and after 1-year post-modality change in the MDI to CSII group, and pre- and post a matched duration of follow-up in the group who remained on MDI. Where applicable, results were analysed with adjustment by least squares method for hospital location, gender, vascular complications, severe hypoglycaemia, age, diabetes duration, mean HbA1c levels, number of included HbA1c measurements, time between HbA1c measurements, years of follow-up, average decile of socioeconomic advantage and disadvantage and decile of education and occupation.

RESULTS

Subject demographics.

Baseline clinical characteristics of 506 adults with T1DM studied over time whilst on a single insulin delivery modality are shown in Table 1, with participants from both hospitals merged. The group is also described based on insulin delivery mode. SVH participants (n = 112) were more likely to be treated by CSII compared to the RNSH participants (66 (59 %) vs. 98 (25 %); P < 0.001) as SVH was an earlier adopter of CSII into their clinical practice. SVH subjects were more likely to be female, had fewer vascular complications, lower socioeconomic status, longer years of HbA1c follow-up and more available HbA1c measurements compared to the RNSH participants

(Supplementary Table 1). The (merged sites, Table 1) CSII users were younger, more likely to be female (in keeping with a noted national trend,(18), and less likely to have vascular complications or a previous documented episode of severe hypoglycaemia and had a significantly lower socioeconomic status relative to the MDI group. There were no significant differences in the years of follow-up between the CSII and MDI groups, nor the number of HbA1c measurements included in the study. CSII users had a slightly shorter mean ± SD time between HbA1c measurements compared to MDI users (213 ± 173 vs. 249 ± 203) days respectively; P = 0.047). There were no significant differences in mean HbA1c levels nor the number of measures evaluated over the study period between the CSII and MDI groups (HbA1c mean (SD) 7.8 ± 1.2 % [62 ± 13] mmol/mol (n = 8 HbA1c measures) CSII, and HbA1c mean (SD) 8.0 ± 1.5 % [64 ± 16] mmol/mol (n = 8 HbA1c measures) MDI; P = 0.13).

Table 1 Clinical characteristics of adults with Type 1 diabetes.

	CSII	**MDI**	**P value**
N	164	342	
Age (years)	34±13.4	39±15.8	**< 0.001**
Women (n (%))	106 (65)	148 (43)	**< 0.001**
Years of diabetes	17±12.5	18±14.3	0.55
Years CSII therapy	6.0±3.6	N/A	-
Vascular complications (n (%))*	49 (30)	143 (42)	**0.008**
Severe hypoglycaemia (n (%))†	14 (14)	70 (21)	**0.045**
Socioeconomic status (decile): Advantage / Disadvantage Education& occupation	 8±2.3 8±2.4	 9±1.9 9±1.9	 **0.005** **< 0.001**
Years follow-up	4.1±2.7	4.1±4.0	0.90
HbA1c measures (n)	8±7	8±8	0.96
Time between HbA1c (days)	213±173	249±203	**0.047**
Mean HbA1c % [mmol/mol]	 7.8±1.2 [62±13]	 8.0±1.5 [64±16]	 0.13

Data are mean ± standard deviation, or n (percentage). * Microvascular and/or macrovascular complications. † Any episode of severe hypoglycaemia recorded in the medical record.

Lower HbA1c GV in CSII users.

CSII-users had significantly lower long-term variability in HbA1c as reflected by both HbA1c SD and CV measures (Fig. 1). The difference remains statistically significant after adjustment (least squares) for gender, hospital location, chronic complication status, severe hypoglycaemia, baseline HbA1c levels, years of follow-up, number of HbA1c measures, time between HbA1c tests, diabetes duration, socioeconomic status and age (both P = 0.003). In order to account for possible differences in glycaemic control by hospital location, insulin modality treatments were compared separately at the two sites and similar significantly lower GV was observed in CSII (vs. MDI) users (Supplemental Figure 1). GV was also analysed by gender, and similarly lower HbA1c SD and CV was observed in CSII compared to MDI participants in both men and women. HbA1c SD in women ((0.6 ± 0.5 % [7 ± 6] mmol/mol) CSII, (0.8 ± 0.7 % [9 ± 8] mmol/mol) MDI, P = 0.005) and in men ((0.4 ± 0.3 % [5 ± 3] mmol/mol) CSII, (0.8 ± 0.7 % [9 ± 8] mmol/mol) MDI, P = 0.002). HbA1c CV in women ((7 ± 5 % [11 ± 12] mmol/mol) CSII, (9 ± 8 % [14 ± 12] mmol/mol) MDI, P = 0.02) and in men ((6 ± 3 % [8 ± 4] mmol/mol) CSII, (9 ± 7 % [15 ± 13] mmol/mol) MDI, P = 0.002).

Similar pattern of HbA1c variability in adults with T1DM by age group and insulin treatment modality.

Analysis by pre-determined age-subgroups (18 - < 26 years and ≥ 26 years) demonstrated that mean HbA1c was lower in the older CSII vs. older MDI users: (7.6 ± 1.1 % [59 ± 12] mmol/mol) CSII and 7.9 ± 1.4 % [62 ± 16] mmol/mol) MDI; P = 0.034), although there was no statistically significant difference in the 18 - < 26 year old group: (CSII vs. MDI; 8.3 ± 1.3 % [66 ± 14] mmol/mol) vs. 8.5 ± 1.6 % [68 ± 18] mmol/mol) (Supplementary Table 2). Furthermore, there were significantly lower HbA1c SD and CV over follow-up amongst both age groups treated with CSII versus those treated with MDI (Figure 2).

HbA1c variability lower in CSII users across all tertiles of mean HbA1c mean. HbA1c GV was assessed by tertile of mean HbA1c (tertile 1 HbA1c ≤ 7.2% [55 mmol/mol], tertile 2 HbA1c ≤ 8.3% [67 mmol/mol], tertile 3 HbA1c ≤ 15.0% [140 mmol/mol] (Table 2). HbA1c CV was significantly lower in CSII vs. MDI users at any tertile of mean HbA1c, whereas HbA1c SD was lower in CSII users only in tertiles 2 and 3. There was no interaction between HbA1c SD and CV and insulin modality at any tertile of mean HbA1c (P = 0.28 and P = 0.65 for SD and CV respectively).

Table 2 HbA1c GV by tertile of mean HbA1c.

	Tertile	CSII	MDI	P value
HbA1c SD	1	0.4±0.2	0.5±0.4	0.99
	2	0.5±0.4	0.6±0.5	0.99
	3	0.8±0.5	1.1±0.9	**0.008**
HbA1c CV	1	5.3±3.1	7.5±5.5	**0.001**
	2	6.5±4.8	8.3±6.5	**0.04**

	3	8.6±5.4	11.7±8.7	**0.007**

Data are mean ± standard deviation

Lower HbA1c GV in adults changing from MDI to CSII.

Fifty-six adults chose to change their insulin delivery modality from MDI to CSII. These individuals had a mean ± SD age of 36 ± 14 years (35 ± 12 for women and 40 ± 17 for men), diabetes duration of 16 ± 13 years and 73% were female. The observation period included 4.3 ± 3.5 years on MDI and 4.6 ± 4.7 years on CSII after excluding the initial 12 months on CSII (P = 0.56), during which the mean HbA1c fell significantly. There was a similar, significantly greater number of HbA1c measurements used to determine GV whilst on CSII compared to MDI; mean ± SD (n = 10 ± 8 and n = 9 ± 7 respectively; P = 0.002), and a shorter duration between HbA1c measurements whilst on CSII compared to MDI (215 ± 158 and 336 ± 501 days respectively; P < 0.001). HbA1c levels significantly decreased following the switch to CSII, including after excluding the first 12 months of HbA1c following modality change, mean ± SD (7.8 ± 0.8 % [62 ± 9] mmol/mol) MDI vs. (7.4 ± 0.9 % [57 ± 10] mmol/mol) CSII; P < 0.001) (Fig. 3 a). In addition, CSII use lowered HbA1c variability, with CSII commencement decreasing both HbA1c SD (0.7 ± 0.5 % [8 ± 5] mmol/mol) MDI vs. 0.4 ± 0.4 % [5 ± 4] mmol/mol) CSII; P < 0.001) and HbA1c CV (9.2 ± 5.5 % [13 ± 8] mmol/mol) MDI vs. (6.1 ± 3.9 % [9 ± 5] mmol/mol) CSII; P = 0.004) (Fig. 3 b, c). There were no statistically significant correlations between the improvement in HbA1c SD or CV with baseline variables such as age and diabetes duration (data not shown). The change in HbA1c,

HbA1c SD and CV was analysed by gender and there were similar improvements in both men and women (Supplementary Table 3)

The 56 adults who changed from MDI to CSII were matched (by age, baseline HbA1c and duration of follow-up) to 56 adults who remained on MDI (Table 3). There were no statistically significant differences in baseline HbA1c, age, years of follow-up nor time between HbA1c measurements. Individuals who changed to CSII had more HbA1c values following the modality change, compared to those who remained on MDI (Post CSII n= 10 ± 8 vs. Time 2 remained on MDI n=8 ± 6; P = 0.048). In contrast to the adults who changed from MDI to CSII, the adults who remained on MDI did not significantly improve mean, standard deviation or coefficient of variation HbA1c.

Table 3. Glycaemic variability in individuals changing from MDI to CSII compared to matched individuals remaining on MDI

	MDI to CSII			**Remained on MDI**		
	Pre CSII	**Post CSII**	**P value***	**Time 1**	**Time 2**	**P value****
N	56			56		
Age (years)	36±13.5			38±15.7		
Baseline HbA1c % [mmol/mol]	7.9±1.4 [63±15.7]			7.9±1.5 [63±16.3]		
Study follow-up (years)	10.0±5.9			9.4±6.5		
HbA1c measurements (n)	9±7	10±8	**0.002**	8±8	8±6	1.00
Time between HbA1c (days)	336±501	215±158	**<0.001**	281±206	238±166	0.18
Mean HbA1c % [mmol/mol]	7.8±0.8 [62±9)]	7.4±0.9 [57±10]	**<0.001**	7.7±1.1 [61±12]	7.7±1.2 61±13]	0.64
HbA1c SD % [mmol/mol]	0.7±0.5 [8±5]	0.4±0.4 [5±4]	**<0.001**	0.6±0.5 [7±5]	0.5±0.3) [5±3]	0.10

HbA1c CV%						
%	9.2±5.6	6.1±3.9	**0.004**	7.8±5.2	6.4±3.5	0.12
[mmol/mol]	[13±8]	[9±5]		[11±7]	[9±5]	

Data are mean ± standard deviation. *Pre-CSII (on MDI) vs. Post-CSII **Remains on MDI time 1 vs. time 2.

DISCUSSION

In this retrospective audit of 506 adults with T1DM from two independent Australian tertiary referral diabetes centres, we report the novel finding that CSII therapy was associated with lower long-term (HbA1c) glycaemic variability than MDI therapy, despite similar mean HbA1c levels across the two modalities. Participants treated by CSII (without regular RT-CGM, low glucose suspend, predictive low glucose suspend or closed loop functions and without regular flash glucose monitoring) had significantly lower HbA1c variability reflected by both SD and CV measures. GV amongst CSII users remained significantly lower after adjustment for age, gender, diabetes duration, hospital location, socioeconomic status, chronic complication status, severe hypoglycaemia, baseline HbA1c levels, years of follow up, number of HbA1c measures and time between HbA1c measures. The groups of emerging and more mature adults showed similar HbA1c GV responses, as did males and females. The impact of CSII on HbA1c CV was consistent across all tertiles of mean HbA1c. Similar statistically significant reductions in both measures of HbA1c GV were seen with 56 patients who changed from MDI to CSII therapy, whilst MDI users who remained on MDI for a similar follow-up time did not significantly change their HbA1c GV.

Glycaemic variability has been identified as an independent risk factor for the chronic complications of diabetes,(6, 7) and in a large Swedish diabetes registry based

epidemiologic study CSII use was independently associated with a significantly lower risk of cardiovascular complications and death,(5). This finding may at least partly relate to GV, and fluctuations between hyper- and hypoglycaemia inducing inflammation and oxidative stress and epigenetic changes,(2, 4). We speculate that lower HbA1c variability, as associated with CSII use in our study, may underpin or at least contribute to the observed reduced chronic complication and death rates amongst CSII users,(5, 6, 8, 19). HbA1c variability has been implicated in the development of microvascular complications in T1DM (20), although the associations with retinopathy have not been as consistent reported as for nephropathy (6, 21-25). Only one study has found an independent association of HbA1c GV with cardiovascular events in T1DM (26). There have been no studies which have reported an association with increased HbA1c GV and mortality risk, although a number of groups have found such an association in Type 2 Diabetes (27-29).

There may be divergent effects of insulin treatment modality on measures of short-term (blood or interstitial fluid glucose level based) and long-term (HbA1c) glucose variability. We have previously demonstrated in 119 adult individuals with T1DM (77 MDI and 42 CSII users) no statistically significant difference in any of 12 accepted measures of short-term glucose variability over 48 hours when analysed by masked CGM,(30). Unfortunately, due to the costly nature of CGM in Australia at the time of the study, when it was predominantly self-funded, only a very small subset of patients used episodic RT-CGM and usually less than the 70% of time described as needed to improve glycaemia(31). These negative results are comparable to other studies assessing short-term (CGM) glucose variability in CSII users,(8, 12, 32) all of which assessed GV over a maximum of three days. Recent consensus guidelines have

recommended that CGM should occur for fourteen days to accurately assess glucose profile (31), and therefore the inconsistencies in GV benefit may reflect inadequate CGM data. Furthermore, improvements in short-term GV with CSII may be impacted by deterioration in HbA1c overtime (32), highlighting the importance of assessing long-term GV. Even in studies in which HbA1c levels were significantly improved by CSII or CSII with RT-CGM, short-term GV did not improve in all participants,(14, 33). More recent studies, including those achieving tight glycaemic control,(34), or using RT-CGM and insulin pumps with low-glucose suspend functions,(35), overnight closed loop insulin delivery,(36) or hybrid closed loop CSII,(37) have demonstrated improved short-term glucose variability. The benefit of RT-CGM on short-term GV in the absence of CSII therapy has been demonstrated in the DIAMOND and GOLD trials (38, 39) which may be a more cost-effective therapeutic option. However, none of these studies have reported HbA1c GV change. We anticipate that technological advances in pumps, sensors and control algorithms will continue to reduce short-term GV, and also long-term GV, in both adults and children with T1DM. It is important to consider whether study participants are in clinical trials, with their inherent selection biases and often additional participant support, or in clinical practice (as herein).

Strengths and limitations. This is a real-world study, rather than a clinical trial with potential for selection bias and the Hawthorne (observer) effect,(40). We assessed relatively large numbers of adults with T1DM from two independent tertiary hospitals and did so over a relatively long follow-up period with good numbers of HbA1c measures from accredited pathology services in both CSII and MDI users, and fortunately with similar mean HbA1c in both groups. We report both HbA1c CV and SD and not unexpectedly (given the mathematical derivation of SD from CV), find

similar results with both measures. The study is strengthened by the analysis of GV over a wide adult age range, as well as by pre-established age groups and by consideration of gender. We assessed the impact of GV amongst tertiles of mean HbA1c, and in contrast to previous studies (10), found that the impact of insulin modality on HbA1c CV persisted across varying levels of glycaemic control. As well as a longitudinal observational study there was also an observation of a group changing from MDI to CSII therapy, and comparison to a matched group who remained on MDI. There was a similar number of HbA1c measurements included in the MDI and CSII groups over a long period of follow up (four years in established users, and 10 years in those who changed from MDI to CSII). HbA1c GV is a low cost measure that could be calculated from routine clinical care data (of HbA1c levels), hence is readily applicable to clinical practice (particularly in the era of electronic medical records), and clinical trials. Study limitations are that this clinical audit does not include many patients attending private practices, except for a small subset of the SVH patients who attended a bulk-billing (no cost to patients) private practice on the public hospital grounds, though in Australia CSII therapy is more commonly provided in public hospitals than in private practice and in order to obtain their insulin pump most CSII users have private health insurance,(41). We acknowledge that there may be treatment differences between the two hospital sites and the bias toward CSII use in the SVH site (due to their interest in and early provision of CSII services in Australia) may impact results. We addressed this by analysing CSII and MDI users by hospital location and found similarly lower GV in the CSII groups. HbA1c measures were performed in different laboratories and likely by different methodologies, though all laboratories were NATA accredited and participants usually attended the same pathology provider. Given the observational nature of the study, we are unable to

account for all differences between the MDI and CSII groups, including treatment adherence, motivation and health literacy. We note that the time interval between HbA1c measures is shorter for CSII than MDI (mean difference of 36 days) and this may reflect behavioural differences or more healthcare involvement. However, time interval and number of HbA1c measures were statistically adjusted for in the data analyses. We did not record patient diabetes education provided to both groups, however all individuals attended clinics with access to diabetes educators, dieticians and clinicians, that were free of charge to them and usually at the same clinic visit. We acknowledge that more time may have been spent with CSII users for initial CSII education,(18), however the initial 12 months of HbA1c data following CSII commencement, when greater education time was likely provided, was excluded from the study. Therefore, the observed prolonged benefit on glycaemic variability is less likely to be due to initial education. Other groups have examined the impact of CSII therapy compared to MDI on glycaemic control when equal education time is provided (16, 42). The results have not been consistent, and a recent RCT failed to show clinical and economic benefit of CSII (42). Neither study measured long-term GV. We acknowledge that figures related to severe hypoglycaemia event rates, retrieved from medical records, may not be accurate.

Future research directions include confirmatory studies in both adult and paediatric groups with T1DM, linkage of both short and long-term measures of glucose variability to hard clinical events and the effects of pumps with RT-CGM, closed loop insulin delivery systems, bihormonal pumps and insulin adjunct therapies (such as SGLT2 inhibitors, metformin and incretin modulating drugs) on glycaemic variability. Mechanistic studies exploring the clinical, cellular and molecular effects of glycaemic

variability are also of relevance. It is imperative that further research addresses the cost benefits of CSII therapy and of RT-CGM therapy to facilitate equitable technology access. Analyses of long-term outcome data to determine recommended HbA1c GV targets are also desirable.

In summary, this study has shown that CSII use is associated with lower HbA1c glycaemic variability in adults with T1DM. HbA1c variability, a simple and low cost measure, thought to modulate chronic diabetes complication risk, should be a routine tool to assess glycaemic control in clinical practice and in clinical research and trials.

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AUTHOR CONTRIBUTIONS

ES researched the RNS data, analysed the data and wrote the manuscript. RM contributed to RNS data collection and reviewed the manuscript. ASJ facilitated SVH data collection and reviewed the manuscript. DC contributed to SVH data collection. AH reviewed the manuscript. DNO contributed to data generation and collection at SVH and reviewed the manuscript. GF contributed to data generation and collection at RNSH and reviewed the manuscript. AJJ contributed to study design, data generation and collection at SVH and contributed to writing of the manuscript. All authors contributed to data interpretation. AJJ is the guarantor.

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COMPETING INTERESTS

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DATA SHARING

This study was a retrospective audit of two tertiary hospital medical records. We do not have ethics approval to share this data.

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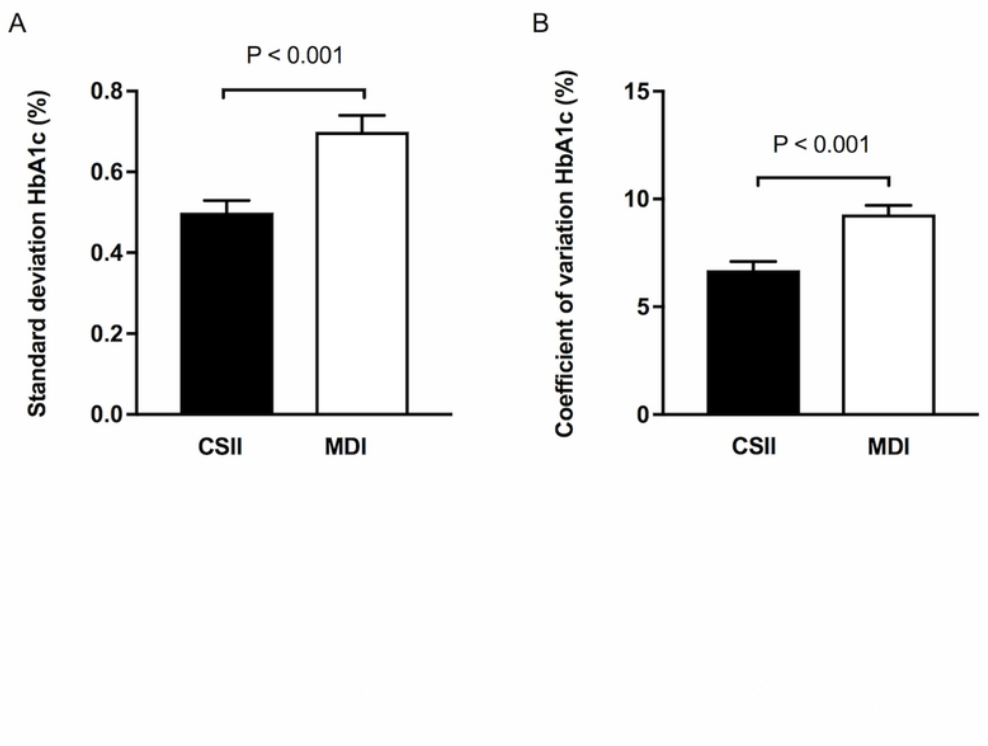
FIGURE LEGENDS

Figure 1. Long-term glycaemic (HbA1c) variability in 164 CSII and 342 MDI participants. Standard deviation of HbA1c over follow-up (0.5 ± 0.4 % [6 ± 6] mmol/mol) CSII, (0.7 ± 0.7 % [9 ± 8] mmol/mol) MDI) (A) and coefficient of variation (CV) of HbA1c over follow-up (6.7 ± 4.6 % [10 ± 10] mmol/mol) CSII, (9.3 ± 7.3 % [14 ± 13] mmol/mol) MDI) (B). Black bars = CSII; white bars = MDI. Graphed values are Mean +/- SEM. P < 0.001.

Figure 2. Long-term glycaemic variability by pre-defined age groups. Adults aged 18 - 26 y (n = 54 on CSII, n = 69 on MDI) standard deviation of HbA1c (0.6 ± 0.4 % [7 ± 8] mmol/mol) CSII, 0.9 ± 0.6 % [11 ± 7] mmol/mol) MDI; P = 0.001) (A) and coefficient of variation HbA1c over follow-up (7.3 ± 5.5 % [12 ± 16] mmol/mol) CSII, 10.5 ± 5.9 % [16 ± 12] mmol/mol) MDI ; P = 0.002) (B). Adults aged ≥ 26 y (110 CSII, 273 MDI) standard deviation of HbA1c (0.5 ± 0.4 % [5 ± 4] mmol/mol) CSII, 0.7 ± 0.7 % [9 ± 8] mmol/mol) MDI; P < 0.001) (C) and coefficient of variation over follow-up (6.3 ± 4.2 % [9 ± 5] mmol/mol) CSII, 8.9 ± 7.6 % [14 ± 13] mmol/mol MDI; P < 0.001**)** (D). Black bars = CSII; white bars = MDI. Graphed values are mean +/- SEM.

Figure 3. Long-term glycaemic variability in individuals changing from MDI to CSII therapy. Fifty-six adults changed from MDI to CSII therapy over the study. Mean HbA1c over follow-up (P < 0.001) (A), standard deviation of HbA1c (P < 0.001) (B) and coefficient of variation of HbA1c over follow-up (P = 0.004) (C). Black circles = MDI; white squares = CSII. Graphed values are mean pre- and post-therapy change.



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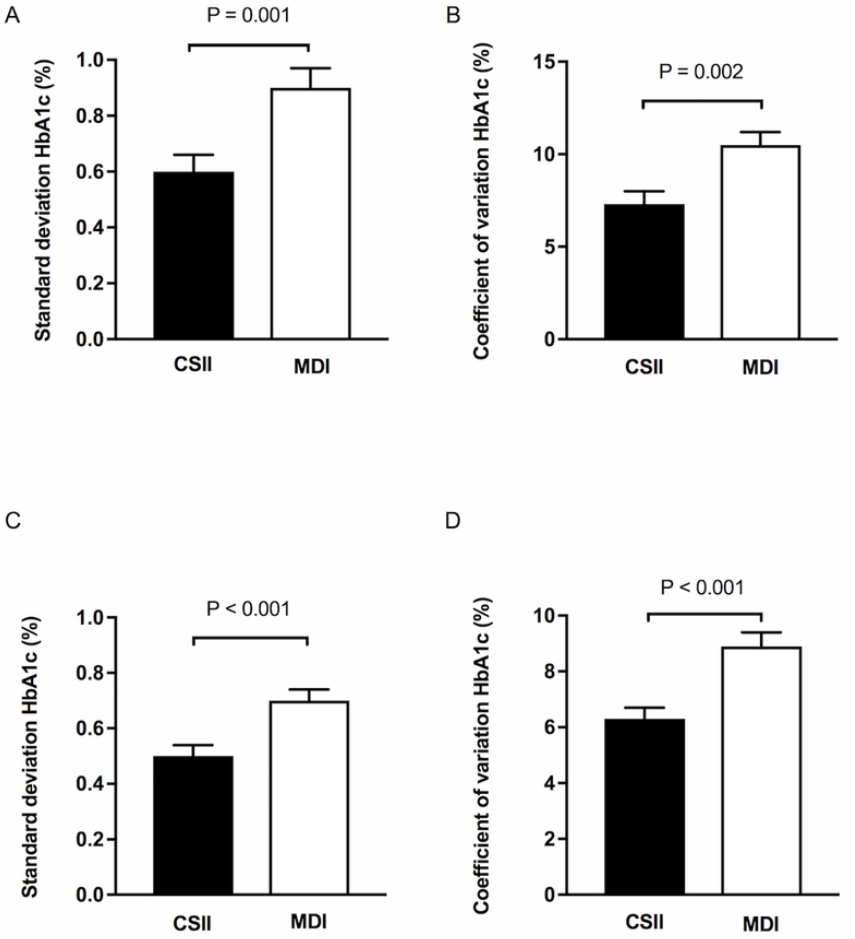

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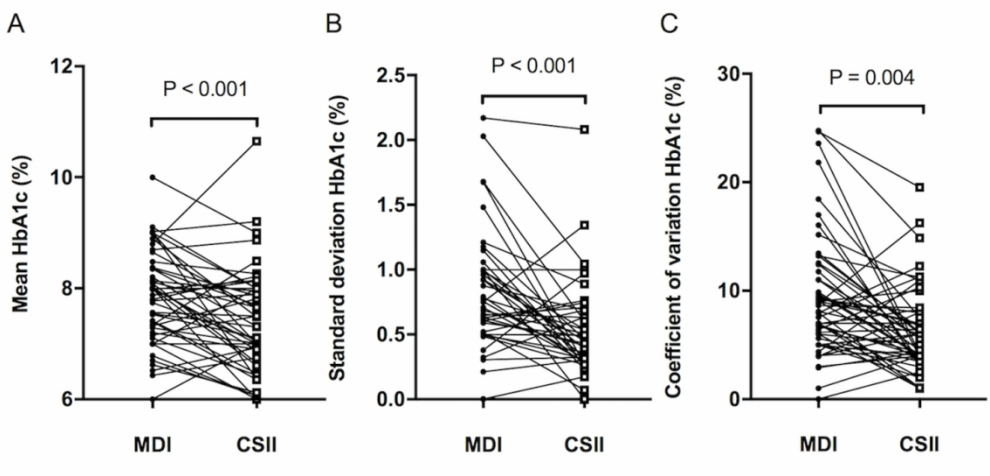

Figure 3. Long-term glycaemic variability in individuals changing from MDI to CSII therapy. Fifty-six adults changed from MDI to CSII therapy over the study. Mean HbA1c over follow-up ($P < 0.001$) (A), standard deviation of HbA1c ($P < 0.001$) (B) and coefficient of variation of HbA1c over follow-up ($P = 0.004$) (C). Black circles = MDI; white squares = CSII. Graphed values are mean pre- and post-therapy change.

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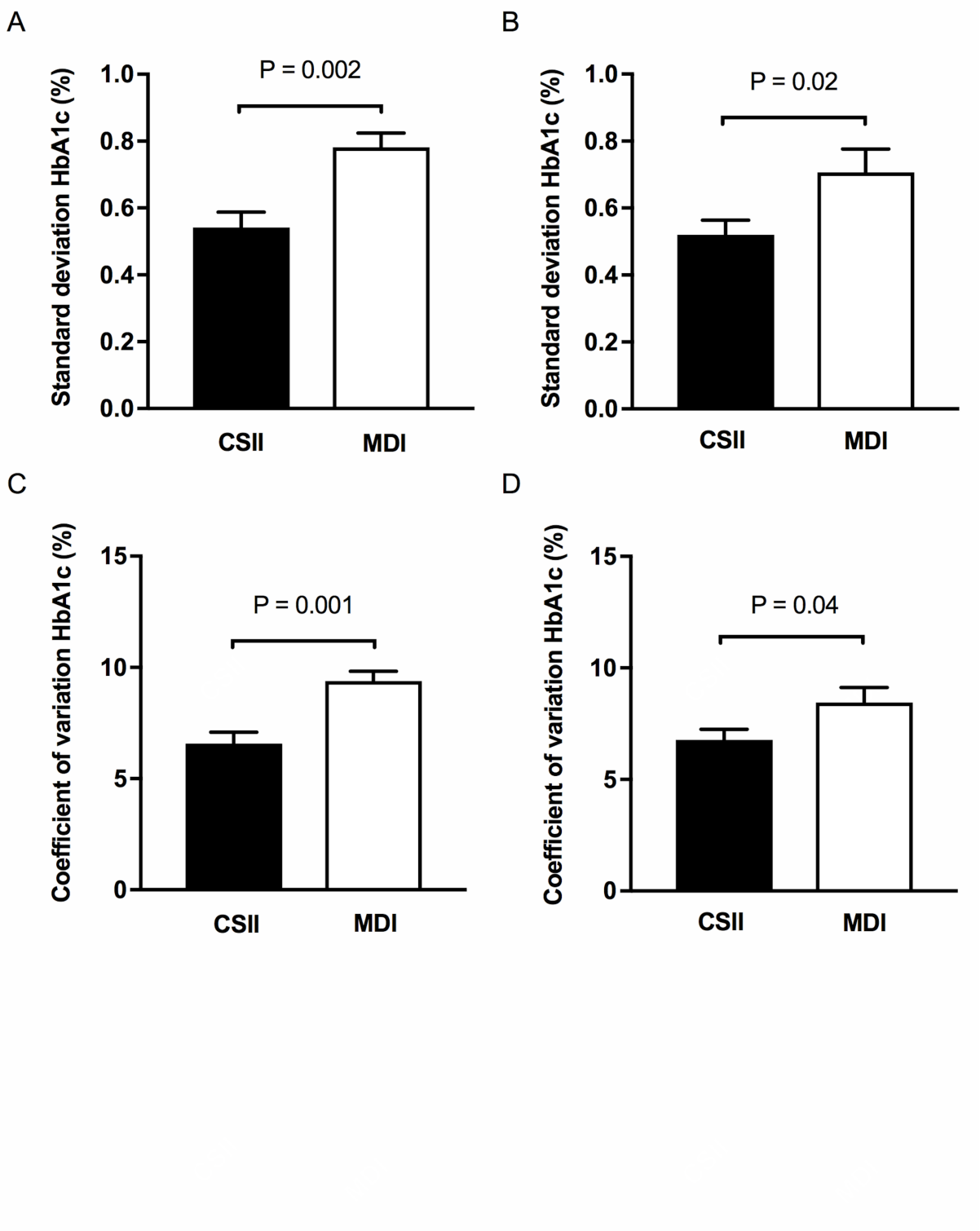
Supplementary Table 1. Clinical characteristics of adults with Type 1 diabetes by location.

Location	Royal North Shore Hospital	St Vincent's Hospital	P value
N	394	112	
CSII (n (%))	98 (24.9)	66 (58.9)	**<0.001**
Age (years)	38±16	36±12	0.23
Women (n (%))	189 (62)	65 (58)	**0.049**
Years of diabetes	17±14	18±13	0.47
Years CSII therapy	5±4	7±3	**0.026**
Vascular complications (n (%))*	161 (41)	31 (30)	**0.04**
Severe hypoglycaemia (n (%))†	84 (22)	-	**-**
Socioeconomic status (decile): Advantage / Disadvantage Education & occupation	 9±2 9±2	 7±2 7±3	 **< 0.001** **< 0.001**
Years follow-up	3.0±1.9	7.0±5.9	**< 0.001**
HbA1c measures (n)	7±4	15±13	**< 0.001**
Time between HbA1c (days)	238±197	237±185	0.98
Mean HbA1c % [mmol/mol]	 8.0±1.5 [64±16]	 7.7±1.5 [60±12]	 0.06

Data are mean ± standard deviation, or n (percentage). * Microvascular and macrovascular complications. † Any episode of severe hypoglyceamia recorded in the medical record.



Supplementary Figure 1. Long-term glycaemic variability in CSII and MDI participants by hospital location. Standard deviation of HbA1c over follow-up (0.5 ± 0.5 % [6 ± 7] mmol/mol) CSII, (0.8 ± 0.7 % [9 ± 8] mmol/mol) MDI, Royal North Shore Hospital (A) and standard deviation of HbA1c (0.5 ± 0.4 % [6 ± 4] mmol/mol) CSII,

(0.7 ± 0.5 % [11 ± 9] mmol/mol) MDI, St Vincent's Hospital (B). Coefficient of variation of HbA1c over follow-up (6.6 ± 5.1 % [10 ± 12] mmol/mol) CSII, (9.4 ± 7.7 % [13 ± 11] mmol/mol) MDI, Royal North Shore Hospital (C) and coefficient of variation of HbA1c (6.8 ± 3.8 % [9 ± 5] mmol/mol) CSII and (8.4 ± 4.6 % [21 ± 20] mmol/mol) MDI, St Vincent's Hospital (D). Black bars = CSII; white bars = MDI. Graphed values are Mean +/- SEM.

Supplementary Table 2. Clinical characteristics of adults with Type 1 diabetes by age subgroups of 18-26 years and greater than or equal to 26 years.

	18-26 y			**≥ 26 y**		
	CSII	**MDI**	**P value**	**CSII**	**MDI**	**P value**
N	54	69		110	273	
Age (years)	20±2	20±2	0.57	40±11	44±14	**0.009**
Women (n (%))	34 (63)	30 (43)	**0.03**	72 (65)	118 (43)	**<0.001**
Years of diabetes	9±5	8±6	0.48	21±13	20±15	0.56
Years CSII therapy	6±3	N/A	-	6±4	N/A	-
Vascular complications (n (%))*	5 (9)	10 (15)	0.35	44 (41)	122 (50)	0.12
Severe hypoglycaemia (n (%))†	4 (10)	5 (10)	0.96	10 (18)	65 (27)	0.17
Socioeconomic status (decile):						
Advantage/ Disadvantage	9±2	9±2	0.12	8±3	9±2	**<0.001**
Education & occupation	9±2	9±2	0.41	8±3	9±2	**<0.001**
Study follow-up (years)	3±2.6	3.6±4.0	0.50	4.5±2.7	4.2±4.0	0.52
HbA1c measurements (n)	7±6	9±10	0.40	9±8	8±8	0.43
Time between HbA1c (days)	221±237	205±127	0.62	20±131	261±216	**0.019**
Mean HbA1c % [mmol/mol]	8.3±1.3 [66±14]	8.5±1.6 [68±18]	0.52	7.6±1.1 [59±12]	7.9±1.4 [62±16]	**0.034**

Data are mean ± standard deviation, or n (percentage). * Microvascular and/or macrovascular complications. † Any episode of severe hypoglycaemia recorded in the medical record.

Supplementary Table 3. Long-term glycaemic variability in individuals changing from MDI to CSII therapy by gender.

Gender	**Male (n = 15)**			**Female (n= 41)**		
	MDI (pre)	**CSII (post)**	**P value**	**MDI (pre)**	**CSII (post)**	**P value**
Mean HbA1c % [mmol/mol]	7.8±0.7 [62±8]	7.4±0.8 [57±8]	**0.014**	7.9±0.8 [62±9]	7.3±1.0 [57±10]	**0.001**
SD HbA1c % [mmol/mol]	0.6±0.4 [7±4]	0.4±0.2 [4±2]	**0.007**	0.8±0.5 [8±5]	0.5±0.4 [5±4]	**<0.001**
CV HbA1c % [mmol/mol]	7.9±4.5 [11±6]	5.1±3.2 [7±5]	**0.013**	9.7±5.8 [14±8]	6.4±4.1 [9±6]	**0.001**

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	3
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	6

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-7
Bias	#9	Describe any efforts to address potential sources of bias	7-8
Study size	#10	Explain how the study size was arrived at	n/a
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
Statistical methods	#12c	Explain how missing data were addressed	n/a
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8

Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	8
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9-11
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
Main results	#16b	Report category boundaries when continuous variables were categorized	9-11
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	16
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12-17
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19