Article:
Evans-Cheun, TC, Campbell, F, Yong, J et al. (2 more authors) (2018) HbA1c values and hospital admissions in children and adolescents receiving continuous subcutaneous insulin infusion therapy. Diabetic Medicine, 36 (1). pp. 88-95. ISSN 0742-3071

https://doi.org/10.1111/dme.13786

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Article type : Research Article

Title: Diabetic Medicine
Created by: Maria Davie
Email proofs to: mt11tcc@leeds.ac.uk
Article no.: DME-00147
Article type: Research Article
Short title/Authors running head: Continuous subcutaneous insulin infusion effects

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HbA_{1c} values and hospital admissions in children and adolescents receiving continuous subcutaneous insulin infusion therapy

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What's new?

- Multi-level modelling found that HbA_{1c} values decreased with continuous subcutaneous insulin infusion (CSII) therapy, including in individuals who eventually discontinued CSII; however, these individuals returned to pre-CSII start HbA_{1c} levels after returning to multiple daily injections.
- HbA_{1c} levels improved for up to 4 years of CSII therapy. For boys/men, this improvement was maintained for 6 years, compared with only 3 years in girls/women. Girls/women were also more likely to discontinue CSII therapy.
- Hospitalization rates increased for diabetic ketoacidosis in the first year of CSII therapy, but was no different from pre-CSII rates thereafter.

Abstract

Aims

To assess HbA_{1c} values and hospitalization rates before, during and after continuous subcutaneous insulin infusion (CSII) therapy.

Methods Demographic and hospitalization data were extracted from 161 individuals with Type 1 diabetes who received continuous subcutaneous insulin infusion (CSII) therapy between 2002 and 2013 at the Leeds Children and Young People's Diabetes Service for those aged < 20 years. The median (range) age at CSII start was 11.9 (1.1–17.6) years. The median (range) follow-up time was 2.3 (0–8.1) years. Random intercept models were used to compare HbA_{1c} values before and during CSII initiation (and after CSII for those who discontinued it). Hospitalization rates were calculated for diabetic ketoacidosis and severe hypoglycaemia.

Results

The mean HbA_{1c} concentration decreased by 7 mmol/mol [95% CI 6–8; 0.6% (95% CI 0.5–0.7)]. For the discontinued group (n=30), mean HbA_{1c} decreased by 5 mmol/mol [95% CI 2–8; 0.4% (95% CI 0.2–0.7%)]. HbA_{1c} returned to pre-CSII start levels at the end of this therapy. Diabetic ketoacidosis admissions increased threefold during CSIIcompared with before CSII start [2.2 per 100 person-years (95% CI 1.3 to 3.6) vs 7.4 per 100 person-years (95% CI 5.1 to 10.8)] and was highest during the first year of CSII. No difference in severe hypoglycaemia incidence rate was found during CSII compared with the pre-CSII period.

Conclusions Despite significant reductions in HbA_{1c} levels for individuals treated with CSII, improvements are needed to reduce diabetic ketoacidosis hospitalizations for those new to the therapy.

Introduction

Multiple daily injections (MDIs) are the default treatment for Type 1 diabetes in England and Wales. Since 2008, continuous subcutaneous insulin infusion (CSII) therapy has been recommended for children aged <12 years where MDIs are inappropriate and for those aged ≥12 years with problems reaching HbA_{1c} targets or who experience disabling hypoglycaemia [1]. Previous studies show reductions in HbA_{1c} levels with CSII therapy [2–9]; however, these studies using t-tests or ANOVA to assess any difference in mean HbA_{1c} before and after CSII initiation do not account for repeated data within the same individuals, violating the assumption of independence between observations, resulting in flawed conclusions [10].

Campbell et al. [11] used a multi-level modelling approach to account for repeated data and found an overall reduction in mean HbA_{1c} of [6 mmol/mol (95% CI 3–9); 0.5% (95% CI 0.3 to 0. 8%] after 1 year of starting CSII therapy in the Leeds Children and Young People's

Diabetes Service (LCYPDS) [11]. They also found a reduction in hospital admissions incidence for severe hypoglycaemia from 8.9 to 2.4 per 100 person-years, whilst hospital admissions for hyperglycaemia remained stable with an incidence rate of 7.6 vs 7.3 per 100 person-years [11]. Data from the LCYPDS now include individuals starting CSII therapy up to 2013, allowing analysis over a longer follow-up period.

Compared with MDIs, CSII therapy can offer more practical benefits but does not eliminate the need for self-management. The permanent attachment of the CSII device can become burdensome, leading to a negative psychological association with the treatment [12,13] and limited clinical success, with some eventually returning to MDIs. There is little published research into the characteristics of individuals with poorer clinical outcomes during CSII therapy. Some evidence suggest that boys/men have lower HbA_{1c} values on CSII than girls/women [14]. In the only previous study, to our knowledge, examining characteristics for individuals who have discontinued CSII, girls were more likely to discontinue CSII than boys [15].

The aim of the present study was to examine changes in HbA_{1c} values using a statistically robust approach of mixed effects multi-level modelling. Hospitalization rates before and after CSII therapy initiation in the LCYPDS were also examined. Differences in these outcomes were assessed by sex, duration of CSII therapy and continuation status of CSII therapy.

Method

Data source

Demographic and clinical data were extracted for <20-year-olds diagnosed with Type 1 diabetes who started CSII therapy at LCYPDS between 2002 and 2013. Data were collected for clinic appointments up to 2015.

Clinical data included HbA_{1c} values at each appointment, any recorded hospitalization since Type 1 diabetes diagnosis (inpatient admission or accident and emergency attendance) and any CSII discontinuation dates for individuals who ended CSII therapy whilst attending the service. Any HbA_{1c} values or hospitalizations recorded on the same day as CSII initiation were classed as pre-CSII start data. Any HbA_{1c} values or hospitalizations recorded from the day after CSII initiation (and before CSII discontinuation date for those who ended CSII) were classed as data during CSII. For those who ended CSII, any HbA_{1c} values and hospitalizations recorded on or after the CSII discontinuation date were classed as data post-CSII. CSII duration was defined as time from the day after CSII initiation to either the last recorded attendance at the LCYPDS for individuals with no recorded CSII discontinuation date or up to the CSII discontinuation date for individuals who ended CSII therapy whilst attending the service.

Individuals without any HbA_{1c} values before and during CSII were excluded. Any individuals with Type 1 diabetes diagnosis at <6 months of age were also excluded. Any hospitalization records occurring prior to their Type 1 diabetes diagnosis date were excluded.

Statistical analysis: differences between HbA_{1c} values before and during CSII

A multi-level random intercept model assumes that the relationship between pre- and during-CSII HbA_{1c} values is the same for all individuals. An overall random intercept model was run for the cohort. Separate models were run for different CSII duration periods by sex, age at diabetes diagnosis, and between those who continued and those who discontinued CSII therapy.

Multi-level random slope modelling assumes that the relationship between pre- and during-CSII HbA_{1c} values differs between individuals. These models were used to determine any differences between individuals who continued and discontinued CSII. These models were compared by model fit with the random intercept models by calculating the Akaike information criterion and Bayesian information criterion.

Any HbA_{1c} values recorded post-CSII were only included where post-CSII was added as a covariate. Any individuals who restarted CSII therapy after discontinuing CSII were included for the first period of CSII therapy only. The mid-point between CSII end date of the previous therapy period and the CSII start date of the next therapy period was used to determine which recorded HbA_{1c} values would be categorized as post-CSII for the first period of CSII. Any HbA_{1c} values recorded after the mid-point were categorized as pre-CSII start values for the subsequent CSII period and were excluded from the analysis.

All models were adjusted for sex and age at diabetes diagnosis. These variables were identified as true confounders after completing a directed acyclic graph, using the DAGitty online tool (Figure S1) [16] to establish a causal diagram for the study. The directed acyclic graph included pre-CSII start HbA_{1c} value set as the exposure variable with HbA_{1c} value and

hospitalization during CSII set as outcome variables, along with pathways for all other variables within our dataset. The variables age at CSII start and pre-CSII start diabetes duration were identified as proxy confounders and pre-CSII start hospitalization status was identified as either a mediator or proxy confounder. These variables were excluded from the modelling. The directed acyclic graph was verified by the clinical authors (F.C. and J.Y.).

Statistical analysis: hospitalization incidence rates

Hospitalization incidence rates were calculated for pre- and during CSII periods by sex overall and separately for those who continued and discontinued CSII. Diabetes-related admissions included severe hypoglycaemia, diabetic ketoacidosis (DKA) and re-stabilization/control of diabetes. All other admissions were classified as non-diabetes-related hospitalizations.

Results

Demographics of the cohort

A total of 179 individuals attended the LCYPDS and started CSII therapy between 2002 and 2013. Eighteen individuals were excluded from analysis; 16 had no recorded HbA_{1c} values before and after their CSII start date and two individuals were diagnosed with diabetes under the age of 6 months.

A final total of 161 individuals were included. One individual had two periods of CSII therapy, and the second instance of CSII therapy was excluded from analysis.

Table 1 shows the total number in the cohort by sex and continued/discontinued CSII status, median age at Type 1 diabetes diagnosis, first HbA_{1c} observations and CSII initiation, total HbA_{1c} observations, follow-up time and total hospitalizations. The median follow-up time from first recorded pre-CSII start HbA_{1c} value to CSII initiation was around three times shorter that the median CSII therapy duration: 0.8 years (range 4 days to 1.9 years) vs 2.3 years (range 17 days to 8 years).

HbA_{1c} levels before and after the initiation of CSII

The median (range) HbA_{1c} value pre-CSII start was 75 (37–150) mmol/mol [9.0 (5.5–15.9)%] compared with 67 (36–134) mmol/mol [8.3 (5.4–14.4)%] during CSII. Table 2 shows results from the random intercept model for the overall cohort. There was a significantly higher reduction in HbA_{1c} value during CSII of 7 mmol/mol (95% CI 6–8; 0.6% (95% CI 0.5–0.7).

HbA_{1c} levels by duration of CSII

Using random intercept models for different periods of CSII duration, a greater reduction in HbA_{1c} values was observed up to 4 years after CSII initiation compared with pre-CSII levels, before returning to pre-CSII start levels after 7 years' CSII duration. The ≥7 years category had the highest change in HbA_{1c} with a decrease of 10 mmol/mol (95% CI 4–15; 0.9%; 95% CI 0.4–1.4), although small numbers (<5) were observed in this category (Fig. 1a).

Figure 1b shows that a significant decrease in HbA_{1c} was sustained up to 6 years whilst remaining on CSII for boys/young men, whereas Fig. 1c shows that this significant decrease was only sustained for 3 years for girls/young women.

Individuals who discontinued CSII therapy

Table 1 shows that 30 individuals discontinued CSII therapy, of whom 22 were female (73%).

The random intercept models (which were better fitting models than the random slope models based on lower Akaike information criterion and Bayesian information criterion values) indicated an overall significant decrease in HbA_{1c} levels during CSII compared with pre-CSII start levels for those who discontinued CSII therapy (Table 2). In terms of difference by gender, girls/women had a significant decrease in HbA_{1c} levels during CSII compared with pre-CSII start levels; however, no significant difference was found for boys/men.

No statistically significant difference in HbA_{1c} levels was found between pre- and post-CSII therapy for the overall cohort. No significant difference in HbA_{1c} values was seen between boys/men and girls/women after CSII compared with their pre-CSII start values.

Hospitalization incidence rates

The incidence rate of all hospitalizations was significantly higher during CSII compared with pre-CSII start: 24.3 per 100 person-years (95% CI 19.5–30.3) vs 8.4 per 100 person-years (95% CI 6.5–10.9). There was no significant difference between pre- and during-CSII incidence rates for severe hypoglycaemia; however, there was more than a threefold increase in incidence for DKA hospitalizations to 7.4 per 100 person-years (95% CI 5.1–10.8). Analysis by CSII duration found that DKA hospitalizations were significantly higher compared with pre-CSII start levels up to 1 year (Fig. 2).

There was a significant increase in overall hospitalizations in boys/men during CSII compared with pre-CSII start. For girls/women, there was a significantly higher incidence rate overall (9.5 per 100 person-years (95% CI 6.9–13.1) vs 30.6 per 100 person-years (95% CI 23.6–39.8), for diabetes-related hospitalizations (although not for severe hypoglycaemia or DKA separately) and non-diabetes related hospitalizations during CSII compared with pre-CSII start.

There were no significant differences in hospitalizations during CSII for those who discontinued CSII overall, nor were there any cases of severe hypoglycaemia in this group after CSII initiation. There was, however, a significantly higher DKA hospitalization rate: 2.5 per 100 person-years (95% CI 1.5–4.3) vs 11.7 per 100 person-years (95% CI 5.6–24.6).

Discussion

In the present study we observed a greater HbA_{1c} reduction within 1 year of CSII therapy compared with our previous study [11]. Other studies have also shown short-term improvements in glycaemic control, particularly within the first year of CSII [4,7,17–19]. Studies with <3 years' follow-up showed sustained improvements in glycaemic control up to the first or second year of CSII [20–22]. The present study included a longer follow-up period with a maximum follow-up time of 8 years, with 57% of the cohort having ≥3 years' follow-up time and approximately one-fifth having >5 years of longitudinal measurements. Another strength of this study is the use of multi-level modelling, a robust statistical modelling method to account for the assumption of independent observations which has been rarely performed previously.

HbA_{1c} improvement was sustained for up to 4 years of CSII duration before HbA_{1c} levels increased to pre-CSII start levels. This trend is similar to the few studies with >5 years' CSII duration, in which HbA_{1c} levels began to increase again between 2 and 6 years [18,23]. One explanation for this could be that this trend corresponds to the different stages of insulin resistance in puberty, where the increase in HbA_{1c} levels may be representative of the later stages of puberty when insulin resistance decreases [18]. Due to lack of data, we could not compare this trend with MDI users, nor could we examine trends beyond the age of 19 years. Nonetheless, the results suggest that there is a need for targeted support in maintaining HbA_{1c} improvement for longer, especially during adolescence.

Characteristics of individuals who discontinued CSII therapy

Nearly one-fifth of the cohort discontinued CSII therapy. This is higher compared with other studies, with the highest proportion reported by de Vries et al. [15] at 11.3%. The median HbA_{1c} value pre-CSII start in the present cohort was relatively high at 75 mmol/mol (9.0%). de Vries et al. [15] also found that those with higher HbA_{1c} levels were more likely to discontinue CSII therapy, which may explain why the present study had a much higher discontinuation rate compared with other countries where median HbA_{1c} levels may be lower. As the present study was based within a single centre, caution must also be exercised when generalizing any findings to the rest of the UK population.

In the present study we observed similar overall HbA_{1c} improvements during CSII therapy to those who continued and discontinued CSII therapy. For those who discontinued CSII, HbA_{1c} returned to pre-CSII start levels post-CSII; therefore, clinical efforts should be prioritized on maintaining patients on CSII within the LCYPDS to improve HbA_{1c} levels.

Understanding the barriers to CSII continuation is key to this objective; however, there is a lack of qualitative research on the experiences and views of CSII therapy from the perspective of children and adolescents. In a recent study by Tanenbaum et al. [12] using survey data for adults on CSII therapy, 46% did not like having diabetes devices on the body; 45% said it was uncomfortable or painful, 20.8% did not trust the device and 12.5% caused other people to ask too many questions about diabetes. It was also reported that even though women had higher CSII therapy uptake, women identified more barriers contributing to higher levels of distress and more concerns about body image because of the attachment of the CSII device [12]. A study by Ritholz et al. [13] also reported body image concerns from women, where attitudes were associated with HbA_{1c} values. Although qualitative data on the reasons for discontinued CSII therapy were unavailable in the present study, we did find that, overall, girls/women had less sustained improvement in HbA_{1c} levels compared with boys/men. The decrease in HbA_{1c} levels was sustained for longer in boys/men by 3 years and more than twice the proportion of girls/women discontinued CSII (23.9% vs 11.4%). Of those who discontinued CSII, however, HbA_{1c} values for boys/men showed no significant differences from pre-CSII start levels during CSII, whilst girls/women had improved HbA_{1c} levels. This suggests that there are clear gender differences during CSII therapy which need to be addressed with specialized intervention.

Differences between ethnicity and deprivation groups could not be examined in the present study because of lack of data. The prevalence of Type 1 diabetes is evenly spread across deprivation groups and is mostly diagnosed in individuals with white ethnic origin in England and Wales [24]. Any indication, therefore, of higher discontinuation in ethnic minority groups and most deprived groups in future research would identify further gaps in support.

Hospitalizations

In our previous study, there was a reduction in hypoglycaemia-related hospital admissions after the start of CSII, whilst DKA admissions remained stable. In the present study, we found that severe hypoglycaemia incidence did not change and DKA increased with CSII therapy. The median (range) pre-CSII start follow-up period (time between earliest recorded HbA_{1c} to CSII start date) was shorter than the follow-up period after CSII initiation [0.8 (0.01–2) years vs 2.3 (0.1–8.1) years], which may indicate that there was less opportunity for a hospitalization pre-CSII start; however, when comparing pre-CSII start incidence rates between the two studies, severe hypoglycaemia admissions decreased eightfold (8.8 per 100 person-years in the previous study [11] to 1.1 per 100 person-years in the present study) and DKA decreased nearly fourfold (7.6 per 100 person-years in the previous study [11] to 2.2 per 100 person-years), whilst during-CSII incidence rates remained similar. This may reflect improved MDI treatment within the LCYPDS; however, it is disappointing that improvements have not been matched with CSII therapy.

In other studies, mild and severe hypoglycaemia has been shown to decrease after the introduction of CSII [3,5,8,14,17,19,21,25–27]. Only a few studies found no change after CSII [9,28]. There is inconsistency between studies, however, in defining hypoglycaemia and distinguishing between mild and severe. Some studies defined cases according to whether the patient experienced consciousness or a seizure, others defined cases as those where assistance was required or in which blood glucose fell beyond a set threshold. In the present study we defined severe hypoglycaemia as an inpatient admission or an accident and emergency attendance. Any cases of hypoglycaemia treated without a hospitalization would not be included in this dataset, therefore, a small number of cases may not have been captured.

For DKA, other studies have shown inconsistent results. Some reported lower admissions after starting DKA [7,14,25,27], others reported no change at all [9,21,28,29] and some have reported higher DKA hospitalization rates [4,26]. The present findings showed that DKA increased after CSII start. Analysis from the latest National Paediatric Diabetes Audit report [30] suggests that CSII therapy increases the risk of a DKA admission; however, contrary to our results where an increase in DKA admissions was limited to the first year of CSII therapy, the National Paediatric Diabetes Audit found that the risk of a DKA admission was higher with longer duration of diabetes. It is difficult to compare our results with national data from the logistic regression model used in the National Paediatric Diabetes Audit, as this included individuals aged up to 25 years and individuals on MDI therapy; however, both results show the need to address this increase in DKA admissions rates at both a national and local level.

In conclusion, despite the benefits of CSII therapy with regard to improved HbA_{1c} levels, the incidence of hospital inpatient admissions and accident and emergency attendances whilst on CSII therapy showed no improvement in the LCYPDS. Gender differences in HbA_{1c} levels and poorer DKA incidence rates within the first year of CSII therapy provide some insight into the patient groups most in need of targeted intervention.

Funding sources

T.C.E.-C. receives funding from the University of Leeds 110 Scholarship.

Competing interests

None declared.

Acknowledgements

The authors acknowledge the clinical team at the LCYPDS. We would also like to thank Carolyn Stephenson and Angela Herbert from the University of Leeds for help with data collection.

Results from this paper were presented at the 43rd ISPAD Annual meeting.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Directed acyclic graph (DAG) for multi-level modelling.

FIGURE 1 Change in mean HbA_{1c} value with 95% CIs from pre-continuous subcutaneous insulin infusion (CSII) values by CSII duration in (a) girls/women only and (b) boys/men only.

FIGURE 2 (a) Hospitalization incidence for diabetic ketoacidosis (DKA) during continuous subcutaneous insulin infusion (CSII) with 95% CIs. (b) Hospitalization incidence for severe hypoglycaemia during CSII with 95% CIs.

Table 1 Demographic summary features of the Leeds Children and Young People's Diabetes Service cohort who started continuous subcutaneous insulin infusion therapy between 2002 and 2013

		Sex		CSII status		Total
		Boys/men	Girls/women	Continued	Discontinued	
Total individuals, n (%)	Boys/men	-	-	62 (88.6)	8 (11.4)	70
	Girls/women	-	-	69 (66.8)	22 (24.2)	91
Age, years Median (range)	Age at diabetes diagnosis	7.0 (0.9–13.7)	5.6 (1.1–14.4)	6.3 (0.9–13.7)	6.5 (1.1–14.4)	6.3 (0.9–14.4)
	Age at first HbA_{1c} observation	11.2 (0.9–16.4)	10.5 (1.8–15.9)	11.6 (5.7–15.9)	11.6 (5.7–15.9)	11 (0.9–16.4)
	Age at CSII initiation	12.1 (1.1–17.6)	11.2 (1.9–16.7)	11.7 (1.1–17.6)	12.7 (6.5–16.7)	11.9 (1.1–17.6)
Total HbA_{1c} observations, n (%)	Pre-CSII	257 (43.2)	338 (56.8)	474 (79.7)	121 (20.3)	595
	During CSII	691 (116.1)	922 (57.2)	1310 (81.2)	303 (18.8)	1,613
	Post-CSII	62 (3.8)	77 (55.4)	-	139 (100.0)	139
Follow-up time, years Median (range)	Pre-CSII (from diabetes diagnosis to first HbA_{1c} recording)	2.4 (0.0–12.9)	2.9 (0.0–12.8)	2.7 (0.0–12.9)	2.1 (0.0–10.7)	2.6 (0.0–12.9)
	Pre-CSII (from first HbA_{1c} recording)	0.8 (0.0–1.9)	0.8 (0.0–1.7)	0.8 (0.0–1.9)	0.8 (0.2–1.6)	0.8 (0.0–1.9)
	During CSII	2.2 (0.1–7.1)	2.5 (0.0–8.1)	2.3 (0.0–8.1)	2.5 (0.1–5.2)	2.3 (0.0–8.1)

	Post-CSII	1.1 (0.1–4.6)	0.9 (0.0–4.2)	-	0.9 (0.0–4.6)	0.9 (0.0–4.6)
Total hospitalizations, n (%)	Pre-CSII	19 (33.3)	38 (66.7)	42 (73.7)	15 (26.3)	57
	Post-CSII	23 (29.1)	13 (16.5)	67 (84.8)	12 (15.2)	79

CSII, continuous subcutaneous insulin infusion.

Table 2 Mean HbA_{1c} value change from pre-continuous subcutaneous insulin infusion start levels with 95% CIs from random intercept multilevel models

		Total number of individuals	Total number of HbA_{1c} observations	HbA_{1c} (mmol/mol) value change from pre-CSII start level (95% CI)	HbA_{1c} (%) value change from pre-CSII start level (95% CI)
During CSII (all individuals)	All individuals	157	2186	-7 (-8 to -6)*	-0.6 (-0.7 to -0.5)*
	Boys/men	67	933	-9 (-10 to -7)*	-0.8 (-0.9 to -0.6)*
	Girls/women	90	1253	-6 (-7 to -4)*	-0.5 (-0.6 to -0.4)*
During CSII (individuals who continued CSII only)	All individuals	128	1766	-7 (-8 to -6)*	-0.7 (-0.8 to -0.6)*
	Boys/men	60	828	-9 (-11 to -8)*	-0.9 (-1 to -0.7)*
	Girls/women	68	938	-6 (-7 to -4)*	-0.5 (-0.6 to -0.4)*
During CSII (individuals who discontinued CSII only)	All individuals	29	557	-5 (-8 to -2)*	-0.4 (-0.7 to -0.2)*
	Boys/men	7	165	-1 (-7 to 4)	-0.1 (-0.6 to 0.4)
	Girls/women	22	392	-6 (-10 to -2)*	-0.5 (-0.9 to -0.2)*
Post-CSII (individuals who discontinued CSII only)	All individuals	29	557	1 (-8 to -2)*	0.1 (-0.7 to -0.2)*
	Boys/men	7	165	0 (-6 to 6)	0 (-0.6 to 0.5)
	Girls/women	22	392	3 (-2 to 7)	0.3 (-0.2 to 0.7)

CSII, continuous subcutaneous insulin infusion.

*****Statistically significant HbA_{1c} value decrease from pre-CSII start level.