PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	HbA1c Variability in Adults With Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion (CSII) Therapy Compared To Multiple Daily Injection (MDI) Treatment.
AUTHORS	Scott, Emma; McGrath, Rachel; Januszewski, Andrzej; Calandro, Daniel; Hardikar, Anandwardhan; O'Neal, David; Fulcher, Gregory; Jenkins, Alicia

VERSION 1 – REVIEW

REVIEWER	Dr Jackie Elliott University of Sheffield, UK Co-author of the REPOSE study
REVIEW RETURNED	09-Sep-2019

GENERAL COMMENTS	I think the summary is a little over-stated. GV may be of interest, but its link to diabetes-related microvascular complications needs confirming before it is used as a routine tool in clinical practice. How much value it adds over and above mean HbA1c measurements is unknown. Several pre-defined sub-analyses were performed, and in my opinion the study would be strengthened by looking at different HbA1c cut-offs, e.g., quartiles. Is GV reduced in CSII users across all HbA1c ranges? As per Ref 10, Lepore. This study has not shown a relationship between HbA1c GV and complications, therefore I suggest the last line of the abstract is changed “Relationships between HbA1c GV and chronic complications may be of interest”. Page 5, line 54 “Predominantly without RT-CGM” – it would have been better to exclude anyone on RT-CGM Page 9, line 10. Time between HbA1cs was lower in pumps 213 vs 249, ? indicating more structured HCP involvement Page 11, line 32, more HbA1c measurements, less time between HbA1cs, therefore indicating greater HCP involvement, therefore not so surprising that HbA1c more stable. Page 12, line 12, CSII had more HbA1c values on CSII 10, vs 8 on MDI. Table 2, SD as expected will be lower in CSII as mean HbA1c is lower Some studies have tried to assess the clinical and cost-effectiveness of CSII therapy over optimised MDI therapy, e.g., Page 16, Line 54 cite REPOSE which controlled for education Page 17, line 22, REPOSE cost effectiveness paper examines the costs of pump therapy vs MDI Typos / formatting

	Page 9, line 18 reads “CSII and 8.0”, remove and Table 2 – Formatting of this table is poor, making it difficult to read, and variable numbers of decimal places provided, line 55 0.6 vs 0.50 for HbA1c SD %

REVIEWER	Katharine Barnard-Kelly Bournemouth University, UK
REVIEW RETURNED	09-Sep-2019

GENERAL COMMENTS	This is a well, designed, well-written comprehensive retrospective data review considering several co-variables. Rigorous analyses methods.

REVIEWER	Hood Thabit Manchester Diabetes Centre and University of Manchester, United Kingdom
REVIEW RETURNED	02-Nov-2019

GENERAL COMMENTS	The analyses presented by Scott and colleagues is interesting and expands on the potential benefit of CSII compared to MDI, beyond HbA1c reduction. The methodology used is generalisable and can be easily implemented in usual clinical practice. The authors have acknowledged the known confounders inherent in such study designs, including the potential attention bias inadvertently given to CSII compared to MDI users. The statistical results are clear and significant, however as stated, whether the magnitude of HbA1c variability reduction from MDI to CSII transition translates into meaningful clinical outcomes, remains to be tested. In clinical practice, HbA1c levels have a tendency to be influenced and fluctuate according to seasonal/temporal factors (i.e. worsening HbA1c post-holiday seasons, periods of stress such as exams etc). Could the author provide information on whether HbA1c measurements were equally distributed over certain periods, to negate this? It is unfortunate that no short-term glycaemic variability data could be provided, as the issues related to the discordance between short-term vs. long term variability referenced by the authors, are likely attributed to the relatively short duration of data capture (Lepore et al, 72 hours, Simon et al, 72 hours, Alemzadeh et al, 48 hours) which is insufficient to reproduce stable glucometrics (minimum 14 days; Riddlesworth TD et al Diabetes Technol Ther. 2018 Apr;20(4):314-316) , or due to glycaemic control deterioration of the study population (Harrington et al). Would suggest highlighting the limitation of these studies, to provide further context on the unclear relationship between the two. The point related to insulin delivery modality being a predictor of glycaemic variability is debatable, as two recent RCTs (Beck et al and Ljnd et al, JAMA. 2017;317(4)) have shown that patients with access to continuous glucose monitoring could potentially achieve the degree of glycaemic control and glycaemic variability improvement comparable to CSII users, without the additional costs of CSII. Would suggest highlighting these studies and its implication in the Discussion section.

REVIEWER	yves reznik Endocrinology Department university Hospital of Caen France
REVIEW RETURNED	02-Nov-2019

GENERAL COMMENTS	The paper by Scott et al emphazises on the ability of CSII treatment to reduce long term glycaemic variability in comparison with MDI treatment in a cohort of 506 adults with Type 1 diabetes. This is a longitudinal comparative study based on a retrospective audit performed in two tertiary hospitals in Australia. In both, serial measures of HbA1c were performed between 1995 and 2018 during a mean period duration of 4 years, corresponding to a mean of 8 HbA1c measurements. CSII treatment was associated with lower HbA1c variability - assessed by the HbA1c standard deviation and the HbA1c coefficient of variation ie SD HbA1c / mean HbA1c –than with MDI treatment. Such reduction of HbA1c variability with CSII was consistently found in both men and women, in older subsets of patients. To reinforce their findings, the authors have individualized a subgroup of 56 adults who had switched during the study period from MDI to CSII, both treatments having more than 4-year duration with the exclusion of the first year of CSII in order to exclude the initial variation of HbA1c which corresponds to the impact of MDI-to-CSII switch. The switch to CSII also allowed a reduction in long term glycaemic variability independently of age, gender and diabetes duration, when compared to matched patients who remained on MDI. These data are original since they address for the first time the influence of CSII independently from the use of other technologic tools (especially real time individual CGM) on long term glycaemic variability, in opposition to short term variability assessed by CGM in previous studies. The strength of the study lies in the adjustment to multiple variables including age, gender, diabetes duration, hospital location, socioeconomic status, chronic complication status, severe hypoglycemia events, baseline HbA1c, years of follow up, number of HbA1c measures and intervalls between HbA1c measures. These data contrast with the lack of short term glucose variability change when switching from MDI to CSII, as found in several studies including one from the authors of the present study. The study is methodologically straightforward, MDI and CSII groups had somehow similar characteristics including baseline HbA1c levels, study duration, number of HbA1c measures. The reviewer has few queries to address : 1- HbA1c measures were performed in different laboratories with different methodologies, as assessed in the discussion. Did the authors worry about intra-patient HbA1c variability due to laboratory change on an individual basis, which should have introduced a major bias in the assessment of HbA1c variability ? in other words, were there individuals having serial HbA1c measurements pereformed in different laboratories which should induce variability ? If yes, does exclusion of such individuals change the results of the study comparison between CSII and MDI ? 2- should the authors characterize different patterns of HbA1c variability observed over time in clusters of patients, like progressive rise ? peaks and trough ? random oscillations ? If yes, did CSII affect specific patterns of HbA1c variability ? 3- should the authors report more precisely in their discussion the impact of long term variability on micro and macrovascular

	complications, according to the litterature on this topic

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr Jackie Elliott
Institution and Country: University of Sheffield, UK

I think the summary is a little over-stated. GV may be of interest, but its link to diabetes-related microvascular complications needs confirming before it is used as a routine tool in clinical practice. How much value it adds over and above mean HbA1c measurements is unknown.
Several pre-defined sub-analyses were performed, and in my opinion the study would be strengthened by looking at different HbA1c cut-offs, e.g., quartiles. Is GV reduced in CSII users across all HbA1c ranges? As per Ref 10, Lepore.
We have incorporated an additional analysis of HbA1c SD and CV by tertiles of mean HbA1c and found that the effect of insulin modality persists across all tertiles. This is incorporated into page 7, 11 and 16.

Page 7
A further subgroup analysis assessed the impact of insulin modality on GV across tertiles of mean HbA1c using a general linear model."

Page 11
"HbA1c variability lower in CSII users across all tertiles of mean HbA1c.
HbA1c GV was assessed by tertile of mean HbA1c (tertile 1 HbA1c 7.2% [55 mmol/mol], tertile 2 HbA1c [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

Page 16
"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."

This study has not shown a relationship between HbA1c GV and complications, therefore I suggest the last line of the abstract is changed "Relationships between HbA1c GV and chronic complications may be of interest".
The sentence relationships between HbA1c GV and chronic complications has been removed.

Page 5, line 54 "Predominantly without RT-CGM" – it would have been better to exclude anyone on RT-CGM
The RT-CGM occurred in a minority of individuals and was not continuously. We have commented page 15

"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)."

Page 9, line 10. Time between HbA1cs was lower in pumps 213 vs 249, ? indicating more structured HCP involvement
We have addressed this on page 17

"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."

Page 11, line 32, more HbA1c measurements, less time between HbA1cs, therefore indicating greater HCP involvement, therefore not so surprising that HbA1c more stable.
As above

Page 12, line 12, CSII had more HbA1c values on CSII 10, vs 8 on MDI.

The 56 adults who transitioned from MDI to CSII were matched to adults who remained on MDI therapy. We acknowledge that the adults who changed to CSII had significantly more HbA1c measurements after the modality change, compared to those who remained on MDI therapy. This may reflect behavioural change or more health care involvement, however the number of HbA1c measurements and the time between measurements was adjusted for in all multivariable analyses.

Page 17
"However, time interval and number of HbA1c measures were statistically adjusted for in the data analyses"

Table 2, SD as expected will be lower in CSII as mean HbA1c is lower
Both measures of glycaemic variability are reduced in CSII group, which is a strength of the study as we do not rely on SD alone. As expected in individuals with a higher mean glucose will have a higher SD.

Page 16
"We report both HbA1c CV and SD and not unexpectedly (given the mathematical derivation of SD from CV), find similar results with both measures."

Some studies have tried to assess the clinical and cost-effectiveness of CSII therapy over optimised MDI therapy, e.g.,
Page 16, Line 54 cite REPOSE which controlled for education
Page 17, line 22, REPOSE cost effectiveness paper examines the costs of pump therapy vs MDI
This has been addressed and REPOSE cited on page 18

"Other groups have examined the impact of CSII therapy compared to MDI on glycaemic control when equal education time is provided (16, 30). The results have not been consistent, and a recent RCT failed to show clinical and economic benefit of CSII (30). Neither study measured long-term GV."

Typos / formatting
Page 9, line 18 reads "CSII and 8.0", remove and
This sentence has been reformatted page 9

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 2 – Formatting of this table is poor, making it difficult to read, and variable numbers of decimal places provided, line 55 0.6 vs 0.50 for HbA1c SD %

Table 2 (now Table 3) has been reformatted, with some information removed from the table and instead described on page 13. Decimal places have been standardised.

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

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

Reviewer: 2
Reviewer Name: Katharine Barnard-Kellytt45
Institution and Country: Bournemouth University, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is a well, designed, well-written comprehensive retrospective data review considering several co-variables. Rigorous analyses methods .

We thank reviewer two for their comments.

Reviewer: 3
Reviewer Name: Hood Thabit
Institution and Country: Manchester Diabetes Centre and University of Manchester, United Kingdom
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The analyses presented by Scott and colleagues is interesting and expands on the potential benefit of CSII compared to MDI, beyond HbA1c reduction. The methodology used is generalisable and can be easily implemented in usual clinical practice.

The authors have acknowledged the known confounders inherent in such study designs, including the potential attention bias inadvertently given to CSII compared to MDI users.

The statistical results are clear and significant, however as stated, whether the magnitude of HbA1c variability reduction from MDI to CSII transition translates into meaningful clinical outcomes, remains to be tested.

In clinical practice, HbA1c levels have a tendency to be influenced and fluctuate according to seasonal/temporal factors (i.e. worsening HbA1c post-holiday seasons, periods of stress such as exams etc). Could the author provide information on whether HbA1c measurements were equally distributed over certain periods, to negate this?

We thank the reviewer for their comments. Because the variability is calculated from the long-term change in HbA1c over many years, the variability measure incorporates HbA1c fluctuations over many seasons or periods. It is therefore not possible to make a temporal assessment. Such a measure could be assessed in future studies with an intermediate measure of GV such as 1,5-anhydroglucitol.

It is unfortunate that no short-term glycaemic variability data could be provided, as the issues related to the discordance between short-term vs. long term variability referenced by the authors, are likely attributed to the relatively short duration of data capture (Lepore et al, 72 hours, Simon et al, 72 hours, Alemzadeh et al, 48 hours) which is insufficient to reproduce stable glucometrics (minimum 14 days; Riddlesworth TD et al Diabetes Technol Ther. 2018 Apr;20(4):314-316) , or due to glycaemic control deterioration of the study population (Harrington et al). Would suggest highlighting the limitation of these studies, to provide further context on the unclear relationship between the two.

We have highlighted the limitations of these studies as suggested on page 15

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.

The point related to insulin delivery modality being a predictor of glycaemic variability is debatable, as two recent RCTs (Beck et al and Ljnd et al, JAMA. 2017;317(4)) have shown that patients with access to continuous glucose monitoring could potentially achieve the degree of glycaemic control and glycaemic variability improvement comparable to CSII users, without the additional costs of CSII. Would suggest highlighting these studies and its implication in the Discussion section.

We have included both references on page 16.

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.

Reviewer: 4
Reviewer Name: yves reznik
Institution and Country: Endocrinology Department, university Hospital of Caen, France
Please state any competing interests or state 'None declared': non declared

Please leave your comments for the authors below

The paper by Scott et al emphazises on the ability of CSII treatment to reduce long term glycaemic variability in comparison with MDI treatment in a cohort of 506 adults with Type 1 diabetes. This is a longitudinal comparative study based on a retrospective audit performed in two tertiary hospitals in Australia. In both, serial measures of HbA1c were performed between 1995 and 2018 during a mean period duration of 4 years, corresponding to a mean of 8 HbA1c measurements. CSII treatment was associated with lower HbA1c variability - assessed by the HbA1c standard deviation and the HbA1c coefficient of variation ie SD HbA1c / mean HbA1c – than with MDI treatment. Such reduction of HbA1c variability with CSII was consistently found in both men and women, in older subsets of patients. To reinforce their findings, the authors have individualized a subgroup of 56 adults who had switched during the study period from MDI to CSII, both treatments having more than 4-year duration with the exclusion of the first year of CSII in order to exclude the initial variation of HbA1c which corresponds to the impact of MDI-to-CSII switch. The switch to CSII also allowed a reduction in long term glycaemic variability independently of age, gender and diabetes duration, when compared to matched patients who remained on MDI.

These data are original since they address for the first time the influence of CSII independently from the use of other technologic tools (especially real time individual CGM) on long term glycaemic variability, in opposition to short term variability assessed by CGM in previous studies. The strength of the study lies in the adjustment to multiple variables including age, gender, diabetes duration, hospital location, socioeconomic status, chronic complication status, severe hypoglycemia events, baseline HbA1c, years of follow up, number of HbA1c measures and intervalls between HbA1c measures. These data contrast with the lack of short term glucose variability change when switching from MDI to CSII, as found in several studies including one from the authors of the present study.
The study is methodologically straightforward, MDI and CSII groups had somehow similar characteristics including baseline HbA1c levels, study duration, number of HbA1c measures. The reviewer has few queries to address :
1- HbA1c measures were performed in different laboratories with different methodologies, as assessed in the discussion. Did the authors worry about intra-patient HbA1c variability due to laboratory change on an individual basis, which should have introduced a major bias in the assessment of HbA1c variability ? in other words, were there individuals having serial HbA1c measurements pereformed in different laboratories which should induce variability ? If yes, does exclusion of such individuals change the results of the study comparison between CSII and MDI ?

We thank the reviewer for their comments. All laboratories used to assess HbA1c in this study were NATA accredited, and have undergone rigorous certification processes to standardise the assays using the National Glycohemoglobin Standardisation Program (NGSP) as stated on page 6 and 17. In order to account for possible difference in assay across the two hospital locations, GV was assessed by hospital location and the benefit of modality persisted at both sites.

2- should the authors characterize different patterns of HbA1c variability observed over time in clusters of patients, like progressive rise ? peaks and trough ? random oscillations ? If yes, did CSII affect specific patterns of HbA1c variability ?

We have analysed the pattern of HbA1c change over time and categorised patients into those whose HBA1c consecutively increased, consecutively decreased and those who fluctuated up and down. There was no difference in the proportion of individuals in any category by insulin modality (consecutive increase (n(%)) 18 (11) CSII vs. MDI 33 (10) P = 0.63; consecutive decrease 21 (13) CSII vs. 31 (9) MDI P = 0.19, fluctuation 125 (76) CSII vs. 278 (81) MDI).

We compared HbA1c mean, SD and CV in those whose A1c consecutively increased (n= 51), consecutively decreased (n=52) and those who fluctuated (n=403). There was no difference in ANOVA by mean, SD or CV (P = 0.514, P = 0.118 and P = 0.139 respectively). The analysis was repeated after excluding individuals with only 2 HBA1c values and again there was no difference (P = 0.54, P = 0.191, P = 0.238 respectively).

3- should the authors report more precisely in their discussion the impact of long term variability on micro and macrovascular complications, according to the litterature on this topic

We thank the reviewer for this comment and have included a lengthier discussion of the impact of long-term GV on complications status on page 15.

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).

VERSION 2 – REVIEW

REVIEWER	Yves Reznik CHU Cote de Nacre 14033 caen cedex France
REVIEW RETURNED	28-Nov-2019