Islet transplantation provides superior glycemic control with less hypoglycemia compared to continuous subcutaneous...
Islet transplantation provides superior glycemic control with less hypoglycemia compared to continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI)

D Jane Holmes-Walker
University of Sydney at Westmead Hospital, Dept Endocrinology NSW, Australia.
Conflicts of interest: The primary author has received honoraria for lectures and participated on advisory board for Medtronic Australasia.

Jenny E Gunton
University of Sydney at Westmead Hospital, Centre for Diabetes, Obesity and Endocrinology Research, The Westmead Institute, University of Sydney. No conflict of interest

Marlene Payk
Dept Diabetes and Endocrinology, Westmead Hospital Westmead, NSW, Australia. No conflict of interest

Susan Donath
Department of Paediatrics, Murdoch Childrens Research Institute and University of Melbourne, Vic, Australia. No conflict of interest.

Wayne J Hawthorne
University of Sydney at Westmead Hospital, National Pancreas Transplant Unit, Westmead Hospital, Westmead, NSW, Australia. No conflict of interest.

Tom Loudovaris
St Vincent’s Institute, University of Melbourne, Victoria, Australia. No conflict of interest

Patricia Anderson
Dept Renal Medicine, Westmead Hospital, NSW, Australia. No conflict of interest.
Glenn M Ward
Departments of Endocrinology and Clinical Biochemistry, St Vincent’s Hospital Melbourne, University of Melbourne Dept Pathology, Vic, Australia. No conflict of interest.

Thomas W H Kay
St Vincent’s Institute, University of Melbourne, Vic, Australia. No conflict of interest.

Philip J O’Connell
Westmead Millennium Institute, Centre for Renal and Transplant Research, University of Sydney at Westmead, NSW, Australia
For the Australian Islet Transplant Consortium. No conflict of interest.

Address for correspondence
DJ Holmes-Walker, Dept Diabetes and Endocrinology, Westmead Hospital
PO Box 533 Westmead NSW 2145. Email jane.holmeswalker@sydney.edu.au

Authorship:

Dr D J Holmes-Walker Research design, writing, performance of research, data analysis. Dr Holmes-Walker has received honoraria for lectures and has participated on advisory board for Medtronic Australiasia. jane.holmeswalker@sydney.edu.au

Professor Jenny E Gunton. Data analysis, writing. No conflict of interest.
jenny.gunton@sydney.edu.au

Ms Marlene Payk. Performance of research. No conflict of interest.
Marlene.payk@health.nsw.gov.au

Associate Professor Susan Donath. Contributed analytic tools, Data analysis. No conflict of interest. susan.donath@mcrl.edu.au

Associate Professor Wayne J Hawthorne, Performance of research, writing. No conflict of interest. wayne.hawthorne@sydney.edu.au

Dr Tom Loudovaris, Performance of research, writing. No conflict of interest
tloudovaris@svi.edu.au

Ms Patricia Anderson, Performance of research. No conflict of interest.

Associate Professor Glenn M Ward. Writing. No conflict of interest.
Glenn.WARD@svhm.org.au

Professor Thomas W H Kay Performance of research, Writing. No conflict of interest.
tkay@svi.edu.au

Professor Philip J O’Connell Performance of research, Writing. No conflict of interest.
Philip.OConnell@sydney.edu.au

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Abbreviations

CGM; continuous glucose monitoring

CONGA4; Continuous overlapping net glycemic action 4 hour interval

CSII Continuous subcutaneous insulin infusion or insulin pump therapy

HYPO score; Edmonton Hypoglycemia Score

MDI; Multiple daily injections, basal bolus insulin therapy

T1D; Type 1 diabetes
Abstract

Background

The aim was to compare efficacy of multiple daily injections, continuous subcutaneous insulin infusion (CSII) and islet transplantation to reduce hypoglycemia and glycemic variability in type 1 diabetes (T1D) subjects with severe hypoglycemia.

Methods

This was a within-subject, paired comparison of multiple daily injections (MDI) and CSII and CSII with 12 months’ post islet transplantation in 10 T1D subjects referred with severe hypoglycemia, suitable for islet transplantation. Individuals were assessed with HbA1c, HYPOscore, continuous glucose monitoring (CGM) and in 8 subjects measurements of glucose variability using standard deviation of glucose (SD glucose) from CGM and continuous overlapping net glycemic action using a 4 hour interval (CONGA4).

Results

After changing from MDI to CSII before transplantation, 10 subjects reduced median HYPOscore from 2028 to 1085 (p<0.05) and hypoglycemia events from 24 to 8 per patient-year (p<0.05). While HbA1c, mean glucose and median percent time hypoglycemic on CGM were unchanged with CSII, SD glucose and CONGA4 reduced significantly (p<0.05). At 12 months post transplant 9 of 10 were C-peptide positive, (5 insulin independent). Twelve months post islet transplantation there were significant reductions in all baseline parameters versus CSII; respectively HbA1c (6.4% cf 8.2%); median HYPOscore (0 cf 1085); mean glucose (7.1 cf 8.6 mmol.L⁻¹); SD glucose (1.7 cf 3.2 mmol/L); and CONGA4 (1.6 cf 3.0).
Conclusion

In subjects with severe hypoglycemia suitable for islet transplantation, CSII decreased hypoglycemia frequency and glycemic variability compared with MDI whereas islet transplantation resolved hypoglycemia and further improved glycemic variability regardless of insulin independence.
**Introduction**

Insulin treatment for type 1 diabetes (T1D) is required because of loss of pancreatic beta cells that sense glucose and secrete insulin. In many cases exogenous insulin is able to control blood glucose within acceptable limits but physiological insulin secretion is difficult to mimic. Hypoglycemia may occur when excess insulin is present. Approximately 1/3 of adult patients attending hospital based clinics self-reported at least 1 severe hypoglycemic episode in the previous 12 months (1). Self-reporting of severe hypoglycemia is associated with a 3.4 fold increase in mortality compared with those who report mild hypoglycemia (2). Recurrent severe hypoglycemia is the main indication for islet transplantation. While some studies have compared the effectiveness of islet transplantation with intensive medical therapy (3), few have compared continuous subcutaneous insulin infusion (CSII) with islet transplantation, although recent publications have recommended CSII before islet transplantation (4) due to the morbidity and cost of islet transplantation. Transplantation carries risks from long term immunosuppression so evaluating its benefits compared with best medical therapy is paramount.

In T1D subjects, CSII, compared with MDI regimens including insulin glargine, has been shown to lower HbA1c (5,6,7,8). Effects of CSII on hypoglycemia frequency are variable but a meta-analysis comparing CSII with MDI found a reduction in frequency of severe hypoglycemia (6). However, the meta-analysis included studies of patients on MDI with isophane or lente insulins, which are known to cause more hypoglycemia than the newer insulins glargine and insulin detemir. While some groups have shown that CSII reduces hypoglycemia compared with MDI (9,10,11) others have shown no difference (1,7). The preexisting severe hypoglycemia rates in the negative studies were relatively low and we hypothesise that the impact of CSII on hypoglycemia frequency may be greater in those with
high baseline rates of hypoglycaemia (6) such as in subjects considered suitable for islet transplantation. In the more recent HypoCOMPASS trial (12), which studied only subjects with severe hypoglycemia and impaired awareness of hypoglycemia, there were similar improvements in severe hypoglycemia rates in both MDI and CSII treated.

Islet transplantation is a promising therapy for patients with T1D and severe hypoglycemia that is resistant to other therapies. Several studies have shown that high levels of insulin independence and good control of hypoglycemia can be achieved in the short term (13,14). In recent years there have been improvements in medium to long term outcomes. Data from the Collaborative Islet Transplant Registry (CITR) shows consistent improvement in the duration of insulin independence (15,16). With new developments in the delivery of exogenous insulin and improvements in islet outcomes it has been difficult to define evidence based guidelines for each of these therapies in patients who suffer repeated severe hypoglycemia.

Glycemic variability improves with islet transplantation (17). It also improves with CSII as compared with MDI (18). Glycemic variability correlates with risk for hypoglycemic events (19,20). Therefore, it is possible that some patients considered suitable for islet transplant due to recurrent severe hypoglycemia may be better managed with CSII than MDI. If so, as the recently published guidelines suggest (4), CSII should be instituted while awaiting islet transplant to reduce glycemic variability, risk for future hypoglycemic events and death, as suggested by the recent hypoglycemia stepped management guideline (4).

The aim of the present study was to assess the impact of CSII as compared with MDI in subjects with severe hypoglycemia and suitable for islet transplantation, as recommended in the recent guidelines for management of severe hypoglycemia (4) and compare the glycemic
control of CSII and MDI therapies with that of islet transplantation at 12 months. A secondary aim was to determine objective measures from continuous glucose monitoring (CGM) such as duration of hypoglycemia and measures of glycemic variability (17,21) which could be used to evaluate comparative benefits of CSII and islet transplantation.

Materials and Methods

Clinical trial of islet transplantation

From 2006, subjects with T1D were referred to the islet transplant units at Westmead Hospital in Sydney, St Vincent’s Hospital, Melbourne and Royal Adelaide Hospital, Adelaide, to be assessed for suitability. Eligibility and exclusion criteria have been reported previously (22). Severe hypoglycemia was defined as hypoglycemia requiring assistance of others to recognise and/or treat, including assistance with administration of oral therapy, ambulance assistance, glucagon administration, or evidence of loss of consciousness, in the 12 months prior to review. The method of islet isolation, preparation and transplantation and the clinical outcomes of the trial have been described in detail elsewhere (22,23). The islet transplantation trial was approved by Institutional Ethics Review Board of the Western Sydney Local Health District (HREC2006/34/4.5-2305), St Vincent’s Hospital Melbourne (SVH HREC-D 103/05), Queen Elizabeth II and Royal Adelaide Hospitals, Adelaide. The trial was registered with the Australian and New Zealand Clinical Trials Registry No. 083020. The current study was a within subject, paired comparison of MDI and CSII and CSII with 12 months’ post islet transplantation of 10 T1D subjects on MDI at initial referral, with severe hypoglycemia, and assessed as suitable for islet transplantation.
Patient characteristics and clinical measurements.

Ten T1D subjects with recurrent severe hypoglycemia participated in the studies. All patients on multiple daily injections (MDI) were referred to the islet transplant program between January 2006 and December 2010 in the trial reported (23) and a further 2 transplanted since 2010. Eight subjects were recruited at Westmead and 2 in Melbourne.

All subjects on MDI at initial assessment were using either insulin Detemir or insulin Glargine as basal insulin, had recurrent severe hypoglycemia and were considered suitable for subsequent islet transplantation. After a period of optimisation of medical therapy on MDI with diabetes educator and dietician review and regular endocrinologist review, all patients on MDI had clinical measurements performed and were subsequently changed to CSII for management of diabetes prior to transplant. Clinical studies were repeated after change to CSII and again at 12 months’ post islet transplantation.

Clinical details recorded included age, duration of diabetes, HbA1c, weight, and insulin requirements (IU.kg⁻¹) were obtained after a minimum of 3 months from initial review on MDI or CSII, or after more than 3 months from changeover to CSII. Hypoglycemia severity was scored using the clinical HYPOscore (17), a clinical measure of frequency of hypoglycemia on routine home blood glucose monitoring, which also records the number of severe hypoglycemia events in the previous year. All patients were confirmed to be C-peptide negative after intravenous glucose load and arginine stimulation tests at initial assessment for suitability for islet transplantation.
Continuous glucose monitoring (CGM) and measures of glycemic variability

CGM was performed initially using the Medtronic Minimed Solutions continuous glucose monitoring system with Minimed paradigm insulin pump (model 522), or Guardian monitor, with Minilink transmitter™. Subsequently the iPRO2™ (Medtronic, Northridge, CA) CGM system was used post islet transplantation. Monitor application, calibration and data retrieval have been previously described (24). A single operator (MP) explained the use of the CGM device to each subject and method of calibration. Patients were not instructed in how to interpret the read-out, and no patients altered insulin delivery during the CGM. Recordings were obtained for a minimum of 72 hours and maximum of 96 hours. If < 72 hours of continuous data was obtained, the recording was repeated. Subjects referred with recurrent severe hypoglycemia and managed with MDI with insulin Glargine or insulin Detemir had CGM performed after a minimum of 3 months from initial referral. Once changed to CSII, a minimum of 3 months was allowed for optimisation of CSII settings before repeating CGM and CGM was again repeated 12 months from first islet transplantation.

From the CGM record, measurements of mean glucose, SD glucose (normal range 0.77 ± 0.24 mmol.L⁻¹ (25)), percentage CV glucose, percentage of readings <4 mmol.L⁻¹, percentage of readings >8 mmol.L⁻¹ and percentage of readings in normal range (4–8 mmol.L⁻¹) were recorded.

The 8 MDI subjects recruited at Westmead, for whom raw data from CGM was available, (data not stored at other centres) had detailed analysis of CGM to measure intra-day glycemic variability using continuous overlapping net glycemic action (26) using data from studies on MDI, CSII and post transplantation. The method was developed as a measure of glycemic variability in patients on CGM and makes use of all values obtained from the record (26).
Higher values indicate greater glycemic variation and in control subjects without diabetes normal values ranged between 0.4 -1.5. Unlike measures previously used in islet transplantation studies, such as the Lability Index (17), it is not affected by frequency of home blood glucose monitoring (27) as it uses all values across a 24-hour period. Values for continuous overlapping net glycemic action at 4 hours (CONGA4) were chosen to reflect the maximum impact of hypoglycemia on rebound hyperglycemia and residual post meal increase in blood glucose after bolus insulin (26). Maximal stimulated C-peptide was measured 12 months posttransplant with glucose followed by arginine as previously described (23).

Statistical analysis

Normally distributed data were analysed using paired Student’s t test. Nonparametric data were compared using Wilcoxon rank-sum test. Proportions were compared with Chi square test. Multiple comparisons were assessed using the Friedman test with Dunn post hoc correction. All analyses following islet transplantation were by intention to treat. Statistics were evaluated with Excel, or SPSS (v21.0). A p-value of <0.05 was considered significant. Data shows mean ± SD or for nonparametric data, median and inter-quartile range.

Results

Clinical data on study subjects is summarised (Table 1). Weight at time of transplant did not change significantly from initial assessment. All subjects were of low body weight, reflecting selection criteria for islet transplantation (insulin requirements <0.7 units.kg⁻¹ and weight <80 kg).
**MDI compared with CSII**

The mean interval from initial assessment on MDI and subsequent assessment on CSII in the same individual was 1.4±1.1 years (table1). There was no difference in HbA1c. In paired comparisons of HYPOscore, the HYPOscore fell significantly from 2028 (651-2342) to 1085 (622-1400), p=0.05 (Figure 1A). There was also a significant reduction in median hypoglycemic events per patient year from 24 (20-49) to 8 (0-18), p<0.05. The median HYPOscore was >90th centile in 100% of MDI treated and 70% of CSII treated patients (p=0.06, NS). While median percentage time spent in hypoglycemia fell from 11.5% (interquartile range 5-18%) in MDI treated to 3% (interquartile range 1-9%) in CSII treated, the difference was not significant. There was also no difference in percentage time spent in optimal range 4-8 mmol/L.

There was no significant difference in mean glucose as measured by CGM in MDI and CSII treated subjects. Changing from MDI to CSII however did result in a significant reduction in glycemic variability as measured by SD glucose, of 1.2±1.1 mmol.L⁻¹ (p<0.05, figure 1b). A difference of 0.55 mmol.L⁻¹ is considered clinically significant (18).

**CSII compared with 12 months’ post islet transplantation**

Mean interval from assessment on CSII to time of first transplant was 1.1±0.9 years (table 1). At 12 months posttransplant, 5 were insulin independent, 4 were insulin requiring with C-peptide >0.1 nmol.L⁻¹ and remained on CSII and 1 failed transplant. Four had 1 islet transplant (1 insulin independent, 2 requiring insulin on CSII and 1 failed transplant) 5 had two transplants (3 insulin independent, 2 requiring insulin) and 1 had three transplants (insulin independent). Insulin requirements fell from 0.4±0.2 IU.kg⁻¹ on CSII to 0.2±0.2 IU.kg⁻¹, 12 months’ post islet transplantation (Figure 2). On CSII, HbA1c was 8.2±1.8%
(65±14 mmol.mol\(^{-1}\)) and by 12 months’ post islet transplant had fallen to 6.4±1.3 (46±11 mmol.mol\(^{-1}\), p=0.01). Maximal C-peptide response and total daily insulin at 12 months posttransplant (ng.ml\(^{-1}\)) is shown for each subject (Figure 2).

There was a clinically significant fall in median HYPOscore from 1085 (inter-quartile range 622-1400) in CSII treated to 0 (0-1) at 12 months following islet transplantation; p <0.01 (Figure 1A). There was also a significant fall in median hypoglycemic events per person year; falling from 8 on CSII (inter-quartile range 0-18) to 0 at 12 months following islet transplantation (inter-quartile range 0-1); p <0.05. The fall in percentage of time with glucose < 4mmol/L from 1% (1-8) in CSII to 0% post transplantation was not significant. However the percentage time with glucose 4-8 mmol.L\(^{-1}\) increased significantly 12 months post islet transplant from 48.5% on CSII (inter-quartile range, 44-66%) to 81% (inter-quartile range, 71-95%, p<0.01).

Mean glucose from CGM fell from 8.6±2.0 mmol.L\(^{-1}\) on CSII to 7.1±1.1 mmol.L\(^{-1}\) at 12 months posttransplant (Table 1, mean difference 1.6±2.7 mmol.L\(^{-1}\); p NS). SD glucose fell from 3.2±1.4 mmol.L\(^{-1}\) on CSII to 1.7±0.5 mmol.L\(^{-1}\) at 12 months posttransplant (mean difference 1.8±1.6 mmol.L\(^{-1}\), p=0.01; Figure 1B).

*Comparison of glycemic variability as measured by CONGA4*

CONGA4 was measured in 8 subjects initially on MDI, all recruited at Westmead and subsequently changed to CSII and 7 of 8 subjects on CSII who had CGM at 12 months post transplantation (1 not studied with failed transplant at 3 months (table 2, Figure 1C). Of those assessed with CONGA4 after transplantation, 5 were insulin independent and 2 were on insulin but all had detectable fasting c-peptide, mean 0.46 nmol.L\(^{-1}\) (range 0.21-0.63 nmol.L\(^{-1}\)).
Paired analyses were again performed. CONGA4 was significantly lower in CSII treated compared with MDI treated (p=0.006) confirming less glycemic variability with CSII and was significantly reduced at 12 months post islet transplantation as compared with CSII (p=0.04), indicating further improvements in glycemic variability following islet transplantation.

Multiple comparison analysis

The Freidman test with Dunn post hoc correction was used to compare results of HYPOscore, SD glucose and CONGA4 across the 3 treatment groups, MDI, CSII and 12 months post islet transplant. The comparison of HYPO score showed improvement in HYPO score between MDI and 12 months post islet transplant remained significant (p=0.0007) however there was no difference between MDI and CSII and no difference between CSII and 12 months post islet transplant.

Similarly, for SD glucose and CONGA the results remained significant for MDI and 12 month post islet transplant (respectively p=0.0003 and p=0.0005, respectively) but comparison of MDI and CSII and CSII with 12 months post transplant were not significant. Therefore, for all treatment parameters there was no difference between MDI and CSII and no difference between CSII and post transplant, which we take to infer that CSII is intermediate between MDI and islet transplant, but only islet transplant has a significant treatment effect on hypoglycemia, glycemic variability and diabetes control as measured by HbA1c and mean glucose in T1D subjects with severe hypoglycemia.

Adverse events in the 12 months following islet transplant.

The clinical outcomes for all transplant recipients in the first 12 months after transplant, including complications, have been reported previously (22). Of the 10 patients reported here
there was transient lymphopenia in 4 (WCC < 3.0 X 10^9/L) and a greater than 20% reduction in glomerular filtration rate in 2. One required laserphotocoagulation of proliferative retinopathy, 1 required a blood transfusion for anemia and 1 required hospitalisation with a respiratory infection secondary to mTOR inhibitor.

**Discussion**

This is the first study to use CGM to assess the benefit of CSII as compared with MDI in paired studies of T1D subjects with severe hypoglycemia who met the criteria for islet cell transplantation. It is, similarly, the first study to use paired studies within the same individuals to assess the effect of CSII with islet transplantation to prevent severe hypoglycemia. The results provide evidence to validate the recent recommendation (4) that subjects awaiting islet transplantation for severe hypoglycemia, should be treated with CSII. It also provides evidence for the superiority of islet transplantation as compared with CSII in selected patients suffering from recurrent severe hypoglycemia.

CSII resulted in a significant reduction in severe hypoglycemia and improvement in glycemic variability as compared with MDI, however, there was no improvement in HbA1c or mean glucose. Severe hypoglycemia improved significantly as measured by HYPOscore and severe events per year but HYPOscore remained above the 90th centile in 70% of subjects, indicating the need for islet transplantation remained. Most importantly, islet transplantation eliminated hypoglycemia regardless of whether insulin independence was achieved as previously demonstrated by others (28,29,30). Frequency, severity and risk of hypoglycemia as measured by, respectively, CGM percentage of time in hypoglycemia, HYPOscore, and glycemic variability at 12 months’ post islet transplantation all returned to levels as good as, or better than, those reported in type 1 diabetes without problems with hypoglycemia.
Transplantation reduced HbA1c and mean glucose at 12 months, benefits that were not seen with changing to CSII from MDI.

Our results confirm the previously reported benefits of islet cell transplantation for reduction in severe hypoglycemia (13,14,16,31) and give greater insight into the comparative benefits of CSII and islet transplant in subjects with severe hypoglycemia. Previous studies have not shown a consistent benefit of CSII for hypoglycemia (8). Our data suggests that in subjects with severe hypoglycemia, CSII was an appropriate therapy, which substantially reduced the frequency and severity of hypoglycemia but did not remove the need for islet transplantation in the majority of individuals. CSII reduced duration of time with blood glucose <4 mmol/L and significantly improved glycemic variation as compared with MDI, the latter potentially accounting for reduced frequency of severe hypoglycemia. These findings may be important in subjects with less severe hypoglycemia in whom there is the possibility of restoring hypoglycemia awareness (12,32,33,34) potentially avoiding the need for islet transplant.

CGM was utilised as an objective and unbiased tool to compare frequency of, and time spent in, hypoglycemia in subjects with recurrent severe hypoglycemia managed with MDI, CSII and following islet transplantation. CGM is a potentially useful addition to standard clinical measures in subjects referred for islet transplant. As most have hypoglycemia unawareness, the majority of hypoglycemic events are not captured using intermittent home blood glucose monitoring. CGM confirmed benefit of both CSII and islet transplantation compared with MDI in subjects with recurrent severe hypoglycemia.

Continuous glucose monitoring (CGM) has been used infrequently as an evaluation tool in patients being assessed for islet transplantation (17,28) although it has been used to evaluate
success of islet transplantation (29,30). It is able to measure both frequency and total duration of hypoglycemia in a 24h period and also can be used to measure glycemic variability. The main flaw of the HYPOscore is that it underestimates hypoglycemia in patients with impaired hypoglycemia awareness as the majority of milder episodes are not documented (35) and the score is correlated with frequency of home blood glucose monitoring (17). However, while underestimating hypoglycemia, Senior et al (27) demonstrated that HYPOscore did correlate with percentage of time in hypoglycemia from CGM.

Potential weaknesses of the study include the relative small patient cohort and study subjects and investigators were not blinded to the CGM data as it was recorded, potentially altering insulin management behaviours. However, as subjects were not educated on how to react to CGM data and changed insulin delivery was not observed. At the time the study began blinded recording was not available. All transplanted subjects who remained on insulin had ‘blinded’ CGM performed. Another potential weakness is that MDI and CSII treated did not receive a specific diabetes education program for hypoglycemia prevention however a single diabetes educator reviewed all participants on MDI and CSII (MP).

In this study we did not use sensor augmented CSII but Langendaum et al (8), in a Cochrane review, suggested that although HbA1c is reduced, sensor augmentation may not improve hypoglycemia unless technologies such as low glucose suspend are added. Severe hypoglycemia with impaired awareness of hypoglycemia as measured by Gold Score >4 was the entry criteria for the HypoCOMPASS trial (12). This study also showed real time CGM did not reduce severe hypoglycemia. Recently, threshold-based insulin pump interruption (34) has been shown to reduce nocturnal hypoglycemic events by 38% and is of benefit for subjects with reduced hypoglycemic awareness.
In this study, SD glucose from continuous glucose monitoring and CONGA were used to assess change in glycemic variability. Previous measures developed to evaluate success of islet transplantation have included glycemic variability, expressed as mean amplitude of glycemic excursions (MAGE) and the Lability Index. Neither MAGE nor the Lability Index can be derived from CGM, hence were not used in this study, which used CGM data as the assessment tool. When CGM was used after islet transplantation glycemic variability was found to correlate with islet graft function (28).

Extreme glycemic excursions and variability can explain the risk of hypoglycemia (20), whereas HbA1c is a poor predictor accounting for only 8% of future episodes (36). From the present study, it would appear that the best means of reducing glycemic variability and hypoglycemia both prior to and following transplant, when insulin may still be required, is to deliver insulin by CSII. A CONGA4 value < 2.5 mmol/L was reliably obtained with a functioning islet transplant and may be a useful measure for assessing clinical benefit from islet cell transplant where insulin is still required.

A significant outcome of this study was that islet transplantation successfully reduced frequency and severity of hypoglycemic episodes even with partial graft function and did not depend on achieving insulin independence as reported by others (15,16,38). While improvement in glycemic variability correlated with C-peptide and beta score (a measure of graft function, 28), restoration of glucagon counter-regulatory responses to hypoglycemia may account for the rapid improvement in hypoglycemia frequency and glycemic variability with islet transplant (38,39).
Retention of beta cell function following islet transplant results in improved glycaemic control and results in reduced long term complications of retinopathy and nephropathy (40, 41). There is also mounting evidence for the effect of glycaemic variability on development of diabetes complications in addition to the effect of elevated HbA1c (42). Therefore, islet transplantation may reduce complications through both improved glycemic control and reduction in glycaemic variability.

One of issues limiting the applicability of this therapy is the requirement for long-term immunosuppression and new approaches in drug-free immunosuppression are required. Approaches such as cotransplantation of mesenchymal stem cells (43) mobilization of hematopoietic stem cells (44) and pruning of alloreactive T cells (45) are recent interventions trialled with clinical potential.

In T1D subjects who have recurrent severe hypoglycemia suitable for islet transplant, CSII therapy as compared with MDI, resulted in a clinically significant reduction in hypoglycemia and improvement in glycemic variability. Our findings, support the recommendation (4) that subjects assessed for islet transplantation should be offered the opportunity to trial CSII. Although “closed loop” therapy with insulin and glucagon, using integrative software with CGM and CSII to control blood glucose, has been shown, to further reduce frequency of hypoglycaemia, few subjects that meet the criteria for islet transplant have been studied (46).

In our study, islet transplantation was the only treatment which reduced severe hypoglycemia to near-normal and improved HbA1c. The present study is further evidence that in appropriately selected patients with severe hypoglycemia with large glycemic variability, islet transplantation provides superior glycemic control and reduction in hypoglycemia over
and above that achieved with CSII and therefore has the potential to have a greater impact on survival and long term complications.

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Australian Islet Transplant Consortium.

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Figure Legends

Figure 1 MDI as compared with CSII and islet transplantation

Figure 2 Maximum stimulated C-peptide response 12 months post islet transplantation and total daily insulin (IU/kg) in 10 recipients.
Figure 1A
Figure 1B
Figure 1C
Figure 2
Table 1

Treatment group characteristics- paired studies group 1 and group 2

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<tr>
<td>HbA1c IFCC (mmol/mol)</td>
<td>62±10</td>
<td>66±14</td>
</tr>
<tr>
<td>Continuous glucose monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean glucose (mmol/L)</td>
<td>8.8±1.9</td>
<td>8.6±2.0&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>SD glucose (mmol/L)</td>
<td>4.5±1.5</td>
<td>3.2±1.4 **</td>
</tr>
<tr>
<td>% time &lt;4.0 mmol/L (median)</td>
<td>11.5&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>3&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>% time &lt;4.0 interquartile range</td>
<td>5-18</td>
<td>1-9</td>
</tr>
<tr>
<td>% time 4-8 mmol/L (median)</td>
<td>44.5&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>48.5&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>% time 4-8 interquartile range</td>
<td>41-60</td>
<td>44-66</td>
</tr>
</tbody>
</table>

* p<0.05  ** p < 0.01  <sup>NS</sup> not significant
Table 2 CONGA4 comparisons for each treatment group

<table>
<thead>
<tr>
<th></th>
<th>MDI</th>
<th>CSII</th>
<th>CSII</th>
<th>Islet 12 mth</th>
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<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Insulin independent</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
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<tr>
<td>CONGA4</td>
<td>5.9 ± 1.9</td>
<td>4.0 ± 1.9</td>
<td>4.0 ± 1.7</td>
<td>1.8 ± 0.9</td>
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<tr>
<td>paired difference</td>
<td>1.8 ± 1.3</td>
<td>1.8 ± 1.3</td>
<td>2.1 ± 2.4</td>
<td>2.1 ± 2.4</td>
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<tr>
<td>P value</td>
<td>0.006</td>
<td>0.04</td>
<td>0.04</td>
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