Low–Blood Glucose Avoidance Training Improves Glycemic Variability in Adults With Type 1 Diabetes Complicated by Impaired Awareness of Hypoglycemia: HypoCOMPaSS Trial

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The Comparison of Optimized MDI Versus Pumps With or Without Sensors in Severe Hypoglycemia (HypoCOMPaSS) trial was a prospective, multicenter, randomized controlled trial examining the restoration of impaired awareness of hypoglycemia (IAH) and the prevention of severe hypoglycemia (SH) in adults with type 1 diabetes using multiple daily injections (MDI) compared with continuous subcutaneous insulin infusion (CSII), with or without adjunctive real-time continuous glucose monitoring (RT-CGM), using a 2 × 2 factorial design (1). Few studies are currently available to compare the difference in glucose variability (GV) between MDI and CSII and between self-monitored blood glucose (SMBG) and RT-CGM (2–4). These studies showed an improvement in GV in favor of CSII and RT-CGM. However, none of them included participants with IAH or history of SH. The aim of this study is to compare the changes in GV between MDI and CSII and between SMBG and RT-CGM group in this specific patient group with type 1 diabetes with IAH or recurrent SH.

A total of 96 participants were recruited for the study. Each participant undertook 7 days of blinded CGM using Medtronic iPro at baseline and prior to each of the four weekly visits during the 24-week randomized controlled trial period. GV was measured as glucose SD and coefficient of variation (%CV), calculated using available Excel formulas published online (5).

Overall, there were decreases in GV between baseline and week 24 measured by SD (3.9 ± 1.0 vs. 3.4 ± 0.8 mmol/L, $P < 0.001$) and %CV (41.3 ± 8.0 vs. 36.8 ± 8.1%, $P < 0.001$).

The MDI group realized improvement in GV from baseline to week 24 as measured by SD (3.8 ± 1.0 vs. 3.3 ± 0.7 mmol/L, $P = 0.007$) and %CV (42.1 ± 8.4 vs. 36.1 ± 6.7%, $P = 0.002$). The CSII group realized similar improvement in SD (4.0 ± 1.0 vs. 3.5 ± 0.8 mmol/L, $P = 0.005$) and %CV (41.7 ± 7.2 vs. 37.5 ± 9.2%, $P = 0.01$). Thus, CSII and MDI therapy did not differ in SD and %CV at baseline and week 24. However, using mixed-effects modeling, taking into account GV at each time point and other covariates, CSII appeared to have a more rapid impact in GV improvement compared with MDI, with an estimated average difference of −3.25 ± 0.96% (95% CI −5.15, −1.36) ($P = 0.001$) in %CV and a trend toward improvement in SD with difference of −0.25 ± 0.13 mmol/L (95% CI −0.50, 0.002) ($P = 0.052$) (Fig. 1).

The SMBG group realized GV improvement in %CV between baseline and week 24 (41.3 ± 6.9 vs. 37.1 ± 6.5%, $P = 0.005$). No differences were seen in SD (3.8 ± 0.9 vs. 3.5 ± 0.7 mmol/L, $P = 0.069$). In the RT-CGM group, GV improvement was seen in both SD (4.0 ± 1.0 vs. 3.4 ± 0.8 mmol/L, $P < 0.001$) and %CV (42.4 ± 8.5 vs. 36.8 ± 9.4%, $P = 0.003$). SMBG and RT-CGM groups did not differ at baseline and week 24. Further, these groups did not differ when GV was analyzed using mixed-effects modeling (Fig. 1).

These data suggest that the educational intervention has played an important part

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A complete list of the members of the HypoCOMPaSS Study Group can be found in the APPENDIX.

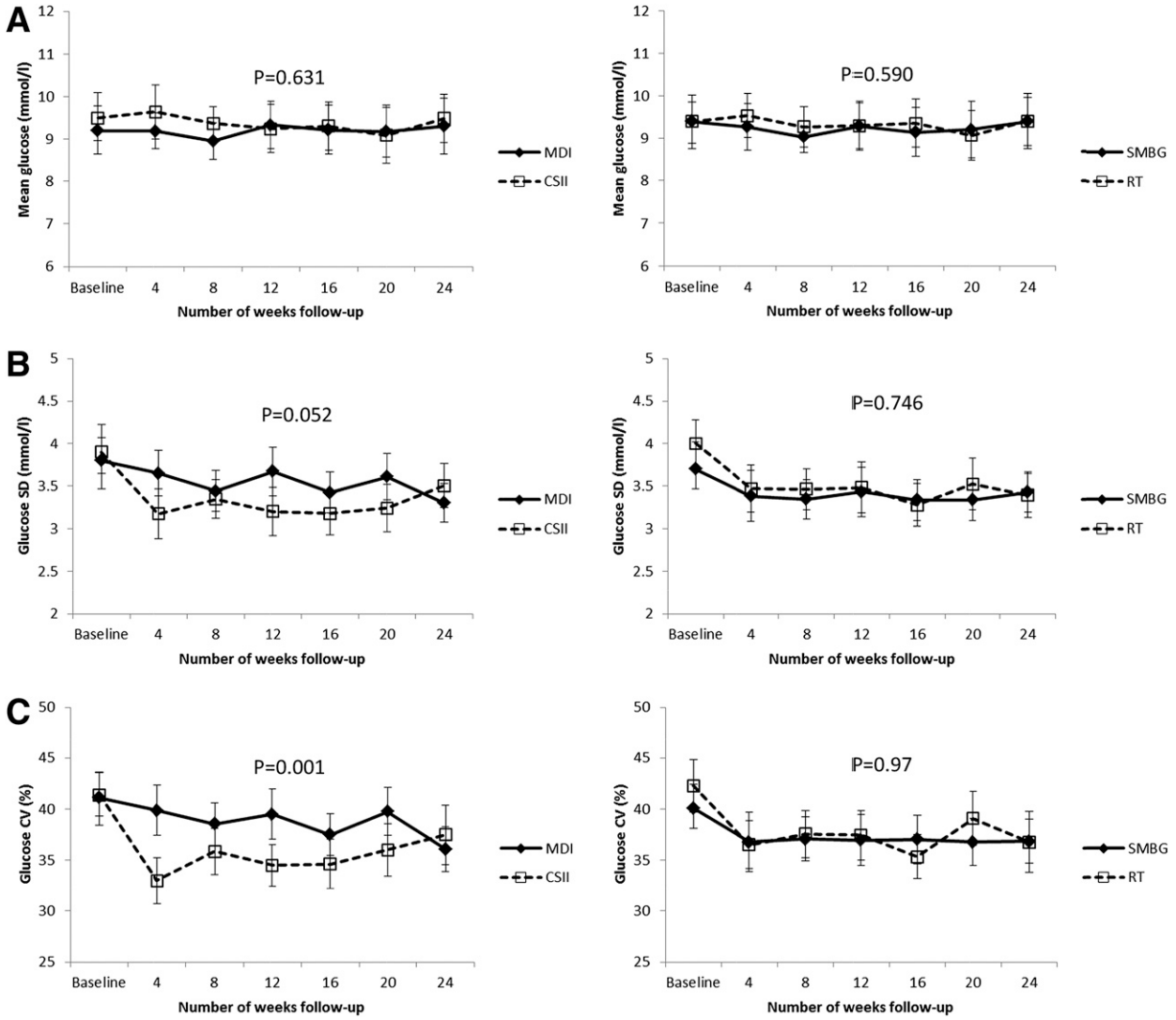

Figure 1—Glucose variability over time (mean, 95% CI) according to insulin comparator group (left) and monitoring comparator group (right). The difference between groups was established using mixed-effects models, taking into account data at all time points. *A*: Mean glucose (mmol/L). *B*: Glucose SD (mmol/L). *C*: Glucose CV (%). RT, RT-CGM.

in improving GV, although there was no specific control group to support this hypothesis.

In conclusion, we have shown that GV can be improved within 24 weeks in adults with long-standing type 1 diabetes complicated by IAH and recurrent SH. This was seen in all four arms of the study, suggesting that the education-based intervention coupled with weekly health care professional input was essential.

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Author Contributions. H.K.T. and D.F. wrote the first draft of the manuscript. H.K.T., S.A.L., L.L., E.W., and A.L.-S. contributed to the collection and review of the study data. Statistical analysis was undertaken by J.H. All authors reviewed and commented on various versions of the manuscript. D.F. is the guarantor of this

work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. An abstract containing some of the reported data was presented at the Diabetes UK Professional Conference, London, U.K.,11–13 March 2015.

Appendix

HypoCOMPaSS Study Group. AHP Research: S.M. Barendse, C.V. McMillan, and J. Speight; Bournemouth: J. Begley, A. Bowes, O. Chapple, D. Kerr, and M. Nation; Cambridge: H. Brown, K. Davenport, M.L. Evans, S. Hartnell, L. Leelarathna, C. Riches, and C. Ward; Newcastle: C. Brennand, C. Gordon, A. Lane, S.A. Little, S.M. Marshall, J.A.M. Shaw, J. Stickland, L. Thompson, and R. Wood; Sheffield: M. Cunningham, S.R. Heller, S. Hudson, A. Lubina-Solomon, C. Nisbet, and E. Walkinshaw; Plymouth: D. Flanagan, S. Read, and H.K. Tan.

Trial Steering Committee. S.A. Amiel (chair), J. Begley, C. Brennand, T. Chadwick, E. Davidson, M.L. Evans, D. Flanagan, L. Hall, S.R. Heller, V. King, S.A. Little, C. Littlewood, J. Matthews, J.A.M. Shaw, C. Speed, J. Speight, and R. Wood.

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