Duration of Hybrid Closed-Loop Insulin Therapy to Achieve Representative Glycemic Outcomes in Adults With Type 1 Diabetes

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Closed-loop insulin therapy increases the time spent in target glucose range (70–180 mg/dL) while reducing the time spent in hypoglycemia (<70 mg/dL) and hyperglycemia (>180 mg/dL) (1), and it is being progressively applied in clinical practice. Randomized clinical trials of closed-loop insulin delivery have been performed over a single day to several months, but the time required to achieve representative glucose outcomes, including control algorithm individualization and behavioral adaptation, is currently unknown. To address this issue we analyzed retrospectively data collected during closed-loop clinical trials in adults with type 1 diabetes and A1C ≥58 mmol/mol (≥7.5%) as such information may be useful in determining the optimal duration of future closed-loop studies as well as follow-up assessments under routine care conditions.

We combined data collected in adults aged 21 years and older during two multinational (U.K., U.S., Austria, and Germany), randomized, day-and-night, hybrid closed-loop studies (2,3) (AP@home04 and APCam11) of 12 weeks' duration (N = 56, mean ± SD A1C 68 ± 7 mmol/mol [8.4 ± 0.6%] [range 58–83 mmol/mol (7.5–9.7%)], age 39 ± 10 years [range 21 to 65 years], diabetes duration 21 ± 9 years [range 6 to 49 years]). The AP@home04 study (2) utilized Dana Diabecare R insulin pump (Sooil, Seoul, South Korea) and FreeStyle Navigator II glucose sensor (Abbott Diabetes Care, Alameda, CA), while the APCam11 study (3) used a modified Medtronic 640G insulin pump and Guardian 3 glucose sensor (Medtronic, Northridge, CA). Both studies used an identical individually adapting, treat-to-target, model-predictive control algorithm residing on a smartphone. Participants were required to deliver a premeal bolus based on carbohydrate content, were not remotely monitored or supervised, and were able to follow usual activities of daily living.

For each participant, glucose sensor metrics were calculated over the full 12-week study period and also restricting data to 60 sampling periods representing day 1, 2, . . .59, 60 of closed-loop use. For each glucose sensor metric, the association between its value over a sampling period and its value calculated over the full 12 weeks of closed loop use was assessed using Pearson (for normally distributed data) or Spearman correlation coefficient (otherwise). The correlation coefficient between the 12-week laboratory A1C value and the mean sensor glucose was also calculated. We used SPSS Version 22 (IBM, Portsmouth, U.K.) for the statistical analyses.

Over 12 weeks, percent time spent in 70–180 (mean ± SD) mg/dL, >180 mg/dL (mean ± SD), <70 mg/dL (median [IQR]) were 67 ± 10%, 30 ± 11%, and 2.4% [1.6, 3.8], respectively. The numbers of days needed to reach a correlation coefficient of 0.95 (explaining 90% of total variance) for percent time 70–180 mg/dL, percent time >180 mg/dL, mean sensor glucose, percent time >250 mg/dL, percent time <70 mg/dL, percent time <54 mg/dL, and coefficient of variation of sensor glucose were 26, 24, 27, 33, 38, 49, and 47 days, respectively (Fig. 1). Closed-loop usage time was stable between 81% and 83% throughout the study period. The correlation coefficient between mean sensor glucose over the full 12-week study period and laboratory A1C level at 12 weeks was 0.82, and over a 4-week sampling period the

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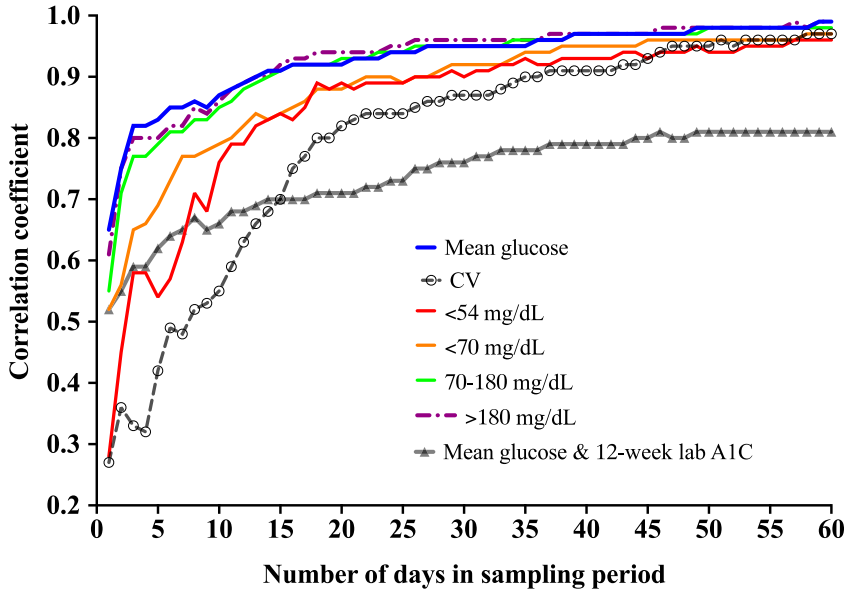

Figure 1—The correlation coefficient between continuous glucose monitoring data over the first 1, 2, ... 60 days of closed-loop use and the respective values collected over the entire 12-week study period for standard glucose metrics. The correlation coefficient between 3-month laboratory A1C value and the mean sensor glucose measured data over the sampling periods is also shown. CV, coefficient of variation.

correlation coefficient was close to the 12-week value at 0.76.

To the best of our knowledge, this is the first analysis to determine the duration of hybrid closed-loop therapy to achieve stable sensor glucose metrics. Previous work has shown that 14 days of continuous glucose monitoring data provide a good approximation of glucose metrics collected over a 12-week period (4). Our results suggest a longer period when closed-loop insulin therapy is applied, which may reflect adaptation/individualization of a closed-loop algorithm and behavioral adjustments. Limitations of our work include retrospective analysis, use of a single closed-loop algorithm, lack of information about prior continuous glucose monitoring, and a maximum duration of data availability of 12 weeks. In conclusion, in adults with type 1 diabetes and baseline A1C ≥58 mmol/mol (≥7.5%), hybrid closed-loop insulin therapy of 4 weeks' duration provides representative data for mean glucose and percentage time spent in normoglycemia and hyperglycemia. For reliable estimates of hypoglycemia and glucose variability, 6 weeks' duration may be required. Our data may inform design of future closed-loop studies.

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Duality of Interest. L.L. reports having received speaker honoraria from Animas, Abbott, Insulet, Medtronic, Novo Nordisk, Roche, and Sanofi; serving on advisory panels for Animas, Abbott, Novo Nordisk, Dexcom, Medtronic, Sanofi, and Roche; and research support from Novo Nordisk and Dexcom. J.K.M. is a member of the advisory board of Boehringer Ingelheim, Eli Lilly, Medtronic, Prediktor A/S, Roche Diabetes Care, and Sanofi and received speaker honoraria from Abbott Diabetes Care, AstraZeneca, Dexcom, Eli Lilly, Medtronic, Merk Sharp & Dohme, Novo Nordisk A/S, Roche Diabetes Care, Sanofi, Servier, and Takeda. T.R.P. is an advisory board member of Novo Nordisk A/S; a consultant for Roche Diabetes Care, Novo Nordisk A/S, Eli Lilly & Co, Infineon, and Carnegie Bank; is on the speakers bureau of Novo Nordisk A/S and AstraZeneca; and is shareholder of decide Clinical Software GmbH. V.N.S. reports grants and personal fees from Sanofi U.S. and Dexcom through the University of Colorado and grants from EyeNuk, Jaeb Center for Health Research, National Institutes of Health (National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Diabetes and Digestive and Kidney Diseases), Novo Nordisk, and vTv Therapeutics, outside the submitted work. A.L.C. reports having received speaker honoraria from Minimed Medtronic, serving on advisory panels for Sanofi and Minimed Medtronic, and as a consultant to Sensionics and Eli Lilly. A.L.C.'s employer, the non-profit HealthPartners Institute, contracts for his services and no personal income goes to A.L.C. R.M.B. has received research support from, consulted for, or been on a scientific advisory board for Abbott Diabetes Care, Dexcom, Eli Lilly, Johnson & Johnson, Medtronic, Novo Nordisk, Onduo, Roche, Sanofi, and United HealthCare. His research is partly funded by the National Institute of Diabetes and Digestive and Kidney Diseases (National Institutes of Health grant DK108611). R.M.B.'s employer, the non-profit HealthPartners Institute, contracts for his services and no personal income goes to R.M.B. M.L.E. has received speaker/writer fees from Novo Nordisk, Eli Lilly, AstraZeneca, Medtronic, and Abbott Diabetes Care; has been on scientific advisory boards for Novo Nordisk, Roche, Eli Lilly, Zucara, PK Vitality, Medtronic, and Dexcom; and has research collaborations with Sanofi, Novo Nordisk, Medtronic, Roche, NGM Pharma, Imcyse, and Boehringer Ingelheim. R.H. reports having received speaker honoraria from Minimed Medtronic, LifeScan, Eli Lilly, BBraun, and Novo Nordisk; serving on advisory panels for Animas, Minimed Medtronic, and Eli Lilly; receiving license fees from BBraun and Beckton Dickinson; and having served as a consultant to Beckton Dickinson, BBraun, Sanofi, and Profil. No other potential conflicts of interest relevant to this article were reported.

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