



Recovery of Hypoglycemia Awareness in Long-standing Type 1 Diabetes: A Multicenter 2 × 2 Factorial Randomized Controlled Trial Comparing Insulin Pump With Multiple Daily Injections and Continuous With Conventional Glucose Self-monitoring (HypoCOMPASS)

Diabetes Care 2014;37:2114–2122 | DOI: 10.2337/dc14-0030

Stuart A. Little,¹ Lalantha Leelarathna,² Emma Walkinshaw,³ Horng Kai Tan,⁴ Olivia Chapple,⁵ Alexandra Lubina-Solomon,³ Thomas J. Chadwick,⁶ Shalleen Barendse,⁷ Deborah D. Stocken,⁶ Catherine Brennand,⁶ Sally M. Marshall,¹ Ruth Wood,⁶ Jane Speight,^{7,8,9} David Kerr,¹⁰ Daniel Flanagan,⁴ Simon R. Heller,³ Mark L. Evans,² and James A.M. Shaw^{1,*}

OBJECTIVE

To determine whether impaired awareness of hypoglycemia (IAH) can be improved and severe hypoglycemia (SH) prevented in type 1 diabetes, we compared an insulin pump (continuous subcutaneous insulin infusion [CSII]) with multiple daily injections (MDIs) and adjuvant real-time continuous glucose monitoring (RT) with conventional self-monitoring of blood glucose (SMBG).

RESEARCH DESIGN AND METHODS

A 24-week 2 × 2 factorial randomized controlled trial in adults with type 1 diabetes and IAH was conducted. All received comparable education, support, and congruent therapeutic targets aimed at rigorous avoidance of biochemical hypoglycemia without relaxing overall control. Primary end point was between-intervention difference in 24-week hypoglycemia awareness (Gold score).

RESULTS

A total of 96 participants (mean diabetes duration 29 years) were randomized. Overall, biochemical hypoglycemia (≤ 3.0 mmol/L) decreased (53 ± 63 to 24 ± 56 min/24 h; $P = 0.004$ [t test]) without deterioration in HbA_{1c}. Hypoglycemia awareness improved (5.1 ± 1.1 to 4.1 ± 1.6 ; $P = 0.0001$ [t test]) with decreased SH (8.9 ± 13.4 to 0.8 ± 1.8 episodes/patient-year; $P = 0.0001$ [t test]). At 24 weeks, there was no significant difference in awareness comparing CSII with MDI (4.1 ± 1.6 vs. 4.2 ± 1.7 ; difference 0.1; 95% CI -0.6 to 0.8) and RT with SMBG (4.3 ± 1.6 vs. 4.0 ± 1.7 ; difference -0.3 ; 95% CI -1.0 to 0.4). Between-group analyses demonstrated comparable reductions in SH, fear of hypoglycemia, and insulin doses with equivalent HbA_{1c}. Treatment satisfaction was higher with CSII than MDI (32 ± 3 vs. 29 ± 6 ; $P = 0.0003$ [t test]), but comparable with SMBG and RT (30 ± 5 vs. 30 ± 5 ; $P = 0.79$ [t test]).

CONCLUSIONS

Hypoglycemia awareness can be improved and recurrent SH prevented in long-standing type 1 diabetes without relaxing HbA_{1c}. Similar biomedical outcomes can be attained with conventional MDI and SMBG regimens compared with CSII/RT, although satisfaction was higher with CSII.

¹Institute of Cellular Medicine, Newcastle University, Newcastle, U.K.

²Wellcome Trust-MRC Institute of Metabolic Science Metabolic Research Laboratories, University of Cambridge, Cambridge, U.K.

³School of Medicine and Biomedical Sciences, Sheffield University, U.K.

⁴Peninsula College of Medicine and Dentistry, Plymouth, U.K.

⁵Bournemouth Diabetes and Endocrine Centre, Royal Bournemouth Hospital, Bournemouth, U.K.

⁶Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, Newcastle, U.K.

⁷AHP Research, Hornchurch, U.K.

⁸The Australian Centre for Behavioural Research in Diabetes, Diabetes Australia–Vic, Melbourne, Australia

⁹Centre for Mental Health and Wellbeing Research, School of Psychology, Deakin University, Burwood, Australia

¹⁰Centre for Postgraduate Medical Research and Education, Bournemouth University, U.K.

Corresponding author: James A.M. Shaw, jim.shaw@ncl.ac.uk.

Received 5 January 2014 and accepted 1 April 2014.

Clinical trial reg. nos. ISRCTN52164803, www.isrctn.org, and EudraCT2009-015396-27, <http://eudract.ema.europa.eu/>.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0030/-/DC1>.

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

© 2014 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

Over 90 years since the discovery of insulin, severe hypoglycemia (SH) requiring the assistance of another person for recovery (1), remains the most feared complication of insulin therapy (2). Prevalence increases with diabetes duration, annually affecting nearly half with type 1 diabetes for >15 years (3).

SH is six times more common in those whose ability to recognize hypoglycemia is impaired (4). This syndrome of impaired awareness of hypoglycemia (IAH) affects ~25% with established type 1 diabetes (5). IAH and recurrent SH impose a major burden on the individual, their families, and the wider community through the ever-present risk of collapse without warning.

The Diabetes Control and Complications Trial provided incontrovertible evidence that intensive glycemic control achieved with multiple daily insulin injections (MDIs) or continuous subcutaneous insulin infusion (CSII) pumps could prevent development and progression of microvascular and macrovascular complications (6,7). Intensive insulin therapy within Diabetes Control and Complications Trial was, however, associated with a threefold increase in SH (8).

Large-scale intervention trials in type 1 diabetes generally focus on attainment of optimal HbA_{1c} using a treat-to-target approach. Despite the desire to show that new treatments/technologies carry less hypoglycemia risk, trials have not been powered robustly to evaluate impact on significant hypoglycemia, with low event rates seen typically through active exclusion of those with IAH/SH.

Reduction in biochemical hypoglycemia has been demonstrated with both short- and long-acting insulin analogs in comparison with human MDI regimens, but impact on IAH/SH has not been confirmed (9). There is some evidence that CSII can reduce SH in comparison with MDIs (10,11), but none of the randomized controlled trials (RCTs) reporting benefit have included long-acting insulin analogs in the control arm. Accruing evidence suggests that real-time continuous glucose monitoring (RT-CGM) can reduce duration of biochemical hypoglycemia (12–14), but whether this can restore counterregulatory hormone response in IAH remains unclear (15).

Single-center studies in adults with type 1 diabetes and SH have shown

that rigorous biochemical hypoglycemia avoidance can restore awareness (16–19). In a 24-week pilot study in this high-risk group, we compared optimized analog MDI and CSII interventions with a control group in which the current insulin regimen was maintained with relaxation of self-monitored blood-glucose targets. All groups were provided with equivalent education and support. Prevention of recurrent SH was achieved in >70% with all interventions, together with better overall glycemic control in MDI and CSII groups than in the education-alone control arm (20).

Informed by this, we undertook a multicenter RCT in participants with established C-peptide-negative type 1 diabetes complicated by IAH, designed to determine robustly whether awareness can be improved and recurrent SH prevented through rigorous prevention of biochemical hypoglycemia without worsening overall glycemic control. CSII was compared with optimized analog MDIs and adjuvant RT with conventional glucose self-monitoring. The null hypothesis to be tested was that when provided with equivalent education, attention, and support, comparable improvement in hypoglycemia awareness, avoidance of recurrent SH, overall glycemic control, and treatment satisfaction would be attained in this high-risk group, independent of insulin delivery modality or ongoing access to RT.

RESEARCH DESIGN AND METHODS

The full study protocol is published (21) and accessible online (<http://www.ncl.ac.uk/nctu/assets/documents/hypoCOMPASS%20Protocol%20version%203.1%20-%2026%20Apr%202012.pdf>).

We undertook a 24-week, multicenter, randomized, 2 × 2 factorial study at five U.K. tertiary-referral diabetes centers, all routinely offering structured type 1 diabetes education with expertise in hypoglycemia assessment/management and use of CSII/RT. A 2 × 2 trial design was used to enable adequately powered comparison of pump with optimized analog insulin delivery and adjuvant RT with conventional glucose monitoring within a single RCT.

Eligible participants were aged 18–74 years with C-peptide-negative type 1 diabetes and IAH confirmed by Gold score ≥4 (5). Full eligibility criteria are detailed in the study protocol (21).

Research Ethics Committee approval and Medicines and Healthcare Products Regulatory Agency clinical trial authorization were obtained.

Using a Web-based system, participants were randomly allocated on an equal allocation basis, stratified by baseline HbA_{1c} (<8.0% [64 mmol/L] and ≥8.0% [64 mmol/mol]) and by site, to one of four groups: MDI with self-monitoring of blood glucose (SMBG); MDI with SMBG and RT-CGM; CSII with SMBG; and CSII with SMBG and RT-CGM. The allocation sequence was generated by an individual not otherwise involved with participant recruitment.

Stratification by HbA_{1c} was included to minimize selection bias, as it was hypothesized that two subgroups may not respond to the trial intervention and achieve improved hypoglycemia awareness or reduction in SH: those with a strong psychobehavioral drive to avoid high glucose even if this leads to recurrent biochemical hypoglycemia (characterized by lower HbA_{1c}); and those with severe autonomic dysfunction precluding satisfactory restoration of awareness despite effective biochemical hypoglycemia avoidance (characterized by suboptimal HbA_{1c}).

Procedures

For 4 weeks after recruitment, participants recorded daily four-point and weekly eight-point glucose profiles (CONTOUR LINK glucometer; Bayer Healthcare) and undertook 7-day blinded CGM (iPro1; Medtronic). At a subsequent baseline visit, diabetes-specific history including frequency and consequences of SH over the preceding 12 months was taken. Hypoglycemia awareness was re-evaluated at baseline using validated Gold (5) and Clarke (22) questionnaires. To improve sensitivity to change over a short period, we used also the Hypoglycemia Awareness Questionnaire (HypoA-Q), recently validated outside the current study (23). Screening was undertaken for undiagnosed thyroid, Addison, and celiac disease (21).

Prior to randomization, all participants attended a single 1- to 2-h standardized education session derived from the pilot study (20), individually or in small groups of up to four. This comprised facilitated discussions targeted specifically toward rigorous avoidance of biochemical

hypoglycemia while maintaining overall glycemic control. The four points of the hypo-compass established the imperatives: never delay hypoglycemia treatment; recognize personalized times of increased risk; detect subtle symptoms; and confirm low glucose levels through regular self-monitoring, particularly for nocturnal hypoglycemia. Also included was advice on self-adjustment of insulin doses according to carbohydrate intake, SMBG, and planned activity and recommendation for oral carbohydrate administration for all glucose levels <4.0 mmol/L.

Randomized Interventions

Following randomization, the number of study visits was the same for all participants, tailored for each group to technical aspects of their insulin administration and glucose monitoring intervention (21). All participants, whether allocated aspart insulin delivery by CSII (Paradigm Veo insulin pump; Medtronic) or MDIs (aspart/glargine) were given an insulin pump enabling benefit from direct transmission of SMBG levels to bolus calculator. Those randomized to RT (REAL-Time Continuous Glucose Monitoring System; Medtronic) were trained on sensor insertion, calibration, and use of monitor including trend analysis and hypo-/hyperglycemia alerts. Participants were able to individualize alarm settings but did not use the low-glucose suspend (LGS) feature. Continuous RT use was encouraged but not mandatory.

Participants recorded SH episodes prospectively and were recalled every 4 weeks up to 24 weeks. All participants were given identical written guidance on insulin titration primarily targeted toward absolute avoidance of biochemical hypoglycemia (21). Glargine was administered before bed with addition of a second dose before breakfast in those with consistent glucose >7.0 mmol/L before the evening meal or highly variable glucose levels between breakfast and the evening meal. Each study visit was preceded by a 7-day retrospective CGM profile, with participants and investigators blinded to data until study completion. Between study visits, participants were telephoned weekly to reinforce insulin titration guidelines and maintain focus on hypoglycemia avoidance.

Outcomes

The prespecified primary outcome was difference in hypoglycemia awareness

(assessed by Gold score at week 24) between MDI and CSII groups and between RT and non-RT groups. Prespecified secondary end points were differences between interventions at 24 weeks in hypoglycemia awareness assessed by Clarke and HypoA-Q scores; biochemical hypoglycemia (identified by blinded CGM profiles); SH rate (annualized) and proportion affected; overall glycemic control by analysis of HbA_{1c}, blinded CGM (mean and SD) and SMBG; total daily insulin dose, body weight; and patient-reported outcomes, primarily fear of hypoglycemia (Hypoglycemia Fear Survey II [HFS-II]) (24) and satisfaction with treatment (Diabetes Treatment Satisfaction Questionnaire [DTSQ]) (25).

Safety end points were hospital admissions, diabetic ketoacidosis, and insulin delivery/glucose monitoring-related infections.

Statistical Considerations

The analysis strategy is published (21). Recruitment of 100 participants was planned to give 80% power at a significance level of 0.05 to detect a difference of 1.1 between the 24-week Gold score (primary outcome) of the 50 participants randomized to CSII and the 50 randomized to MDI when using Student *t* test. Difference of 1.1 was based on the pilot study and deemed clinically significant as reduction from an integer score of 4 to 3 equates to restoration of awareness (20).

Data were analyzed on an intention-to-treat basis retaining ineligible participants and protocol violators in their randomized groups. Data were assessed for normality, transformed where necessary, and are presented as mean (SD) and proportions with 95% CIs as appropriate.

Following the 24-week CSII versus MDI analysis using Student *t* test (equivalent to Model 1), the factorial structure of treatment and monitoring regimen effects on difference in Gold score at 24 weeks was examined using ANCOVA. These analyses accounted for all stratification factors (Model 2), baseline scores, and important baseline covariates including patient age (listed in Table 1) following screening of these covariates according to univariate significance (Model 3) in multivariate generalized linear models. Analyses of other outcomes followed a broadly similar

strategy, although alternative tests (Wilcoxon signed-rank, Mann-Whitney *U*, McNemar, χ^2 , and Fisher exact test) were used as appropriate.

Planned per-protocol analyses of selected outcomes were also undertaken for RT users only to allow use of the covariate of low or high RT use (<50 vs. $\geq 50\%$ of days in study).

Data analysis took the form of a complete case analysis. Missing data were not deemed sufficient to justify imputation of values. Significance levels were set at $\alpha = 0.05$ throughout.

RESULTS

Participants

A total of 110 adults with IAH (defined as Gold score ≥ 4) were recruited, but 6 participants did not meet C-peptide inclusion criterion, and 8 withdrew from the study before randomization (Supplementary Fig. 1). Ninety-six were randomized, all with long-standing (mean duration 29 years) C-peptide-negative (<50 pmol/L in all except two: 87; 103 pmol/L) type 1 diabetes. Six participants did not adhere to their randomized treatment but have been included as randomized in the intention-to-treat analysis.

At baseline, 97% were using MDI regimens and 3% CSII (Supplementary Fig. 1). The annualized SH rate over the preceding 6 months was 8.9 episodes/patient-year. A total of 77% of participants were affected over the preceding 6 months and 92% over the preceding 12 months. A total of 18% had required glucagon administration, 19% paramedic assistance, and 6% hospital attendance/admission for SH over the preceding 6 months, with 32, 33, and 12%, respectively, over the preceding 12 months.

Two-thirds of the participants had diabetic retinopathy, with other microvascular and macrovascular complications less common (Table 1). Injection-site lipohypertrophy and postural hypotension were frequent, with 8% reporting gastroparesis. A total of 29% had treated thyroid disease, 3% celiac disease, and one was taking corticosteroid replacement for primary adrenal insufficiency. Mean HbA_{1c} was 8.3% (67 mmol/mol) and $<8.0\%$ (64 mmol/mol) in 43%.

Demographic and clinical characteristics were similar in all groups (Table 1). After 4 weeks of intervention, 50% of

Table 1—Demographic and clinical characteristics of participants at baseline

| | All | Insulin comparison | | Monitoring comparison | |
|--------------------------------------|-------------|--------------------|-------------|-----------------------|-------------|
| | | MDI | CSII | SMBG | RT |
| Site† | | | | | |
| Bournemouth | 16 (17) | 8 (16) | 8 (17) | 7 (15) | 9 (19) |
| Cambridge | 21 (22) | 11 (22) | 10 (22) | 11 (23) | 10 (21) |
| Newcastle | 22 (23) | 12 (24) | 10 (22) | 11 (23) | 11 (23) |
| Plymouth | 17 (18) | 10 (20) | 7 (15) | 9 (19) | 8 (17) |
| Sheffield | 20 (21) | 9 (18) | 11 (24) | 10 (21) | 10 (21) |
| Baseline HbA _{1c} † | | | | | |
| <8% | 41 (43) | 22 (44) | 19 (41) | 21 (44) | 20 (42) |
| ≥8% | 55 (57) | 28 (56) | 27 (59) | 27 (56) | 28 (58) |
| HbA _{1c} (%)* | 8.2 ± 1.2 | 8.2 ± 1.3 | 8.2 ± 1.2 | 8.3 ± 1.3 | 8.2 ± 1.1 |
| HbA _{1c} (mmol/mol) | 66 ± 12 | 66 ± 13 | 66 ± 12 | 67 ± 13 | 66 ± 11 |
| Age (years) | 48.6 ± 12.2 | 47.0 ± 12.3 | 50.3 ± 12.0 | 47.1 ± 11.8 | 50.1 ± 12.6 |
| Male | 35 (36) | 16 (32) | 19 (41) | 20 (42) | 15 (31) |
| Diabetes duration (years)* | 28.9 ± 12.3 | 29.5 ± 12.5 | 28.2 ± 12.2 | 26.7 ± 12.1 | 31.0 ± 12.2 |
| Body weight (kg)* | 74.7 ± 14.2 | 74.9 ± 13.9 | 74.5 ± 14.6 | 74.5 ± 14.6 | 75.0 ± 13.9 |
| BMI (kg/m ²)* | 26.5 ± 4.4 | 26.7 ± 4.6 | 26.3 ± 4.4 | 26.1 ± 4.3 | 26.9 ± 4.7 |
| Insulin dose (units/kg/24 h)* | 0.64 ± 0.23 | 0.63 ± 0.21 | 0.66 ± 0.26 | 0.61 ± 0.19 | 0.68 ± 0.27 |
| Current smokers* | 21 (22) | 14 (28) | 7 (16) | 11 (23) | 10 (21) |
| Ex-smokers | 26 (28) | 12 (24) | 14 (32) | 14 (30) | 12 (26) |
| Never smoked | 47 (50) | 24 (48) | 23 (52) | 22 (47) | 25 (53) |
| Alcohol consumers* | 62 (65) | 32 (65) | 30 (65) | 35 (75) | 27 (56) |
| Lipohypertrophy* | 35 (38) | 15 (32) | 20 (44) | 18 (38) | 17 (38) |
| Retinopathy* | 61 (64) | 36 (73) | 25 (54) | 29 (62) | 32 (67) |
| Laser photocoagulation | 24 (25) | 15 (30) | 9 (20) | 10 (21) | 14 (29) |
| Microalbuminuria* | 22 (24) | 13 (27) | 9 (21) | 10 (22) | 12 (26) |
| Creatinine (μmol/L)* | 74.4 ± 20.5 | 75.7 ± 25.9 | 73.0 ± 12.4 | 72.3 ± 19.3 | 76.5 ± 21.6 |
| Peripheral neuropathy | 18 (19) | 8 (16) | 10 (22) | 8 (17) | 10 (21) |
| Atherosclerotic disease | 13 (14) | 4 (8) | 9 (20) | 8 (17) | 5 (10) |
| Treated thyroid disease | 28 (29) | 14 (28) | 14 (30) | 17 (35) | 11 (23) |
| Postural hypotension* | 26 (27) | 14 (29) | 12 (26) | 13 (27) | 13 (28) |
| Mean study visits/person (maximum 7) | 6.6 | 6.6 | 6.6 | 6.5 | 6.8 |

Data are number of patients (%) or mean ± SD. Alcohol consumers were defined as those who reported drinking one or more units of alcohol per week at baseline. *Excludes participants with data missing for indicated variable (number missing: HbA_{1c}, one; duration of diabetes, one; body weight, one; BMI, one; insulin dose, two; smoking status, two; alcohol consumption, one; lipohypertrophy, four; retinopathy, one; microalbuminuria, four; creatinine, four; and postural hypotension, one). †Stratification variables.

participants in the MDI arm were injecting glargine twice daily, increasing to 68% at 24 weeks.

Overall Outcomes

In the overall study population, biochemical hypoglycemia assessed by blinded 7-day CGM was significantly reduced according to all prespecified criteria (Supplementary Table 1). Time ≤3.0 mmol/L was reduced by more than half from 53 ± 63 min/24 h at baseline to 24 ± 56 min at end point (Fig. 1A). This was achieved rapidly over the first 4 weeks and maintained throughout the study in tandem with an early and sustained eight-unit reduction in mean total daily insulin dose.

Awareness of hypoglycemia improved, with significant reductions in

Gold, Clarke, and HypoA-Q IAH subscale scores (Table 2). Clarke and HypoA-Q scores correlated ($r = 0.53$ – 0.74) with Gold score at baseline and study end point. Annualized SH rate fell >10-fold, with 20% of participants experiencing severe events during the RCT in comparison with 77% over the preceding 6 months. Three (3%) participants required glucagon administration and three (3%) paramedic attendance during the RCT.

Other aspects of glycemic control assessed by HbA_{1c}, SMBG, and CGM mean glucose (Supplementary Table 1) did not deteriorate, with improvement in glucose variability determined by CGM SD. HbA_{1c} remained within target (<8.0% [64 mmol/mol]) in those with a value below this cutoff at baseline, with a

nonsignificant 0.3% (3 mmol/mol) improvement in HbA_{1c} in those with baseline HbA_{1c} ≥64 mmol/mol (Fig. 1B). Perceived frequency of hypoglycemia and hyperglycemia, fear of hypoglycemia, and treatment satisfaction improved significantly (Table 2).

Insulin Delivery Comparison

There was no significant unadjusted (Model 1) difference in hypoglycemia awareness at 24 weeks between those randomized to MDI (Gold score: 4.1 ± 1.6) and CSII (Gold score: 4.2 ± 1.7) (Table 3) (difference: 0.1; 95% CI -0.6 to 0.8 ; $P = 0.76$ [t test]). Adjusting for covariates (stratification factors: Model 2; and baseline covariates: Model 3) gave comparable results (Supplementary Table 1).

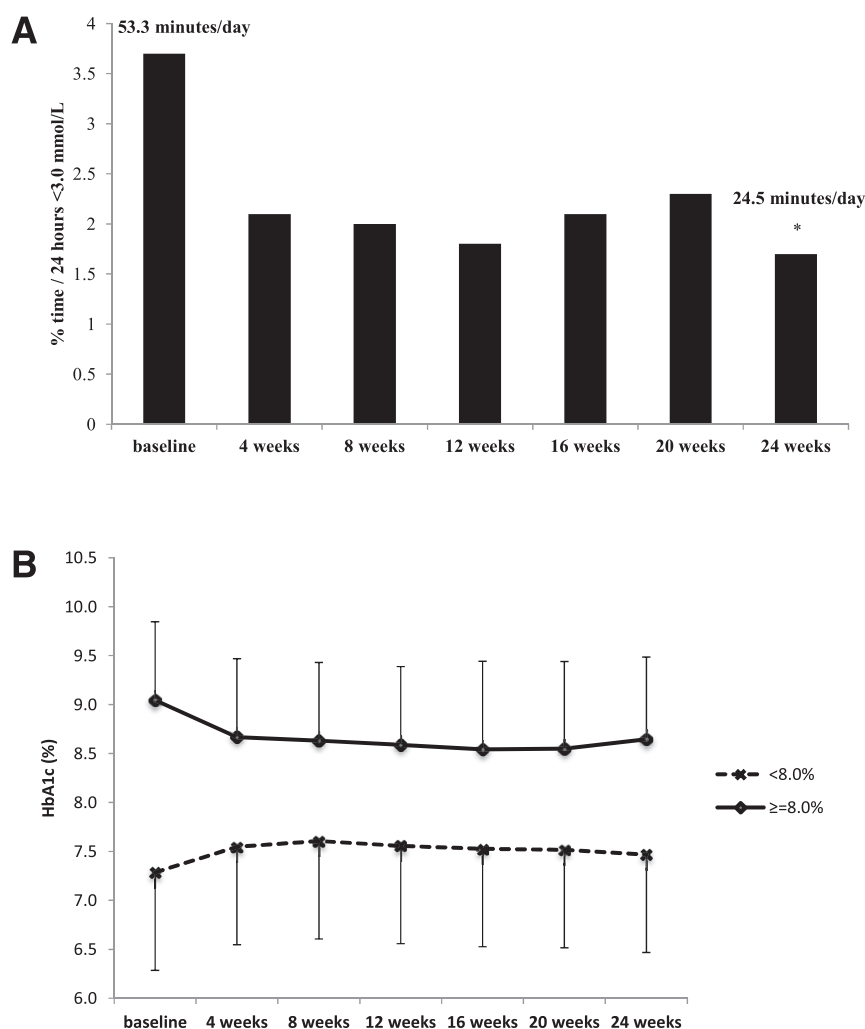


Figure 1—A: Percentage of time with glucose <3.0 mmol/L during monthly blinded CGM in the overall study population. B: Mean HbA_{1c} over time in the overall study population stratified by baseline value <8.0% (64 mmol/mol) and ≥8.0% (64 mmol/mol). *Paired *t* test (complete pairs only between week 24 end point and baseline [*P* = 0.004]).

Reductions in SH and metabolic secondary outcome measures were also similar in the MDI and CSII groups, with comparable reductions in insulin doses (Supplementary Table 1). Fear of hypoglycemia was reduced equally, as were perceived frequency of hypoglycemia and hyperglycemia. Overall treatment satisfaction was, however, higher in those randomized to CSII (Table 3).

ANCOVA adjusted for indicated covariates supported absence of influence of the insulin treatment group (Supplementary Table 1) on the majority of secondary outcome measures, either through analyses of change over the study period or explicit adjustment for baseline values. The CSII group experienced a significantly larger increase in treatment satisfaction than MDI participants across all three fitted models.

Monitoring Regimen Comparison

The 24-week Gold and other IAH scores were similar in those continuing with conventional SMBG in comparison with those randomized to adjuvant RT (Table 3) (unadjusted [Model 1] Gold score difference: -0.3 ; 95% CI -1.0 to 0.4 ; *P* = 0.42 [*t* test]). Adjusting for covariates (stratification factors: Model 2; and baseline covariates: Model 3) gave comparable results (Supplementary Table 1).

All secondary outcome measures including treatment satisfaction were comparable between these two interventions (Table 3 and Supplementary Table 1). ANCOVA adjusted for indicated covariates also supported absence of influence of the glucose-monitoring group (Supplementary Table 1). Comparing adjuvant RT and conventional SMBG groups, there was a significantly larger

decrease in annualized SH rate (RT: 11.3 events/patient-year at baseline reduced to 0.8 events/patient-year at 24 weeks; SMBG: 6.4 vs. 0.8 events). This was driven by baseline differences in incidence and should be interpreted with caution, as events during the trial were directly comparable between groups.

Low-glucose alerts were used in 46 (96%) and predictive low-glucose alerts in 45 (94%) RT participants. At the end of the study, 35 (75%) stated that RT was beneficial in preventing SH, and 13 (28%) felt that RT was beneficial in preventing symptomatic/severe high-glucose levels. The most useful feature in preventing SH was deemed the predictive low-glucose alert: 48%; low-glucose alert: 34%; and trend analysis: 18%. Sensor-site bleeding was reported in 44% and local reactions in 34% of participants.

Table 2—SH, hypoglycemia awareness, and patient-reported outcomes in overall study population at baseline and 24-week end point

| | Baseline | Week 24 (end point) | P value* |
|--|---|--|-------------------------------|
| SH | | | |
| Annualized rate (patient-year) | 8.9 ± 13.4 4 [2–7] (n = 96) | 0.8 ± 1.9 0 [0–0] (n = 90) | <0.001 <0.001† (n = 90) |
| Proportion affected (%) | 77 (n = 96) | 20 (n = 90) | <0.001 (n = 90) |
| IAH | | | |
| Gold score | 5 [4–6] (2–7) 5.1 ± 1.1 (n = 96) | 4 [3–5] (1–7) 4.1 ± 1.6 (n = 85) | <0.001 (n = 85) |
| Clarke score | 5 [4–6] (1–7) 4.1 ± 1.6 (n = 87) | 3 [2–4] (0–7) 3.2 ± 1.7 (n = 80) | <0.001 (n = 74) |
| HypoA-Q | 14 [11–16] (5–20) 13.4 ± 3.4 (n = 92) | 9.5 [6–12] (0–19) 9.1 ± 4.2 (n = 84) | <0.001 (n = 80) |
| Fear of hypoglycemia and treatment satisfaction | | | |
| HFS II–Total | 58 ± 26 (n = 94) | 45 ± 24 (n = 87) | <0.001 (n = 85) |
| HFS II–Behavior | 24 ± 11 (n = 94) | 20 ± 10 (n = 87) | <0.001 (n = 85) |
| HFS II–Worry | 35 ± 17 (n = 96) | 24 ± 17 (n = 87) | <0.001 (n = 87) |
| DTSQ–Total satisfaction | 25 ± 6 (n = 95) | 30 ± 5 (n = 84) | <0.001 (n = 84) |
| DTSQ2–Perceived frequency of hyperglycemia | 4 ± 1.29 (n = 95) | 3 ± 1.17 (n = 84) | <0.001 (n = 84) |
| DTSQ3–Perceived frequency of hypoglycemia | 4 ± 1.29 (n = 95) | 3 ± 1.18 (n = 84) | <0.001 (n = 84) |

Data are median [interquartile range] (range) or mean ± SD. Number with available data denoted by *n* number in parentheses. *Paired *t* test (complete pairs only) between week 24 end point and baseline. †Wilcoxon signed-rank test.

RT participants wore sensors for a median of 57% of the time in study with sensor usage >80% in 17 individuals (Supplementary Fig. 2). Outcomes were not significantly different in those who used sensors for >50% of time compared with less frequent users (Supplementary Table 1), although higher users showed trends toward greater reduction in biochemical hypoglycemia and improved overall glycemic control.

ANCOVA analyses (Supplementary Table 1) were also conducted for the subgroup allocated to RT use, dichotomized by use of RT (≥50 or <50% of the time). Higher RT use was associated with significantly larger decrease in time ≤3.0 mmol/L but without evidence of impact on IAH scores or SH.

Interaction between insulin and monitoring regimen was considered for primary outcome analysis but found nonsignificant.

Safety

There were no hospital admissions related to SH or injection/cannula/sensor-site infections throughout the RCT. There were

three episodes of diabetic ketoacidosis requiring hospitalization: two in participants randomized to CSII without RT and one in a participant randomized to MDI without RT. All resolved without adverse sequelae. Seven other severe adverse events were reported in the CSII group and four in the MDI group. These include episodes of acute-angle closure glaucoma, pneumonia, gastroenteritis, fractured radius, and need for intravenous antibiotics for pre-existing neuropathic foot ulceration. None were deemed related to trial intervention.

CONCLUSIONS

Our results show that hypoglycemia awareness can be improved and recurrent SH prevented in adults with long-standing type 1 diabetes and IAH through strategies deliverable in routine clinical practice, targeted at rigorous avoidance of biochemical hypoglycemia without relaxation of overall control. When provided with equal education and attention, equivalent biomedical outcomes and reduction in fear of hypoglycemia were attained with conventional

MDI and SMBG regimens compared with CSII/RT, although treatment satisfaction was higher in CSII users.

Statistically significant improvement in hypoglycemia awareness from baseline but absence of difference between groups at study end point has been confirmed in an adequately powered study in those at highest risk. Due to hypothesized relative insensitivity of the Gold score to change, a second validated IAH score and a newly designed measure were also included. The latter showed good correlation with existing measures but with much greater magnitude of clinical improvement at end point.

In contrast to many previous trials comparing newer technology with conventional therapy, there was an absolute focus on ensuring equivalent education, support, attention, and therapeutic targets for all groups. This was within the context of achievability within routine care without access to retrospective CGM profiles. Biochemical hypoglycemia was reduced rapidly in all groups within the first 4 weeks, driven by the insulin-dose

Table 3—Hypoglycemia awareness, SH, and patient-reported outcomes in MDIs vs. CSII and SMBG vs. RT comparisons at 24-week end point

| | Insulin comparison | | | Monitoring comparison | | |
|--|--|---|-----------------|---|--|-----------------|
| | MDI | CSII | <i>P</i> value* | SMBG | RT | <i>P</i> value* |
| SH | | | | | | |
| Annualized rate | 1.0 ± 2.1 0 [0–0] (<i>n</i> = 47) | 0.6 ± 1.7 0 [0–0] (<i>n</i> = 43) | 0.34 | 0.9 ± 2.1 0 [0–0] (<i>n</i> = 44) | 0.8 ± 1.8 0 [0–0] (<i>n</i> = 46) | 0.95 0.92† |
| Proportion affected (%) | 23 (<i>n</i> = 47) | 16 (<i>n</i> = 43) | 0.399 | 21 (<i>n</i> = 44) | 20 (<i>n</i> = 46) | 0.92** |
| IAH | | | | | | |
| Gold* | 4 [3–5] (2–7) | 4 [3–5.5] (1–7) | 0.756 | 4 [3–5] (1–7) | 4 [3–6] (1–7) | 0.42 |
| Clarke | 4.1 ± 1.6 (<i>n</i> = 45) 4 [2–5] (0–7) | 4.2 ± 1.7 (<i>n</i> = 40) 3 [2–4] (0–6) | 0.305 | 4.3 ± 1.6 (<i>n</i> = 42) 3 [2–4] (0–6) | 4.0 ± 1.7 (<i>n</i> = 43) 3 [2–4] (0–7) | 0.83 |
| HypoA-Q | 3.3 ± 1.8 (<i>n</i> = 41) 9 [5.5–12] (0–19) | 3.0 ± 1.6 (<i>n</i> = 39) 10 [6–12.5] (0–18) | 0.601 | 3.3 ± 1.6 (<i>n</i> = 39) 10 [5–12] (0–16) | 3.1 ± 1.8 (<i>n</i> = 41) 9 [6–12] (3–14) | 0.83 |
| | 8.9 ± 4.3 (<i>n</i> = 44) | 9.4 ± 4.2 (<i>n</i> = 40) | | 9.2 ± 4.1 (<i>n</i> = 40) | 9.0 ± 4.4 (<i>n</i> = 44) | |
| Fear of hypoglycemia and treatment satisfaction | | | | | | |
| HFS II–Total | 45 ± 25 (<i>n</i> = 46) | 44 ± 23 (<i>n</i> = 41) | 0.824 | 45 ± 24 (<i>n</i> = 42) | 45 ± 25 (<i>n</i> = 45) | 0.96 |
| HFS II–Behavior | 21 ± 10 (<i>n</i> = 46) | 20 ± 10 (<i>n</i> = 41) | 0.613 | 21 ± 9 (<i>n</i> = 42) | 20 ± 11 (<i>n</i> = 45) | 0.94 |
| HFS II–Worry | 25 ± 17 (<i>n</i> = 46) | 24 ± 17 (<i>n</i> = 41) | 0.985 | 25 ± 17 (<i>n</i> = 42) | 24 ± 17 (<i>n</i> = 45) | 0.98 |
| DTSQ–Total satisfaction | 29 ± 6 (<i>n</i> = 45) | 32 ± 3 (<i>n</i> = 39) | <0.001 | 30 ± 5 (<i>n</i> = 41) | 30 ± 5 (<i>n</i> = 43) | 0.79 |
| DTSQ2–Perceived frequency of hyperglycemia | 3 ± 1.29 | 3 ± 1.01 | 0.248 | 3 ± 1.17 | 3 ± 1.18 | 0.70 |
| DTSQ3–Perceived frequency of hypoglycemia | 3 ± 1.13 | 3 ± 1.25 | 0.240 | 3 ± 1.09 | 3 ± 1.27 | 0.75 |

Data are median [interquartile range] (range) or mean ± SD. Number with available data denoted by *n* number in parentheses. Number completing DTSQ2 and DTSQ3 in each group are the same as those completing DTSQ–Total satisfaction questions. †Mann-Whitney *U* test. *Two-sample *t* test between groups at week 24 (except ** χ^2 test).

adjustment algorithm and sustained throughout the 24-week trial.

Given the severe baseline phenotype, potential for some improvement in outcomes through regression to the mean is acknowledged. This informed our choice of IAH as mandatory inclusion criterion and primary outcome measure [with Gold score previously shown to be associated with high rate of SH over the preceding and following year (4,5)] as opposed to actively selecting individuals who have recently experienced SH and may be perceived as less likely to experience further events in the near future. Nevertheless, the 10-fold reduction in SH rate and frequency of glucagon administration/paramedic attendance from very high baseline rates appears highly clinically significant.

Stratification according to baseline HbA_{1c} was undertaken to ensure equal allocation of participants with tight and suboptimal glycemic control to each intervention. A nonsignificant trend toward improved HbA_{1c} in those with higher levels at baseline was observed, in keeping with our pilot study findings. Greater regression to the mean may have been

predicted, and absence of evidence for this suggests that the biopsychobehavioral determinants of each participant's personal target glucose may be relatively unaffected by conventional educational and medical interventions, perhaps indicating the need for more profound cognitive/motivational psychotherapeutic approaches (26).

Although a published meta-analysis concluded that SH rates are lower during CSII than MDI, it was acknowledged that trial designs were often mired by increased attention and education provision to the technology intervention (10). Moreover, previous studies have not included optimized basal analog MDI regimens.

In the HypoCOMPaSS study, those randomized to MDIs benefited from access to a twice-daily basal analog regimen and bolus calculator, mirroring as closely as possible basal-bolus CSII without insulin pump. It is striking that insulin dose reduction (a familiar correlate with insulin pump initiation) (20) was seen equally in those remaining on MDI. Importantly, dose reduction was not associated with any worsening of

glycemic control (HbA_{1c}). Our findings provide support for widespread clinical implementation of simple strategies in this high-risk group based upon initial re-education and targeted treatment algorithms (driving overall insulin dose reduction through rigorous avoidance of biochemical hypoglycemia), with regular follow-up support from healthcare professionals.

Prior to our study, there was no RCT evidence for SH prevention using RT, despite evidence that biochemical hypoglycemia can be reduced (12,13). Exclusion of those with IAH and SH from previous studies necessitated this trial. Uninterrupted use of RT was not achieved and may be viewed as a limitation, given the established correlation between greater use and larger clinical benefit (13). While continuous use was encouraged, this was not mandatory, and our data may more closely reflect real-world use and impact of this technology (in the iteration studied) in the overall population with IAH in a routine clinical setting. Problems with sensor discomfort and irritation were fairly common but all alert features were used actively by the majority.

Those using RT for >50% of the time appeared more successful in avoiding biochemical hypoglycemia and achieving best overall glycemic control, in keeping with published studies in those without IAH (12). Translation to greater improvement in IAH and reduction in SH was not confirmed in our very high-risk group, however.

Importantly, given the focus on detection of nocturnal hypoglycemia leading to protocol-driven insulin dose reduction, those randomized to SMBG alone benefited from weekly 4 A.M. glucose tests. This potentially mirrors some of the benefits of RT when not used continuously to provide alarms and enable use of automated LGS capabilities (27).

Recent data have demonstrated greater reduction in nocturnal hypoglycemia with sensor-augmented pump (SAP) therapy with automated suspension of insulin delivery for 2 h on detection of low interstitial glucose, in comparison with the control group using CSII and RT without LGS (28). An RCT in young people (mean age 19 years) with relatively short duration of type 1 diabetes complicated by IAH showed a reduction in rate of SH requiring assistance from another person with SAP including LGS versus CSII alone without RT (14). Coincidentally, as in our study, SH rate at randomization was higher in those allocated to RT, with comparable rates in both arms during the trial.

In the study by Ly et al. (14), no evidence for restoration of counterregulatory hormone response was detected in hypoglycemic clamp studies undertaken in a subgroup. A retrospective case-note audit of RT with or without LGS in adults with IAH reported reduced SH without restoration of hypoglycemia awareness (15), and it has been suggested that RT offers the potential of replacing physiological awareness with technological awareness (29). In a hypoglycemic clamp substudy in 18 participants within the current trial, the glucose level at which hypoglycemia was recognized and catecholamine response were improved by study participation without significant differences detected between interventions (30).

Although perceived frequency of hypoglycemia and hyperglycemia were comparable in those randomized to MDI and CSII, those using CSII reported greater treatment satisfaction than

those remaining on MDI, consistent with previous RCTs (31). Treatment satisfaction in those randomized to RT was no greater than in those continuing on conventional SMBG, in keeping with other studies reporting both benefits and hassles with RT (32). Our study demonstrated similar reduction in fear of hypoglycemia in all groups, whereas previous studies have tended to favor technology over MDI/SMBG regimens (33).

Much of the most convincing previous evidence for improved hypoglycemia awareness has accrued from structured educational programs. Reduced SH has been demonstrated in participants following the Blood Glucose Awareness Training (BGAT) (34) and HyPOS behavioral interventions (35). Forty percent of participants in the DAFNE education program had IAH at baseline with restored awareness after intervention in 43% of these (36). Typically, studies of educational interventions have been observational in design, although HyPOS was evaluated in a 164-participant RCT (35). Baseline SH rate has been much lower in education-focused studies (HyPOS: 0.8 vs. HypoCOMPaSS: 8.9/patient-year). These positive outcomes underline the absolute importance of providing equivalent education to all arms in trials designed to evaluate technological interventions. For example, in the recent study by Ly et al. (14), it is clear that additional education, therapeutic targets, and ongoing support were provided to the SAP group.

In conclusion, restoration of hypoglycemia awareness and prevention of SH, without worsening overall metabolic control, can be achieved with conventional MDI and SMBG. When truly optimized using short-acting and basal insulin analogs with appropriate therapeutic targets and regular finger-prick glucose monitoring including interval nighttime testing, outcomes are comparable to those attainable with CSII and RT. Sustainability of benefit will be determined at 2 years after trial commencement, following return to routine clinical care on completion of the 24-week RCT.

Acknowledgments. The authors thank the study participants and staff at Clinical Research Facilities at participating sites, in addition to Prof. Brian Frier, University of Edinburgh, Edinburgh, U.K., for advice on study design and Dr. Pratik Choudhary, King's College, London, U.K., for

advice on CGM analysis. The authors also thank Bayer Healthcare for providing contour glucose strips for the study duration without charge and David Wilson (AHP Research) for data entry of psychosocial measures. Statistical analysis was undertaken in the statistical package STATA version 12.

Funding. The study was funded by a peer-reviewed grant from Diabetes UK (07/0003556). The National Institute for Health Research and the Cambridge National Institute for Health Research Biomedical Research Centre funded data entry and trial support.

Duality of Interest. No pharmaceutical company or medical device manufacturer has had any role in the design or funding of this trial. Diabetes UK funded the study but played no part in its conduct. The authors alone were responsible for study design, data collection, analysis, interpretation, and report writing.

J.S. is a member of the Accu-Check Advisory Board (Roche Diagnostics Australia), and her research group has received unrestricted educational grants from Medtronic and Sanofi Diabetes, sponsorship to host or attend educational meetings from Eli Lilly and Company, Medtronic, Merck Sharp & Dohme, Novo Nordisk, Roche Diagnostics Australia, and Sanofi Diabetes, and consultancy income from Roche Diagnostics Australia and Sanofi Diabetes. D.K. has received honoraria for participation in educational events and consultancy fees from Abbott Diabetes Care, manufacturers of glucose sensors. D.F. has received speaker's fees from Animas and Novo Nordisk. S.R.H. has carried out consultancy work for pump/meters, insulin companies, LifeScan, Sanofi, Novo Nordisk, and Eli Lilly and Company, received research support from Medtronic, and speaker's fees from Novo Nordisk, Eli Lilly and Company, and LifeScan. M.L.E. has received travel support from Roche and Medtronic, received support for studies from Roche, Medtronic, and Abbott Diabetes Care, sits on advisory boards for Medtronic, Roche, and CellNovo, and has received speaker's fees from Animas. J.A.M.S. has in the past taken part in Medical Advisory Boards for Novo Nordisk, Sanofi, Johnson & Johnson, and Medtronic and received travel support for conference attendance and grant funding from Medtronic, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.A.L. (HypoCOMPaSS coordinating research fellow) and J.A.M.S. (Chief Investigator) wrote the first draft of this report and contributed to the conduct of the study and the collection and review of study data. The report writing group included S.A.L., D.D.S., S.M.M., J.S., D.K., D.F., S.R.H., M.L.E., and J.A.M.S. L.L., E.W., H.K.T., O.C., A.L.-S., S.B., D.D.S., S.M.M., J.S., D.K., D.F., S.R.H., and M.L.E. contributed to the conduct of the study and the collection and review of study data. C.B. was the Trial Manager, with R.W. responsible for data management, wrote the report, and contributed to the conduct of the study and the collection and review of study data. T.J.C. led the statistical analysis, supported by D.S., wrote the report, and contributed to the conduct of the study and the collection and review of study data. All authors reviewed and commented on various versions of the report and suggested

revisions. J.A.M.S. 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. Portions of this study were presented in abstract form at the 73rd Scientific Sessions of the American Diabetes Association, Chicago, IL, 21–25 June 2013.

Appendix

The HypoCOMPaSS Study Group members: 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. Brennan, 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, E. Walkinshaw; and Plymouth: D. Flanagan, S. Read, and H.K. Tan. Trial Steering Committee: S.A. Amiel (chair), J. Begley, C. Brennan, T. Chadwick, E. Davidson, M.L. Evans, D. Flanagan, L. Hall, S.R. Heller, V. King, S. Little, C. Littlewood, J. Matthews, J.A.M. Shaw, C. Speed, J. Speight, and R. Wood. Data Monitoring and Ethics Committee: S. Ashwell, M. Campbell, P.D. Home (chair), D. Kyne, and L. Nesbitt.

References

1. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384–1395
2. Pramming S, Thorsteinsson B, Bendtsen I, Binder C. Symptomatic hypoglycaemia in 411 type 1 diabetic patients. *Diabet Med* 1991;8:217–222
3. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;50:1140–1147
4. Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes. *Diabet Med* 2008;25:501–504
5. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 1994;17:697–703
6. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
7. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003;290:2159–2167
8. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 1997;46:271–286
9. Little S, Shaw J, Home P. Hypoglycemia rates with basal insulin analogs. *Diabetes Technol Ther* 2011;13(Suppl. 1):S53–S64
10. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 2008;25:765–774
11. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2010;(1):CD005103
12. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011;34:795–800
13. Beck RW, Hirsch IB, Laffel L, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383
14. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA* 2013;310:1240–1247
15. Choudhary P, Ramasamy S, Green L, et al. Real-time continuous glucose monitoring significantly reduces severe hypoglycemia in hypoglycemia-unaware patients with type 1 diabetes. *Diabetes Care* 2013;36:4160–4162
16. Fanelli C, Pampanelli S, Epifano L, et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. *Diabetologia* 1994;37:1265–1276
17. Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. *Lancet* 1994;344:283–287
18. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 1993;42:1683–1689
19. Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. *Diabetes* 1994;43:1426–1434
20. Thomas RM, Aldibbiat A, Griffin W, Cox MA, Leech NJ, Shaw JA. A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone. *Diabet Med* 2007;24:778–783
21. Little S, Chadwick T, Choudhary P, et al. Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). *BMC Endocr Disord* 2012;12:33
22. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995;18:517–522
23. Speight J, Barendse SM, Inkster B, Frier BM, Shaw JAM. Psychometric Validation of a Novel Measure of Impaired Awareness of Hypoglycaemia; the Hypoglycaemia Awareness Questionnaire (HypoA-Q). *Diabetes* 2013;62(Suppl. 1A):LB8.
24. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. *Diabetes Care* 2011;34:801–806
25. Bradley C. *Handbook of Psychology and Diabetes*. Switzerland, Harwood Academic Publishers, 1994
26. de Zoysa N, Rogers H, Stadler M, et al. A psychoeducational programme to restore hypoglycemia awareness: the DAFNE-HART pilot study. *Diabetes Care* 2014;37:863–866
27. Choudhary P, Shin J, Wang Y, et al. Insulin pump therapy with automated insulin suspension in response to hypoglycemia: reduction in nocturnal hypoglycemia in those at greatest risk. *Diabetes Care* 2011;34:2023–2025
28. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232
29. Choudhary P. Insulin pump therapy with automated insulin suspension: toward freedom from nocturnal hypoglycemia. *JAMA* 2013;310:1235–1236
30. Leelarathna L, Little SA, Walkinshaw E, et al. Restoration of self-awareness of hypoglycemia in adults with long-standing type 1 diabetes: hyperinsulinemic-hypoglycemic clamp sub-study results from the HypoCOMPaSS trial. *Diabetes Care* 2013;36:4063–4070
31. Bolli GB, Kerr D, Thomas R, et al. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study. *Diabetes Care* 2009;32:1170–1176
32. Tansey M, Laffel L, Cheng J, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Satisfaction with continuous glucose monitoring in adults and youths with Type 1 diabetes. *Diabet Med* 2011;28:1118–1122
33. Rubin RR, Peyrot M; STAR 3 Study Group. Health-related quality of life and treatment satisfaction in the Sensor-Augmented Pump Therapy for A1C Reduction 3 (STAR 3) trial. *Diabetes Technol Ther* 2012;14:143–151
34. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care* 2001;24:637–642
35. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. Long-term effect of an education program (HyPOS) on the incidence of severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care* 2010;33:e36
36. Hopkins D, Lawrence IG, Mansell P, Thompson G, Amiel S, Heller S. Improved biomedical and psychological outcomes one year after structured education in flexible insulin therapy for people with Type 1 diabetes mellitus: the UK DAFNE experience. *Diabetes Care* 2012;35:1638–1642