Sustained Reduction in Severe Hypoglycemia in Adults With Type 1 Diabetes Complicated by Impaired Awareness of Hypoglycemia: Two-Year Follow-up in the HypoCOMPaSS Randomized Clinical Trial

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OBJECTIVE

Severe hypoglycemia is a feared complication of type 1 diabetes; yet, few trials have targeted prevention using optimized self-management (educational, therapeutic, and technological support). We aimed to investigate whether improved awareness and reduced severe hypoglycemia, achieved during an intensive randomized clinical trial (RCT), were sustained after return to routine care.

RESEARCH DESIGN AND METHODS

Ninety-six adults with type 1 diabetes (29 ± 12 years' duration) and impaired awareness of hypoglycemia at five U.K. tertiary referral diabetes centers were recruited into a 24-week 2 × 2 factorial RCT (HypoCOMPaSS). Participants were randomized to pump (continuous subcutaneous insulin infusion [CSII]) or multiple daily injections (MDIs) and real-time continuous glucose monitoring (RT-CGM) or self-monitoring of blood glucose (SMBG), with equal education/attention to all groups. At 24 weeks, participants returned to routine care with follow-up until 24 months, including free choice of MDI/CSII; RT-CGM vs. SMBG comparison continued to 24 months. Primary outcome was mean difference (baseline to 24 months [between groups]) in hypoglycemia awareness.

RESULTS

Improvement in hypoglycemia awareness was sustained (Gold score at baseline 5.1 ± 1.1 vs. 24 months 3.7 ± 1.9; $P < 0.0001$). Severe hypoglycemia rate was reduced from 8.9 ± 12.8 episodes/person-year over the 12 months prestudy to 0.4 ± 0.8 over 24 months ($P < 0.0001$). HbA_{1c} improved (baseline 8.2 ± 3.2% [66 ± 12 mmol/mol] vs. 24 months 7.7 ± 3.1% [61 ± 10 mmol/mol]; $P = 0.003$). Improvement in treatment satisfaction and reduced fear of hypoglycemia were sustained. There were no significant differences between interventions at 24 months.

CONCLUSIONS

Optimized insulin replacement and glucose monitoring underpinned by hypoglycemia-focused structured education should be provided to all with type 1 diabetes complicated by impaired awareness of hypoglycemia.

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Hypoglycemia is one of the most feared complications of type 1 diabetes (1), as it can result in collapse, coma, seizures, injury and, in rare instances, sudden death. One in five adults with type 1 diabetes have experienced severe hypoglycemia (requiring assistance for recovery [2]) in the previous 6 months, regardless of overall glycemic control (3). Approximately half of those with type 1 diabetes for at least 15 years experience an episode each year (4). Severe hypoglycemia is sixfold more common in those with impaired awareness of hypoglycemia (5), which affects 20–25% of adults with type 1 diabetes (3,6), rising to almost 50% after 25 years (1).

Randomized clinical trials (RCTs) of continuous subcutaneous insulin infusion (CSII) pump therapy and continuous glucose monitoring (CGM) have demonstrated that technological approaches can help prevent severe hypoglycemia (7,8), albeit without improving awareness of hypoglycemia. However, studies are short-term (typically 6 months) and it is unclear how much of the observed benefit is due to increased education/attention provided alongside the active technological intervention. Indeed, much of the evidence to date for sustained reduction (at least 1 year) in severe hypoglycemia and restoration of hypoglycemia awareness comes from studies investigating the impact of structured type 1 diabetes education (9) or targeted hypoglycemia-focused psycho-educational intervention (10,11).

In the 24-week HypoCOMPaSS (Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia) RCT, we demonstrated that improved hypoglycemia awareness and prevention of recurrent severe hypoglycemia is possible in a high-risk population of adults with long-standing type 1 diabetes without worsening overall glycemic control (12). We compared insulin pumps (CSII) with multiple daily injections (MDIs) and adjuvant real-time continuous glucose monitoring (RT-CGM) with conventional self-monitoring of blood glucose (SMBG)—importantly, with equal education/attention for all groups irrespective of randomization. We found no difference in outcomes at 24 weeks by insulin delivery or glucose monitoring modality.

After 24-week RCT completion, participants returned to routine clinical care, with data collection every 6 months until 24 months. While participants were able to change insulin delivery modality at 24 weeks, the RT-CGM versus SMBG randomized comparison continued to 24 months. Our aim in the current study was to determine whether the improved awareness and prevention of recurrent severe hypoglycemia previously seen across all intervention groups at 24 weeks were sustained to 24 months.

RESEARCH DESIGN AND METHODS

Study Design and Participants

We have previously reported the study protocol (13) and 24-week RCT results (12). The protocol (13) was approved by a central research ethics committee and the Medicines and Healthcare products Regulatory Agency, with independent chaired trial steering committee and data-monitoring and ethics committee oversight. All participants provided written informed consent.

In summary, HypoCOMPaSS was a multicenter, 24-week, 2 × 2 factorial study at five U.K. tertiary referral diabetes centers providing structured education in type 1 diabetes with specialist expertise in the management of hypoglycemia and the use of CSII/RT-CGM technologies. Eligible participants were aged 18–74 years with C-peptide–negative type 1 diabetes and impaired awareness of hypoglycemia, confirmed by Gold score ≥4 (6).

In addition to previously documented baseline and 24-week visits, all participants were asked to return at 12, 18, and 24 months for data collection. Participants prospectively recorded episodes of severe hypoglycemia. Before each visit, participants underwent 7 days' blinded CGM (Medtronic iPRO).

Randomization and Masking

Using a Web-based system, and stratified by baseline HbA_{1c} (< and ≥8% [< and ≥64 mmol/mol]) and by center, participants were allocated randomly on an equal allocation basis to one of four groups: MDI (insulin aspart/glargine) with SMBG, MDI with SMBG and RT-CGM, CSII (insulin aspart) with SMBG, and CSII with SMBG and RT-CGM. Allocation sequence was generated by an individual not otherwise involved in participant recruitment. Neither participants nor investigators were blind to study allocation.

Procedures

After baseline assessment, all participants attended a brief (1–2 h), education session in small groups or one to one, guided by a standardized workbook (13). In summary, the aim was to facilitate reflection on personalized factors associated with dangerous hypoglycemia with formulation of individualized plans to prevent further significant events while maintaining overall glycemic control. The session was structured around the four points (N, E, S, W) of "my hypo compass" to *Never* delay hypoglycemia treatment, establish times of *Extra* risk, recognize *Subtle* hypoglycemia symptoms, and be *Wary* about detecting and preventing nocturnal hypoglycemia. Beyond this session, all participants received equivalent support including 4-weekly follow-up visits throughout the RCT.

At the end of the 24-week RCT, participants returned to routine clinical care without further study-related attention/support beyond data collection every 6 months. All had the option of switching insulin delivery modality within the context of U.K. clinical guidance, given confirmed problematic hypoglycemia at baseline (14). Decision to change insulin delivery modality was not dictated by study design or influenced by study investigators. Those randomized to RT-CGM continued to be provided with sensors providing the potential for uninterrupted use for a further 18 months (24 months in total). Those randomized to SMBG continued without access to RT-CGM.

Outcomes

All RCT outcome measures have previously been reported in detail (13). The primary outcome was difference (between baseline and 24 months and between randomized groups) in hypoglycemia awareness determined by Gold score (6).

Prespecified secondary outcomes were differences (as described above) in hypoglycemia awareness (assessed by Clarke questionnaire [15] and Hypoglycaemia Awareness Questionnaire (HypoA-Q) "impaired awareness" subscale score [16]), severe hypoglycemia rate and proportion affected, biochemical hypoglycemia (identified by blinded CGM profile: percentage time with glucose ≤3 mmol/L), overall glycemic control (HbA_{1c}), total daily insulin dose, body weight, and

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patient-reported outcomes—primarily fear of hypoglycemia (Hypoglycemia Fear Survey-II [HFS-II]) (17) and satisfaction with diabetes treatment (Diabetes Treatment Satisfaction Questionnaire [DTSQ]) (18).

Safety end points were hospital admissions, diabetic ketoacidosis, and infections related to insulin delivery and glucose sensor sites.

Follow-up for all primary and secondary outcome measures was planned to occur at 24 months postrandomization.

Statistical Analysis

The primary trial comparison was CSII vs. MDI and RT-CGM vs. SMBG alone, as previously described (12). Long-term analyses were based on preplanned secondary outcomes at 24-month follow-up in addition to changes between baseline and 24 months in the overall study population. Per-protocol analyses were planned based on knowledge of participant behavior and undertaken for insulin delivery modality, given that participants had freedom to choose after the 24-week RCT (MDI only throughout, switched with use of both MDI and CSII over the 24 months, or CSII only throughout) and for RT-CGM 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. Secondary long-term outcome analyses were exploratory, based mainly on descriptive and graphical representations. Hypothesis testing for the primary comparison was preplanned, with significance levels set at $\alpha = 0.05$ throughout. Data are presented as mean $\pm$ SD or proportions. For 24-month data, analysis was performed using *t* test or χ^2. Statistical analysis was undertaken using STATA (versions 12 and 14).

RESULTS

Participants

Ninety-six adults with type 1 diabetes and impaired awareness of hypoglycemia were randomized. At baseline, mean $\pm$ SD age was 49 $\pm$ 12 years and diabetes duration 29 $\pm$ 12 years, 35 (36%) were men, 97% were using MDI (3% using CSII), and none had previously used RT-CGM. Full demographic and clinical characteristics were similar in all groups, as previously described (12).

At 24 months, 76 (79%) were retained (Supplementary Fig. 1). Baseline characteristics in those lost to follow-up were comparable with characteristics of those retained for the study duration (Table 1). Thirty-nine (78%) participants randomized to MDI were retained at 24 months, with 10 (26%) still using MDI. Thirty-seven (80%) participants randomized to CSII were retained, with 25 (68%) still using CSII. Thirty-nine (81%) participants randomized to SMBG alone were retained at 24 months, and all were still using SMBG alone, as commencement of RT-CGM during study follow-up was precluded. Thirty-seven (77%) participants randomized to RT-CGM plus SMBG were retained, with 11 (30%) still using RT-CGM at study completion.

Long-term Outcomes

The improvement in hypoglycemia awareness attained during the RCT irrespective of randomized intervention (12) was sustained in the overall study population throughout the post-RCT follow-up (Table 2). Maintained benefit at 24 months was confirmed by significant reductions in Gold, Clarke, and HypoA-Q "impaired awareness" scale scores compared with preintervention baseline. In parallel, the significantly reduced rate of severe hypoglycemia attained during the RCT was sustained during long-term follow-up, with $\leq$20% of participants experiencing events over each 6-month period (Table 2).

Comparison of severe hypoglycemia over the 24-month follow-up with the 12-month period prior to randomization confirmed a 95% reduction in annualized rate from 8.9 $\pm$ 12.8 to 0.4 $\pm$ 0.8 episodes/person-year ($P < 0.0001$) (Fig. 1). Over the 24-month follow-up, 36% of participants were affected versus 92% over the 12 months prestudy. All who experienced severe hypoglycemia events during the study had reported severe hypoglycemia within the 12 months prestudy. In those who experienced severe

Table 1—Baseline characteristics of participants retained at 24 months and of participants lost to follow-up

	Retained at 24 months	Lost to follow-up by 24 months
n	76	20
Age, years	49.4 $\pm$ 12.3 (76)	45.5 $\pm$ 11.4 (20)
Median (IQR)	50.5 (41–59)	46 (39–50.5)
Female, *n* (%) (*n* with available data)	48 (63%) (76)	13 (65%) (20)
Diabetes duration (years)	29.2 $\pm$ 12.6 (75)	27.6 $\pm$ 11.4 (20)
Median (IQR)	30 (21–37)	25 (19.5–36.5)
Hypoglycemia awareness		
Gold score	5.0 $\pm$ 1.2 (76)	5.2 $\pm$ 1.0 (20)
Median (IQR)	5 (4–6)	5 (4.5–6)
Clarke score	5.0 $\pm$ 1.4 (69)	4.7 $\pm$ 1.9 (18)
Median (IQR)	5 (4–6)	4.5 (3–7)
HypoA-Q "impaired awareness"	13.5 $\pm$ 3.3 (72)	13.1 $\pm$ 3.7 (20)
Median (IQR)	14 (11.5–16)	14 (11–16)
Severe hypoglycemia (12 months prestudy)		
Annualized rate per person-year	9.0 $\pm$ 13.9 (76)	8.3 $\pm$ 7.4 (20)
Median (IQR)	3.5 (1–7.5)	7.5 (2.8–13)
Proportion affected, *n* (%) (*n* with available data)	68 (89) (76)	20 (100) (20)
HbA_{1c}, mmol/mol	65 $\pm$ 11 (76)	70 $\pm$ 14 (19)
Weight (kg)	74.9 $\pm$ 14.7 (76)	74.2 $\pm$ 12.3 (19)
Total daily insulin dose (units/kg)	0.7 $\pm$ 0.2 (75)	0.6 $\pm$ 0.2 (19)
Biochemical hypoglycemia, % time interstitial glucose $\leq$3 mmol/L	3.6 $\pm$ 4.2 (75)	4.2 $\pm$ 5.2 (19)
Satisfaction with diabetes treatment: DTSQ		
Total satisfaction	25.4 $\pm$ 5.5 (76)	23.8 $\pm$ 6.1 (19)
Perceived frequency of hyperglycemia	3.7 $\pm$ 1.4 (76)	3.8 $\pm$ 1.1 (19)
Perceived frequency of hypoglycemia	3.8 $\pm$ 1.2 (76)	3.5 $\pm$ 1.5 (19)
Fear of hypoglycemia: HFS-II		
Total	55.9 $\pm$ 25.7 (74)	66.9 $\pm$ 25.1 (20)
Behavior	23.0 $\pm$ 10.6 (74)	26.5 $\pm$ 13.8 (20)
Worry	33.2 $\pm$ 17.2 (76)	40.4 $\pm$ 15.5 (20)

Data are mean $\pm$ SD (*n* with available data) unless otherwise indicated. IQR, interquartile range.

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Table 2—Overall study population: hypoglycemia awareness, severe hypoglycemia, and biomedical and patient-reported outcomes at baseline and every 6 months through to 24-month end point

	Baseline	Month 6 (RCT end point)	Month 12	Month 18	Month 24 (study end point)	$P_{\text{baseline vs. month 24}}$ (*n* with available data)
Hypoglycemia awareness						
Gold score	5.1 ± 1.1 (96)	4.1 ± 1.6 (85)	3.9 ± 1.7 (75)	3.5 ± 1.8 (63)	3.7 ± 1.9 (56)	<0.0001 (56)
Median (IQR)	5 (4–6)	4 (3–5)	4 (2–5)	3 (2–5)	4 (2–5)	
Clarke score	4.2 ± 1.6 (87)	3.2 ± 1.7 (80)	3.0 ± 2.0 (66)	2.9 ± 2.1 (61)	2.5 ± 2.1 (50)	<0.0001 (47)
Median (IQR)	5 (4–6)	3 (2–4)	3 (1–5)	3 (1–5)	2 (0–4)	
HypoA-Q "impaired awareness"	13.4 ± 3.4 (92)	9.1 ± 4.2 (84)	8.6 ± 4.5 (74)	8.1 ± 4.7 (65)	8.4 ± 5.0 (57)	<0.0001 (55)
Median (IQR)	14 (11–16)	9.5 (6–12)	8.5 (5–12)	8 (5–12)	9 (4–11)	
Severe hypoglycemia						
Annualized rate/person-year	8.9 ± 13.4 (96)	0.8 ± 1.8 (90)	0.3 ± 0.8 (86)	0.2 ± 0.8 (73)	0.7 ± 2.0 (70)	<0.0001 (70)
Median (IQR)	4 (2–7)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	
Percent affected (*n* with available data)	77 (96)	20 (90)	14 (86)	12 (75)	17 (76)	0.02 (76)*
HbA_{1c} (mmol/mol)	66 ± 12 (95)	65 ± 10 (89)	65 ± 12 (74)	63 ± 10 (63)	61 ± 10 (72)	0.003 (72)
Weight (kg)	74.7 ± 14.2 (95)	75.3 ± 13.6 (87)	75.9 ± 13.7 (84)	75.1 ± 13.7 (69)	75.2 ± 13.4 (74)	0.93 (74)
Total daily insulin dose (units/kg)	0.64 ± 0.23 (94)	0.53 ± 0.17 (87)	0.53 ± 0.16 (73)	0.55 ± 0.14 (50)	0.54 ± 0.15 (51)	<0.0001 (51)
Biochemical hypoglycemia, % time interstitial glucose ≤3 mmol/L	3.7 ± 4.4 (94)	1.7 ± 3.9 (83)	2.3 ± 3.6 (55)	2.7 ± 4.5 (59)	2.6 ± 4.1 (55)	0.13 (54)
Satisfaction with diabetes treatment: DTSQ						
Total satisfaction	25.1 ± 5.6 (95)	30.3 ± 5.1 (84)	31.6 ± 4.2 (78)	31.8 ± 4.3 (65)	31.1 ± 4.8 (56)	<0.0001 (56)
Perceived frequency of hyperglycemia	3.7 ± 1.3 (95)	3.1 ± 1.2 (84)	2.9 ± 1.2 (78)	2.8 ± 1.4 (65)	3.1 ± 1.3 (57)	0.0003 (57)
Perceived frequency of hypoglycemia	3.7 ± 1.3 (95)	2.7 ± 1.2 (84)	2.7 ± 1.1 (77)	2.8 ± 1.4 (65)	2.7 ± 1.3 (57)	0.0001 (57)
Fear of hypoglycemia: HFS-II						
Total	58.3 ± 25.8 (94)	44.9 ± 24.3 (87)	39.8 ± 21.8 (60)	35.1 ± 21.1 (58)	40.3 ± 26.6 (47)	<0.0001 (46)
Behavior	23.8 ± 11.4 (94)	20.4 ± 10.1 (87)	20.2 ± 10.0 (64)	17.1 ± 8.6 (58)	19.3 ± 11.2 (49)	0.001 (47)
Worry	34.7 ± 17.1 (96)	24.4 ± 16.5 (87)	20.2 ± 15.0 (67)	18.4 ± 15.2 (65)	21.6 ± 17.3 (52)	<0.0001 (52)

Data are mean ± SD (*n* with available data) unless otherwise indicated. Severe hypoglycemia: annualized rates are based on the 6 months prior to the stated time points. *P* values compare month 24 (end point) against baseline, using paired *t* test (complete pairs only), except $*\chi^2$ test (complete pairs only).

hypoglycemia over the 24-month follow-up, annualized rate was reduced to 1.5 ± 1.0 episodes/person-year. Only five (5%) participants experienced two or more severe hypoglycemic events/person-year, compared with 56 (58%) over the 12 months prestudy. In comparison of consequences of severe hypoglycemia over the 24-month follow-up with the 12 months prestudy, 8 vs. 32% of participants required glucagon administration, 7 vs. 33% paramedic assistance, and 2 vs. 6% hospital attendance/admission.

HbA_{1c} at 24 months was significantly lower than at baseline (Table 2). In participants with baseline HbA_{1c} ≥8% (≥64 mmol/mol), glycemic control improved incrementally throughout the 24-month study period, while in those with baseline HbA_{1c} <8%, glycemic control was not "relaxed," with average remaining <7.5% (58 mmol/mol) (Fig. 1).

Previously observed improvements in treatment satisfaction, perceived frequency of hypoglycemia and hyperglycemia, and fear of hypoglycemia were sustained throughout the 24-month study (Table 2).

Although the reduction in clinically important (19), biochemical hypoglycemia (interstitial glucose ≤3 mmol/L) achieved in the RCT (baseline 53 ± 63 min/24 h vs. 24 weeks 24 ± 56 min/24 h) was maintained throughout post-RCT follow-up (Table 2), this was no longer statistically significant at 24 months (37 ± 56 min/24 h). The significant reduction in mean total daily insulin dose seen within the RCT, equating to 8 units per participant, was sustained at 24 months with weight unchanged throughout the study (Table 2).

Insulin Delivery Comparison

At 24 months, there was no significant difference in hypoglycemia awareness between those initially randomized to CSII and those to MDI (Supplementary Table 1). Reductions in severe hypoglycemia, HbA_{1c}, daily insulin dose, and other secondary end points were all equivalent in the MDI versus CSII group intention-to-treat analysis.

Having completed the primary 24-week RCT on randomized intervention, participants were free to change insulin delivery modality supported by their clinical team on return to routine care without any further study-specific support. Nevertheless, all participants remained in specialist

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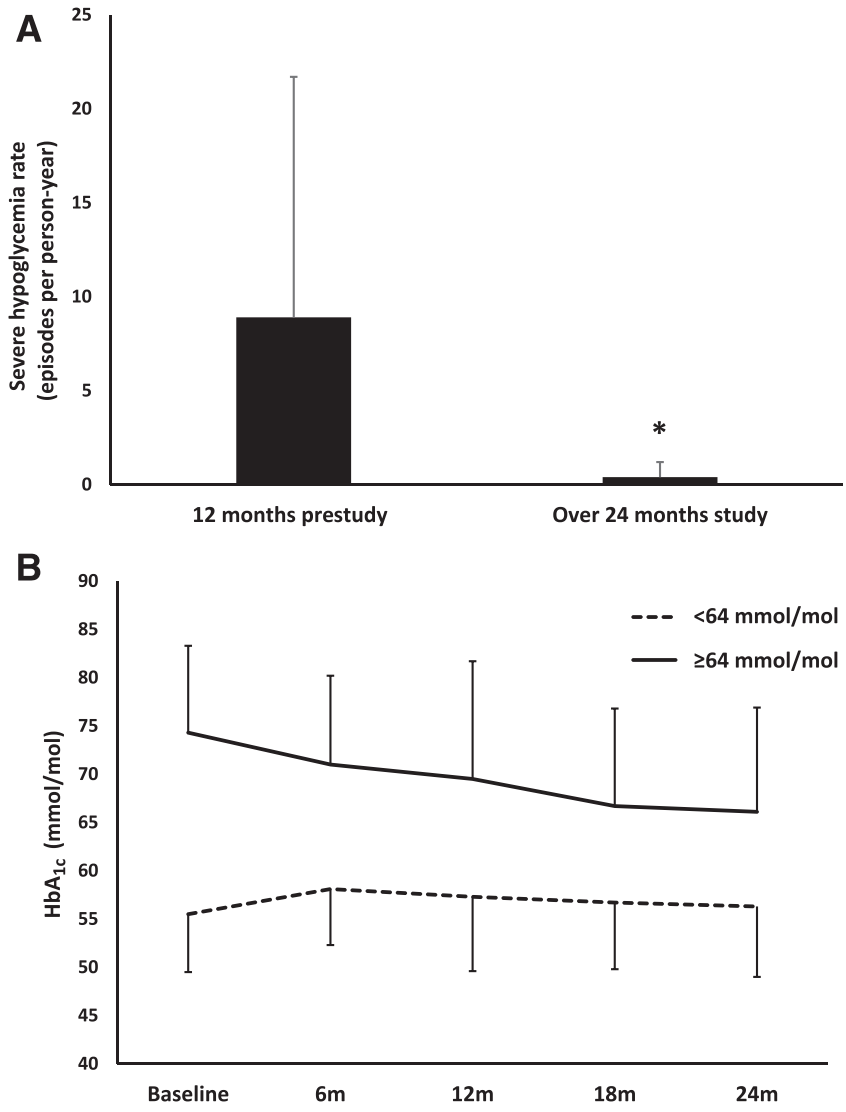

Figure 1—Severe hypoglycemia rate (*A*) and HbA_{1c} (*B*) at baseline and during the 24-month study. *A*: Annualized rate of severe hypoglycemia in the overall study population was reduced by 95% during the 24-month study compared with the 12 months prior to randomization (mean ± SD). *$P < 0.0001$ using paired *t* test with complete pairs only ($n = 96$ at baseline and $n = 69$ at 24 months). *B*: HbA_{1c} reduced incrementally over the 24-month study in those with baseline HbA_{1c} ≥8% (≥64 mmol/mol) and remained optimal in those with baseline HbA_{1c} <8% (<64 mmol/mol). m, months.

centers, and those transitioning to CSII received additional training and support according to established center-specific practice. Per-protocol analysis confirmed comparable outcomes in those who used both MDI and CSII over the 2-year study period and those using only MDI or CSII (Supplementary Table 1). The greater satisfaction with treatment (DTSQ total) observed with CSII compared with MDI at 24 weeks was no longer apparent at 24 months (Supplementary Table 2). Although statistical analyses were not deemed appropriate owing to low numbers, possible associations were seen between improved hypoglycemia awareness, reduced severe hypoglycemia, and lower hypoglycemia worry in those choosing to remain on MDI throughout. Higher HbA_{1c} in those who remained on MDI was also noted (Supplementary Table 2).

Monitoring Regimen Comparison

At 24 months, there were no significant differences between those randomized to SMBG alone and those to RT-CGM in terms of hypoglycemia awareness, severe hypoglycemia, or any secondary outcomes (Supplementary Table 1).

Despite provision of sensors for uninterrupted RT-CGM use, only 11 (30%) of the RT-CGM group continued to use this technology throughout the full 24-month follow-up. Exploratory per-protocol analysis of the 14 participants with complete RT-CGM usage data compared those using RT-CGM <50 vs. ≥50% of the time (Supplementary Table 2). Although small numbers precluded statistical analysis, there were no severe hypoglycemic events and there was a trend toward improved hypoglycemia awareness observed in those using RT-CGM <50% of the time. As in the primary RCT, higher RT-CGM use was associated with a trend toward less biochemical hypoglycemia.

Comparison of outcomes between all participants (Table 2), those randomized to RT-CGM (Supplementary Table 1), and the subgroup who used this monitoring modality throughout the study (Supplementary Table 2) suggests no differences between groups, with the exception of fear of hypoglycemia, which appears particularly low in those who used RT-CGM throughout the 24 months.

Safety

Over the 24-month study, six episodes of ketoacidosis required hospitalization: five during CSII and one during MDI. All resolved without sequelae. Twelve other severe adverse events (CSII, $n = 7$, and MDI, $n = 5$) were unrelated to trial interventions. These included episodes of acute-angle closure glaucoma, pneumonia, gastroenteritis, fractured radius, and preexisting neuropathic foot ulceration requiring intravenous antibiotics.

CONCLUSIONS

Improved hypoglycemia awareness and reduced rate of severe hypoglycemia observed in a short-term intensive RCT was maintained at 24 months after return to routine clinical care. This was paralleled by a clinically meaningful 0.5% reduction in mean HbA_{1c}, sustained improvement in treatment satisfaction, and reduced fear of hypoglycemia. This study demonstrates that a brief educational intervention with intensive support over 24 weeks leads to benefits sustained over 24 months in a high-risk cohort with long-standing type 1 diabetes and impaired awareness of hypoglycemia. It confirms that avoiding severe hypoglycemia does not need to be achieved at the expense of higher overall glucose levels.

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HypoCOMPaSS provides further evidence that structured education and support should underpin interventions targeting impaired awareness of hypoglycemia in type 1 diabetes. This corroborates a meta-analysis concluding that structured education reduces rates of severe hypoglycemia (20). Most previous studies have adopted a before-and-after design with small numbers and short-term follow-up. Only two RCTs with at least 12 months of follow-up have specifically recruited participants with impaired awareness of hypoglycemia. In both the HyPOS and Hypoglycemia Anticipation, Awareness and Treatment Training (HAATT) studies (10,21), reduction in severe hypoglycemia was greater, over 18 and 31 months, respectively, in those who received the psycho-educational program than in the control group. Unlike HypoCOMPaSS, neither reported improved HbA_{1c}. It is striking that substantial reductions in total daily insulin dose were observed throughout the current 24-month study without any protocol-driven insulin dose titration regimen beyond the 24-week RCT.

Participants had completed standardized type 1 diabetes education in insulin dose adjustment according to glucose levels and carbohydrate intake prior to study recruitment, and all received the "my hypo compass" psycho-educational intervention prior to randomization. The absence of a group not receiving hypoglycemia-focused structured education is a limitation discussed previously (12), although the durability of the impact in this high-risk group prone to recurrent severe hypoglycemia is reassuring. Sustained effective behavior change enabled through a short-term psycho-educational intervention, despite withdrawal of trial-specific input at 24 weeks, supports cost-effectiveness for wider implementation, although formal health economic analysis was not undertaken. An important caveat is that all participants remained under specialist care, in keeping with national guidance recommending this for those with a history of problematic hypoglycemia (22). A qualitative process evaluation is underway to explore facilitators of long-term benefit, in addition to a further RCT comparing standard medical management of impaired awareness of hypoglycemia with and without the "my hypo compass" psycho-educational program.

Although previous studies have reported lower severe hypoglycemia rates with CSII compared with MDI (23), only the current RCT has provided equivalent education and attention/support to both groups in addition to optimized basal analog MDI. As all participants fulfilled national criteria for pump therapy (14) at study recruitment, those randomized to MDI were aware that they could switch to CSII at the end of the 24-week RCT and 57% did so supported by their usual clinical team. In parallel, 30% of those randomized to CSII switched to MDI. This crossover (anticipated and supported by the study protocol) occurred despite the RCT demonstrating no differences in biomedical outcomes, fear, or perceived frequency of hypoglycemia between insulin interventions. At 6 months, satisfaction with treatment had been higher in those randomized to pump but was comparable at 24 months after 18 months of preferred insulin delivery. This is consistent with the overall findings that benefits comparable with those of CSII (including treatment satisfaction) can be achieved in individuals favoring MDI. A trend toward lowest mean HbA_{1c} in those using CSII throughout was seen, although numbers remaining on MDI were small. Recently, the Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) trial reported comparable biomedical benefits for those randomized to CSII or MDI with equivalent structured education and attention/support (24). While supporting the conclusion that sustained benefits can be achieved in long-standing type 1 diabetes complicated by impaired awareness of hypoglycemia regardless of chosen insulin delivery modality, the a priori, pragmatic decision to allow crossover after 24 weeks in HypoCOMPaSS was a potential limitation, as it precluded definitive RCT comparison of MDI versus CSII over the full 24-month follow-up period. Further work is needed to establish the relative benefits of CSII over optimized MDI, and individual participant drivers to switch from MDI to CSII and vice versa during the post-RCT follow-up are being explored through the qualitative process evaluation noted above.

In the current 24-month randomized comparison of SMBG with RT-CGM, both interventions were equally effective in restoring hypoglycemia awareness and preventing severe hypoglycemia without compromising average glycemic control. This may reflect the specific focus on augmenting conventional finger-prick glucose monitoring with targeted postprandial and 4:00 A.M. testing—in contrast to standard clinical practice (25). It is important to note that although at 24 weeks in HypoCOMPaSS >95% of participants were using low-glucose alerts and 75% stated that RT-CGM was beneficial in preventing severe hypoglycemia, more than two-thirds were no longer using this modality at 24 months. This is a limitation, as previous trials have reported higher sensor use, together with an association between greater use and optimal impact (25,26). Mirroring the current study, decreased use and discontinuation over time have been a concern in the nontrial community setting, with >40% of RT-CGM users on enrolment to the U.S. T1D Exchange Clinic Registry having stopped using the technology 12 months later (27). Discomfort wearing and difficulties inserting sensors were the commonest reasons for cessation. Ongoing improvements in reliability and accuracy have been associated with greater use (26,28). The factors underlying cessation of RT-CGM in HypoCOMPaSS are being further investigated through qualitative analysis of participant semistructured interviews.

Relatively few participants used RT-CGM ≥50% of the time, but 38% of these continued to experience severe hypoglycemia, whereas none of those using RT-CGM <50% of the time experienced any events. It may be that those at highest risk of severe hypoglycemia are those who used RT-CGM virtually uninterrupted as a "lifeline" to provide "technological hypoglycemia awareness" (20).

Median sensor use of nearly 90% was attained in a recent 16-week crossover trial evaluating RT-CGM in 52 participants with type 1 diabetes and impaired awareness of hypoglycemia on MDI or CSII therapy (29). Biochemical hypoglycemia and number of severe hypoglycemia events were lower during the RT-CGM period. This was associated with reduced fear of hypoglycemia, a possible association with continued RT-CGM in the current study.

With use of subcutaneous sensor-based "flash glucose monitoring" (where readings over the preceding 8 h are obtained by bringing a reader in close proximity to

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the sensor), significant reduction in biochemical hypoglycemia has been achieved in an RCT comparison with conventional SMBG among adults with type 1 diabetes and optimal HbA_{1c} ($\leq$7.5%) (30). High participant satisfaction and system utilization ($>$90%) were reported, though time with glucose $<$3.1 mmol/L remained substantial even in the intervention arm (3.3%). Participants with "diagnosed hypoglycemia unawareness" were excluded from the trial, and there was no reduction in fear of hypoglycemia. An 8-week pilot RCT comparing RT-CGM with flash glucose monitoring in participants with impaired hypoglycemia awareness and/or recent severe hypoglycemia achieved reduced biochemical hypoglycemia only in the RT-CGM group (31).

The automated CGM-driven low glucose suspend (LGS) feature was not activated in HypoCOMPaSS. This is an important limitation, as greater reduction in nocturnal hypoglycemia compared with CSII and RT-CGM without LGS has been reported with sensor-augmented pumps enabling automated suspension of insulin delivery for 2 h on detection of low interstitial glucose (32). Reduced severe hypoglycemia in those randomized to sensor-augmented pump therapy including LGS compared with those receiving CSII alone has been reported in young people with relatively short-duration type 1 diabetes (8). Access to this combination technology has recently been approved by the U.S. Food and Drug Administration and National Institute for Health and Care Excellence (33).

Recovery of hypoglycemia awareness has not been reported in other trials of RT-CGM (with [7,8] or without [29] LGS), possibly because a psycho-educational component was not included. Reversal of hypoglycemia-associated autonomic failure leading to restored awareness (34) may have required even greater reduction in time spent with low glucose levels, as absolute avoidance of biochemical hypoglycemia has not yet been attained (35). In a detailed prospective study of 11 participants with impaired awareness of hypoglycemia who used RT-CGM for $>$70% of the time over 18 months, questionnaire-reported hypoglycemia awareness improved with a reduction in severe hypoglycemia incidence but only a modest increase in endogenous glucose production in response to experimental hypoglycemia, demonstrating that physiological counterregulation remains impaired (36). Taken together, existing study findings underline the complex bio-psycho-behavioral components of hypoglycemia recognition and successful self-management (37), suggesting that reliance on RT-CGM without heightened attendance to personal cues may lead to reduced mindfulness and recognition of hypoglycemia symptoms, leading to continued high risk of severe hypoglycemia during any periods "off sensor." Analysis of associations with persisting impaired awareness of hypoglycemia despite participation in the current study, with its primary goal of biochemical hypoglycemia avoidance, is planned.

A weakness of this study is that only 79% of participants completed full post-RCT follow-up, with only 58% completing the 24-month hypoglycemia awareness Gold score. However, the baseline characteristics of those completing the study were comparable with characteristics of those lost to follow-up, and all outcomes were stable from 6 months (with much higher participant retention) through all intermediate time points to 24 months. It could be argued that recall of severe hypoglycemia at baseline may not provide the best comparator for the data collected prospectively during the 24-month follow-up. Good correlation between retrospective and prospective recording of severe hypoglycemia over 12 months has been confirmed but with a tendency to underreporting overall rate when relying on retrospective recall (38).

In conclusion, brief structured education in addition to informed support in active insulin dose self-adjustment underpinned by targeted self-monitoring of blood glucose leads to sustained falls in severe hypoglycemia rates in those at high risk. These should be provided, regardless of the choice of insulin delivery and glucose monitoring modality.

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