Predictors of Recurrent Severe Hypoglycemia in Adults With Type 1 Diabetes and Impaired Awareness of Hypoglycemia During the HypoCOMPaSS Study

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Anneliese J.S. Flatt,[1,2] Stuart A. Little,[1,2] Jane Speight,[3,4,5] Lalantha Leelarathna,[6] Emma Walkinshaw,[7] Horng Kai Tan,[8] Anita Bowes,[9] Alexandra Lubina-Solomon,[7] Elizabeth Holmes-Truscott,[2,3] Thomas J. Chadwick,[10] Ruth Wood,[11] Timothy J. McDonald,[12] David Kerr,[9,13] Daniel Flanagan,[8] Augustin Brooks,[9] Simon R. Heller,[7] Mark L. Evans,[6] and James A.M. Shaw[1,2]

OBJECTIVE

The HypoCOMPaSS study was designed to test the hypothesis that successful avoidance of biochemical hypoglycemia without compromising overall glycemic control would restore sufficient hypoglycemia awareness to prevent recurrent severe hypoglycemia in the majority of participants with established type 1 diabetes. Before starting the study, we planned to investigate associations between baseline characteristics and recurrent severe hypoglycemia over 2 years' follow-up.

RESEARCH DESIGN AND METHODS

A total of 96 adults with type 1 diabetes and impaired awareness of hypoglycemia participated in a 24-week 2 × 2 factorial randomized controlled trial comparing insulin delivery and glucose monitoring modalities, with the goal of rigorous biochemical hypoglycemia avoidance. The analysis included 71 participants who had experienced severe hypoglycemia in the 12-month prestudy with confirmed absence (complete responder) or presence (incomplete responder) of severe hypoglycemia over 24 months' follow-up.

RESULTS

There were 43 (61%) complete responders and 28 (39%) incomplete responders experiencing mean ± SD 1.5 ± 1.0 severe hypoglycemia events/person-year. At 24 months, incomplete responders spent no more time with glucose ≤3 mmol/L (1.4 ± 2.1% vs. 3.0 ± 4.8% for complete responders; $P = 0.26$), with lower total daily insulin dose (0.45 vs. 0.58 units/24 h; $P = 0.01$) and greater impairment of hypoglycemia awareness (Clarke score: 3.8 ± 2.2 vs. 2.0 ± 1.9; $P = 0.01$). Baseline severe hypoglycemia rate (16.9 ± 16.3 vs. 6.4 ± 10.8 events/person-year; $P = 0.002$) and fear of hypoglycemia were higher in incomplete responders. Peripheral neuropathy was more prevalent in incomplete responders (11 [39%] vs. 2 [4.7%]; $P < 0.001$) with a trend toward increased autonomic neuropathy.

CONCLUSIONS

Recurrent severe hypoglycemia was associated with higher preintervention severe hypoglycemia rate, fear of hypoglycemia, and concomitant neuropathy.

[1]*Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, U.K.*
[2]*Newcastle Diabetes Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, U.K.*
[3]*School of Psychology, Deakin University, Geelong, Victoria, Australia*
[4]*The Australian Centre for Behavioural Research in Diabetes, Diabetes Victoria, Melbourne, Victoria, Australia*
[5]*AHP Research, Hornchurch, U.K.*
[6]*Wellcome Trust-MRC Institute of Metabolic Science Metabolic Research Laboratories, University of Cambridge, Cambridge, U.K.*
[7]*School of Medicine and Biomedical Sciences, The University of Sheffield, Sheffield, U.K.*
[8]*Peninsula College of Medicine and Dentistry, Plymouth, U.K.*
[9]*Bournemouth Diabetes and Endocrine Centre, Royal Bournemouth Hospital, Bournemouth, U.K.*
[10]*Institute of Health & Society, Newcastle University, Newcastle upon Tyne, U.K.*
[11]*Newcastle Clinical Trials Unit, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, U.K.*
[12]*Institute of Biomedical and Clinical Science, College of Medicine and Health, University of Exeter, Exeter, U.K.*
[13]*Sansum Diabetes Research Institute, Santa Barbara, CA*

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

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Severe hypoglycemia requiring the assistance of another person for recovery was reported as a dangerous potential consequence of insulin therapy within a few months of its clinical implementation almost a century ago. It affects up to 50% of those with long-standing type 1 diabetes every year and may occur regardless of overall glycemia, measured by HbA_{1c} (1,2).

Avoidance of serious clinically important biochemical hypoglycemia (<3 mmol/L) is increasingly being targeted in trials of education, technology, immunotherapy, and transplantation in type 1 diabetes (3). This is leading to rapidly accruing evidence for successful reduction in severe hypoglycemia following both education (4) and technology interventions (5,6) so that severe hypoglycemia should no longer be accepted as an inevitable consequence of established type 1 diabetes (7).

The HypoCOMPaSS (Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycemia) study compared continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI) and real-time continuous glucose monitoring (RT-CGM) with finger-prick self-monitored blood glucose (SMBG) in a 24-week 2 × 2 factorial randomized controlled trial (RCT) in type 1 diabetes complicated by impaired awareness of hypoglycemia (8). It was designed to test the hypothesis that successful avoidance of biochemical hypoglycemia would lead to improved hypoglycemia awareness and prevention of recurrent severe hypoglycemia in the majority of participants. Assessment of associations between baseline parameters and further episodes of severe hypoglycemia over 2 years of follow-up despite trial intervention was planned prior to study commencement, with two a priori hypotheses proposed (8): First, that a strong preference for avoiding high glucose levels would be associated with significant ongoing biochemical hypoglycemia exposure, maintained impaired awareness of hypoglycemia, and ongoing risk of severe hypoglycemia. Second, that diabetic neuropathy will be associated with irreversible impaired awareness of hypoglycemia and unremitting severe hypoglycemia.

In this analysis, we consider participants in the HypoCOMPaSS study who experienced severe hypoglycemia in the year preceding the RCT and investigate predictors of incomplete response defined by at least one further severe hypoglycemia event over the 24-month follow-up period.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The protocol was approved by Sunderland Research Ethics Committee and has previously been reported (9). In summary, eligible participants were aged 18–74 years with C-peptide–negative diabetes and impaired awareness of hypoglycemia, confirmed by Gold score ≥4. Ninety-six participants, recruited across five U.K. tertiary referral centers, were allocated to intervention groups in a 2 × 2 factorial design (MDI or CSII and SMBG or RT-CGM) by a web-based randomization system with stratification for baseline HbA_{1c} (< and ≥8% [64 mmol/mol]). All participants completed a brief standardized behavioral intervention session ("my hypo compass") after randomization (9). Participants returned to their usual care at 24 weeks. While participants were able to change insulin delivery modality at 24 weeks, the RT-CGM versus SMBG randomized comparison continued to 24 months. The mixed-meal tolerance test substudy was approved by Leeds West Research Ethics Committee and undertaken following main study completion and collection of 24-month outcome data. All individuals remaining under the care of the participating centers were invited to take part.

Procedures

Only participants who experienced severe hypoglycemia in the year preceding the RCT were included in the current analysis. As previously published, baseline data including diabetes-specific history were recorded using standardized case report forms. This included specific questions regarding autonomic neuropathy. Presence/absence of peripheral neuropathy was recorded, informed by specific questions regarding numbness/paresthesiae/neuropathic pain in hands and/or feet underpinned by confirmatory neurological examination to differentiate from mononeuropathy. Participants completed validated questionnaires at baseline and 24 months (9): impaired awareness of hypoglycemia questionnaires (Gold score, Clarke score, and Hypoglycaemia Awareness Questionnaire [HypoA-Q]) (10–12), Hypoglycemia Fear Survey-II (HFS-II) (13), Hyperglycemia Avoidance Scale (HAS) (14), and Diabetes Treatment Satisfaction Questionnaire (DTSQ) (15), with baseline completion of the Autonomic Symptom Profile (ASP) questionnaire (16). The ASP Composite Autonomic Symptom Scale (COMPASS) is a validated measure of autonomic dysfunction (16) comprising 72 questions across 11 domains: orthostatic intolerance, vasomotor, secretomotor, gastroparesis, autonomic diarrhea, constipation, bladder, pupilomotor, sleep disorder, and syncope. The male sexual/erectile dysfunction domain was excluded to enable comparison across sexes. Domains are weighted according to severity and frequency to create a total score indicative of the severity of autonomic dysfunction. Participants underwent a 7-day period of blinded CGM (Medtronic iPro) before each study visit with prospective collection of severe hypoglycemia events. Post-RCT data continued to be collected at 6-monthly intervals to 24 months.

Detection of ACE Gene Polymorphism

DNA was extracted from frozen whole blood. The insertion/deletion polymorphism of the ACE gene was identified by PCR using two primers flanking the site of insertion. Fragments of 191 base pairs (bp) (D allele) and 479 bp (I allele) were separated on a 2% agarose gel and stained with SYBR Safe DNA Gel Stain (17).

Mixed-Meal Tolerance Test Substudy

HypoCOMPaSS eligibility criteria included C-peptide–negative type 1 diabetes determined by quality-assured assay within each participating center on a random serum sample in the absence of biochemical hypoglycemia (plasma glucose <4 mmol/L). C-peptide was undetectable or <50 pmol/L in all except two participants, with values of 87 and 103 pmol/L at baseline (8). Highly sensitive C-peptide assays have confirmed the presence of residual C-peptide microsecretion in a proportion of people with established type 1 diabetes (18), although clinical significance remains uncertain. Following HypoCOMPaSS study completion, 47 participants (representing 49% of the original RCT population) completed a standardized mixed-meal tolerance test (19). Participants attended

the participating center Clinical Research Facility fasting with omission of short-acting but continued basal insulin. Participants consumed 240 mL Fortisip (18.4 g/100 mL carbohydrate) comprising a total mixed meal of 44.2 g carbohydrate, 14.4 g protein, and 13.9 g fat. Serum samples were obtained at 0 and 90 min for C-peptide and glucose assay with collection of urine for assessment of urine C-peptide–to–creatinine ratio at 0 and 120 min. All samples were aliquoted and stored at −80°C before shipment to Exeter Central Laboratory for analysis. C-peptide samples were analyzed using the automated E170 Immunology Analyzer (Roche Diagnostics, Mannheim, Germany) with a serum detection limit of 3 pmol/L and urine detection limit of 0.03 nmol/L.

Following completion of study follow-up, three incomplete responders received an allogeneic islet transplant for recurrent life-threatening severe hypoglycemia despite optimized medical management. All were from a single center and underwent a mixed-meal tolerance test pretransplant between 2011 and 2013 as part of the assessment for listing. All had undetectable stimulated serum C-peptide with assay limit of detection <30 pmol/L.

Outcomes

Twenty-four-week RCT and 24-month outcomes have previously been reported (8,20). The current analysis was planned before study commencement, with definitions of complete and incomplete response formalized post-RCT and 24-month analysis but before consideration of data. Only participants who reported one or more severe hypoglycemia events over the 12 months before baseline visit were included in the analysis. Complete response required full 24-month prospective severe hypoglycemia data. Incomplete responders required data verifying at least one severe hypoglycemia event during the RCT or overall 24-month study period and could be allocated without full follow-up data.

Predefined end points were differences between complete and incomplete responder groups at baseline and 24 months in severe hypoglycemia rate (annualized) and proportion affected; impaired awareness of hypoglycemia, assessed by Gold, Clarke, and HypoA-Q scores; biochemical hypoglycemia, glucose time in range, and mean glucose and SD (assessed by blinded CGM); overall glycemic control (HbA_{1c}); total daily insulin dose; body weight; and patient-reported outcome measures, including fear of hypoglycemia (HFS-II), diabetes treatment satisfaction (DTSQ), and hyperglycemia avoidance (HAS).

Statistical Analysis

Analysis was undertaken using simple tabulations (mean ± SD, median [interquartile range]), and proportions) with *t* test or χ^2 test comparisons between groups at baseline and 24 months as appropriate. No modeling of change from baseline to 24 months was undertaken due to the small sample size in the incomplete responder group for outcome measures at 24 months. Significance levels were set at $\alpha = 0.05$ throughout. No formal correction for multiple testing has been applied during the analysis. Significant results should therefore be treated with caution.

RESULTS

Seventy-one (81%) HypoCOMPaSS participants who experienced at least one severe hypoglycemic event in the 12-month prestudy were included in the analysis. Forty-three (61%) participants were complete responders with data at all study time points confirming absence of severe hypoglycemia throughout the 24-month follow-up period. Twenty-eight (39%) participants were incomplete responders with evidence of at least one severe hypoglycemia event over the RCT and follow-up. There was no difference in intervention arm allocation or switch between groups over the RCT and follow-up period. Twenty-two (51%) complete responders and 12 (43%) incomplete responders were initially randomized to CSII. Thirteen (31% from $n = 42$) complete responders completed 24-month follow-up who were randomized to CSII, 7 (17%) completed follow-up randomized to MDI, and 22 (52%) switched insulin delivery modality after 24 weeks. Eight (32% from $n = 25$) incomplete responders completed follow-up who were randomized to CSII, 3 (12%) who were randomized to MDI, and 14 (56%) who switched insulin delivery modality after 24 weeks. Nineteen (44%) complete responders and 16 (57%) incomplete responders were randomized to RT-CGM. Despite uninterrupted provision of sensors, only six (32% from $n = 19$) complete responders and three (21% from $n = 14$) incomplete responders randomized to RT-CGM were still using this at 24 months. Switching from SMBG to RT-CGM was not permitted within the study design and did not occur.

The number of severe hypoglycemia events experienced by incomplete responders was reduced by 91% over 24 months' follow-up from 16.9 ± 16.3 to 1.5 ± 1.0 events/person-year (Table 1), and only five (18%) individuals experienced more than two events. By definition, resolution of severe hypoglycemia occurred in all 43 complete responders.

Hypoglycemia awareness at 24 months assessed by the Clarke score was worse in the incomplete response group (Table 2), with unresolved impaired awareness (Clarke ≥4) reported in eight (62%) incomplete responders versus nine (29%) complete responders.

Seven-day blinded CGM profile before the 24-month visit showed 50% less time spent with glucose ≤3 mmol/L in the incomplete response group, although this did not reach statistical significance (Table 1). A nonsignificant trend toward reduced glucose variability determined by SD was seen in incomplete responders. Other CGM parameters including time in range and time ≥10 mmol/L were comparable. HbA_{1c} was similar between groups despite incomplete responders taking less insulin.

There was greater fear of hypoglycemia in the incomplete response group at 24 months (Table 2). No differences were observed between groups in the hyperglycemia avoidance and diabetes treatment satisfaction scores.

Comparison of Baseline Metabolic Parameters and Hypoglycemia/Hyperglycemia/Treatment Satisfaction Questionnaires as Potential Predictors of Incomplete and Complete Response

All participants in this analysis had at least one severe hypoglycemia event over the 12 months preceding the RCT. However, incomplete responders experienced a higher number of events, with 16.9 ± 16.3 vs. 6.4 ± 10.8 events/person-year for complete responders

Table 1—Measures of hypoglycemia experience, hypoglycemia exposure, and insulin dose at baseline and 24 months

	Complete response, n = 43 (60.6%)	Incomplete response, n = 28 (39.4%)	P value
Severe hypoglycemia			
Events/person-year			
Baseline	6.4 ± 10.8 (43)	16.9 ± 16.3 (28)	0.002
24 months	—	1.5 ± 1.0 (19)	
Impaired awareness of hypoglycemia			
Gold score			
Baseline	4.8 ± 1.2 (43)	5.1 ± 1.1 (28)	0.28
24 months	3.2 ± 1.9 (32)	4.2 ± 1.8 (17)	0.07
Clarke score			
Baseline	4.9 ± 1.4 (39)	5.4 ± 1.6 (25)	0.25
24 months	2.0 ± 1.9 (31)	3.8 ± 2.2 (13)	0.01
HypoA-Q Impaired Awareness subscale			
Baseline	13.1 ± 3.5 (42)	14.4 ± 2.7 (25)	0.13
24 months	7.3 ± 5.1 (34)	10.3 ± 4.3 (16)	0.047
Insulin dose (units/kg)			
Baseline	0.69 ± 0.25 (42)	0.61 ± 0.22 (28)	0.15
24 months	0.58 ± 0.17 (28)	0.45 ± 0.11 (14)	0.01
HbA_{1c} (mmol/mol)			
Baseline	65.1 ± 10.1 (43)	66.9 ± 12.4 (28)	0.50
24 months	62.9 ± 10.1 (41)	61.5 ± 11.5 (20)	0.64
CGM (mmol/L)			
% time ≤3			
Baseline	3.8 ± 4.1 (42)	3.9 ± 5.4 (28)	0.91
24 months	3.0 ± 4.8 (33)	1.4 ± 2.1 (13)	0.26
% time in range 3–10			
Baseline	57.2 ± 17.5 (42)	56.8 ± 18.9 (28)	0.94
24 months	60.6 ± 16.5 (33)	56.7 ± 24.0 (13)	0.53
% baseline ≥10			
Baseline	39.0 ± 18.8 (42)	39.2 ± 19.7 (28)	0.97
24 months	36.3 ± 17.5 (33)	41.8 ± 24.4 (13)	0.40
Sensor mean			
Baseline	9.3 ± 1.9 (42)	9.6 ± 2.2 (28)	0.58
24 months	9.3 ± 2.0 (33)	9.7 ± 2.4 (13)	0.63
Glucose SD			
Baseline	3.8 ± 0.8 (42)	4.0 ± 1.2 (28)	0.62
24 months	3.8 ± 0.9 (33)	3.2 ± 1.0 (13)	0.06

Data are mean ± SD (*n*).

(Table 1). Substantial and comparable proportions of participants in both groups reported third-party glucagon administration, paramedic attendance, and hospital attendance (Table 3). Impaired awareness of hypoglycemia was an RCT inclusion criterion, with no statistical difference between groups at baseline.

CGM parameters obtained from the 7-day period of blinded CGM preceding the baseline visit were comparable in incomplete and complete responders. HbA_{1c} and insulin doses were similar at study commencement, with baseline HbA_{1c} <8% in 12 (43%) incomplete responders and 20 (47%) complete responders.

Baseline fear of hypoglycemia was greater in incomplete responders across both behavior and worry subscales (Table 2). Hyperglycemia avoidance and diabetes treatment satisfaction scores were comparable prior to study commencement in those with incomplete and complete avoidance of severe hypoglycemia during the RCT and follow-up (Table 2).

Comparison of Other Baseline Parameters Including Micro-/Macrovascular Complication Status in Incomplete and Complete Responders

Participant age, weight, and duration of diabetes were comparable between complete and incomplete response groups (Table 3). A greater proportion of participants were women, with no difference across response groups. Forty-five percent of participants had a history of current or past smoking, with two-thirds reporting alcohol intake. Fifty percent of incomplete responders and 65% of complete responders had someone else at home with them during the day, increasing to 82% of incomplete responders and 93% of complete responders at night.

In this cohort with long-duration type 1 diabetes, a high percentage had lipohypertrophy, although this was not more common in either response group. All participants were screened for secondary autoimmune disease before RCT recruitment, with no difference in treated hypothyroidism across responder status. Three participants had celiac disease (one incomplete and two complete responders), with primary adrenal insufficiency in one participant (incomplete responder).

Macrovascular and microvascular disease complication statuses were comparable, with retinopathy in two-thirds of participants and microalbuminuria observed in one in four participants. Peripheral

Table 2—Patient-reported outcomes at baseline and 24 months

	Complete response, n = 43 (60.6%)	Incomplete response, n = 28 (39.4%)	P value
Fear of hypoglycemia: HFS-II			
Total			
Baseline	52.4 ± 26.4 (41)	69.0 ± 24.9 (28)	0.01
24 months	34.0 ± 23.6 (28)	53.9 ± 29.6 (13)	0.03
Behavior			
Baseline	21.7 ± 10.6 (41)	28.8 ± 12.0 (28)	0.01
24 months	16.6 ± 8.7 (30)	25.8 ± 14.3 (13)	0.01
Worry			
Baseline	31.3 ± 18.0 (43)	40.3 ± 15.2 (28)	0.03
24 months	18.6 ± 17.0 (30)	29.3 ± 16.4 (15)	0.051
Hyperglycemia avoidance: HAS			
Avoid extremes			
Baseline	3.2 ± 2.8 (43)	3.9 ± 3.0 (28)	0.35
24 months	2.3 ± 2.6 (34)	3.2 ± 2.6 (17)	0.25
Immediate action			
Baseline	9.0 ± 3.3 (43)	9.1 ± 3.6 (28)	0.93
24 months	7.4 ± 3.6 (34)	7.2 ± 3.2 (17)	0.84
Low blood glucose preference			
Baseline	6.0 ± 3.6 (43)	6.4 ± 3.6 (28)	0.68
24 months	3.7 ± 3.6 (34)	4.5 ± 3.8 (17)	0.48
Worry			
Baseline	23.7 ± 9.3 (43)	26.1 ± 8.6 (28)	0.27
24 months	20.8 ± 9.1 (34)	20.6 ± 9.0 (16)	0.94
Treatment satisfaction: DTSQ			
Total satisfaction			
Baseline	24.9 ± 5.8 (43)	26.0 ± 5.9 (28)	0.42
24 months	30.5 ± 5.3 (33)	31.3 ± 4.2 (16)	0.59
Perceived frequency hyperglycemia			
Baseline	3.8 ± 1.4 (43)	3.7 ± 1.4 (28)	0.74
24 months	3.1 ± 1.5 (34)	2.7 ± 1.1 (16)	0.27
Perceived frequency of hypoglycemia			
Baseline	3.8 ± 1.2 (43)	3.7 ± 1.4 (28)	0.73
24 months	2.6 ± 1.3 (34)	2.8 ± 1.4 (16)	0.54

Data are mean ± SD (n).

neuropathy was more than eightfold more common in incomplete responders (39.3% vs. 4.7% affected). Autonomic neuropathy symptoms were also more commonly reported in incomplete responders, without statistically significant differences between groups. COMPASS was higher (borderline significance) in incomplete responders.

The ID polymorphism of the ACE genotype was the most commonly observed in both responder groups, with no difference in the DD polymorphism.

Mixed-Meal Tolerance Test Subgroup Analysis

Rerecruitment to the substudy was comparable in both groups with 25 (58%) complete responders and 13 (46%) incomplete responders taking part. Stimulated serum C-peptide microsecretion was detectable in seven (18%) participants (range 4–99 pmol/L) (Supplementary Table 1). Fasting C-peptide microsecretion was observed in only three participants (all complete responders). Four participants (all complete responders) had detectable urine C-peptide. Three further incomplete responders had nonstudy mixed-meal tolerance tests excluding C-peptide microsecretion prior to undergoing pancreatic islet transplantation for recurrent life-threatening hypoglycemia.

CONCLUSIONS

In this analysis, planned before trial commencement, in a cohort of adults with long-standing type 1 diabetes and impaired awareness of hypoglycemia, higher baseline rate of severe hypoglycemia, fear of hypoglycemia, and peripheral neuropathy were predictors of further severe hypoglycemia during the 24-month follow-up despite the HypoCOMPaSS study intervention.

Following the "my hypo compass" psychoeducational intervention, optimized insulin delivery, and glucose monitoring targeting avoidance of biochemical hypoglycemia without relaxing overall glycemic control, the HypoCOMPaSS RCT demonstrated recovery of hypoglycemia awareness and 95% reduction in severe hypoglycemia over 2-year follow-up of a cohort with long-standing type 1 diabetes (20). The current analysis of participants experiencing severe hypoglycemia over the 12 months prior to randomization demonstrates "complete response" (defined as no further severe hypoglycemia over the 2-year study duration) in the majority (61%). The remaining 39%, defined as "incomplete responders," achieved >90% reduction in severe hypoglycemia rate. Severe hypoglycemia during the study was associated with persistent impairment in hypoglycemia awareness, in keeping with the well-established associations between validated awareness questionnaires and risk of severe events (21).

Table 3—Baseline demographic and clinical characteristics of complete and incomplete response groups

	Complete response, $n = 43$ (60.6%)	Incomplete response, $n = 28$ (39.4%)	*P* value
Age (years)	49.0 ± 13.8	50.4 ± 9.4	0.65
Female	26 (60.5)	18 (64.3)	0.75‡
Diabetes duration (years)	29.0 ± 11.1	32.3 ± 12.6 ($n = 27$)	0.26
Body weight (kg)	75.8 ± 14.5	74.9 ± 15.9	0.80
BMI (kg/m^2)	26.7 ± 4.2	26.9 ± 5.4	0.90
HbA_{1c} ≥64 mmol/mol	23 (53)	16 (57)	N/A
HbA_{1c} (mmol/mol)	65.1 ± 10.1	66.9 ± 12.4	0.50
Insulin dose (units/kg)	0.69 ± 0.25	0.61 ± 0.22	0.15
Smoking status: never, former, current	23 (54.8), 13 (31.0), 6 (14.3) ($n = 42$)	15 (53.6), 7 (25.0), 6 (21.4)	0.70‡
Alcohol consumers	27 (63)	17 (61)	N/A
Someone at home during day	28 (65)	14 (50)	N/A
Someone at home at night	40 (93)	23 (82)	N/A
Glucagon requirement for SH over last 12 months	15 (37) ($n = 41$)	12 (43)	N/A
Paramedic attendance for SH over last 12 months	20 (48) ($n = 42$)	9 (32)	N/A
Hospital attendance for SH over last 12 months	3 (7) ($n = 42$)	2 (7)	N/A
Lipohypertrophy	14 (33.3) ($n = 42$)	11 (42.3) ($n = 26$)	0.46‡
Treated thyroid disease	14 (32.6)	7 (25.0)	0.50‡
Atherosclerotic disease	7 (16.3)	3 (10.7)	0.51‡
Peripheral vascular disease	4 (9.3)	2 (7.1)	0.75‡
Microalbuminuria	11 (26.2) ($n = 42$)	7 (26.9) ($n = 26$)	0.95‡
Creatinine (mmol/L)	74.8 ± 20.1	76.4 ± 26.9 ($n = 27$)	0.78
Retinopathy	28 (65.1)	18 (66.7) ($n = 27$)	0.89‡
Laser photocoagulation	11 (25.6)	8 (28.6)	0.78‡
Peripheral neuropathy	2 (4.7)	11 (39.3)	<0.001‡
Postural hypotension	10 (23.8) ($n = 42$)	11 (39.3)	0.17‡
Gastroparesis	2 (4.7)	5 (17.9)	0.07‡
Bowel disturbance	8 (18.6)	8 (28.6)	0.33‡
Autonomic sweating	5 (11.6)	4 (14.3)	0.74‡
Autonomic bladder dysfunction	2 (4.7)	2 (7.1)	0.66‡
Male erectile/female sexual dysfunction	9 (22.5) ($n = 40$)	7 (25.9) ($n = 27$)	0.75‡
ACE genotype: DD, ID, II	9 (23.7), 25 (65.8), 4 (10.5) ($n = 38$)	8 (34.8), 11 (47.8), 4 (17.4) ($n = 23$)	0.38‡
COMPASS	18.2 ± 18.4 ($n = 36$)	28.1 ± 18.3 ($n = 24$)	0.046

Data are mean ± SD or *n* (%). *n* also reported where data completion less than $n = 43$ for complete response group and less than $n = 28$ for incomplete response group. N/A, no formal statistical testing, as not included in a priori statistical analysis plan. ‡χ^2 test. SH, severe hypoglycemia.

All participants had impaired awareness of hypoglycemia at baseline, with no differences between complete and incomplete responders. Baseline severe hypoglycemia rate was 2.5-fold higher in incomplete responders. An association between >10 severe hypoglycemia events per annum at baseline and continued episodes during follow-up despite optimized medical intervention has previously been reported in a retrospective cohort study (22).

We have previously reported comparable reductions in severe hypoglycemia rates and proportion affected irrespective of allocated insulin delivery (CSII vs. MDI) or glucose monitoring (RT-CGM vs. SMBG) modality, and all interventions were comparably represented in complete and incomplete responders in the current analysis (8). Treatment satisfaction at baseline and study completion was also comparable.

A subgroup of adults with type 1 diabetes expressing "low concern" regarding hypoglycemia unawareness and high associated risk of dangerous hypoglycemia has been identified through semi-structured qualitative interviews (23). In addition, the pre-HypoCOMPaSS qualitative study, which informed the "my hypo compass" psycho-educational intervention, found similar psychological and behavioral barriers to severe hypoglycemia prevention (24). It was hypothesized that this subgroup would show incomplete response to the study intervention, as they would continue to experience and be "unconcerned" by ongoing biochemical hypoglycemia. On the contrary, incomplete responders spent less than half the time with glucose <3 mmol/L compared with complete responders. Baseline total daily insulin doses were comparable, but dose was significantly lower at 24 months in incomplete responders. This supports appropriate insulin reduction to avoid biochemical hypoglycemia—as opposed to persistence with inappropriately high doses due to a strong preference for hypoglycemia over hyperglycemia. HbA_{1c} was also comparable in both groups at baseline and study completion. Incomplete responders did not show low concern regarding hypoglycemia, with higher HFS-II scores at baseline and study

completion. This is consistent with published data reporting associations among fear of hypoglycemia, impaired awareness, nocturnal hypoglycemia, and frequency of severe hypoglycemia (25,26). A small subgroup of ~10% of those with type 1 diabetes and severe hypoglycemia reporting low fear of hypoglycemia has, however, been reported in a large cross-sectional study (26). In HypoCOMPaSS, the HFS-II Behavior subscale scores remained particularly high in incomplete responders, potentially reflecting active hypoglycemia avoidance strategies (27).

The HAS was designed to assess anxieties related to high glucose levels and avoidance behaviors, which may increase risk of hypoglycemia (14). Scores in all subscales were lower at study completion in both groups, reflecting reduced "worry" regarding high glucose levels, attenuated "low blood glucose" preference, less "avoidance of glucose extremes," and lower drive to take "immediate action" for high glucose levels. HAS scores were comparable in incomplete and complete responders at baseline and 24 months, suggesting that the trial focus on safely avoiding low glucose levels without increasing hyperglycemia, underpinned by the "my hypo compass" brief psycho-educational intervention, was equally effective regardless of underlying preference for lower or higher glucose levels.

Our alternative hypothesis proposed that incomplete response would be predicted not by greater biochemical hypoglycemia exposure but, rather, by a phenotype associated with irreversible impairment in hypoglycemia awareness and counterregulation, evidenced by significant established diabetic neuropathy. It is clear that hypoglycemia-associated autonomic failure can be rapidly induced by biochemical hypoglycemia exposure and that counterregulatory response can be restored through rigorous hypoglycemia avoidance (28,29). Indeed, this conceptual framework was core to the HypoCOMPaSS trial design and is consistent with overall study results. This paradigm has led to the conclusion that classical diabetic neuropathy is not associated with impaired awareness of hypoglycemia (30). In larger cross-sectional studies, however, peripheral neuropathy, cardiac autonomic neuropathy, and gastroparesis have been associated with severe hypoglycemia (31–33). Previous studies have not been designed to assess the impact of neuropathy on reversibility in those with established impaired awareness of hypoglycemia. In the current study, peripheral neuropathy was more than eightfold more common in incomplete responders, with trends toward increased proportion reporting autonomic neuropathy symptoms and a higher integrated autonomic neuropathy score. In contrast, age, duration of diabetes, proportion with a second autoimmune disease, and other microvascular/macrovascular complications of diabetes were not higher in incomplete responders.

Circulating serum ACE levels are associated with the insertion/deletion (I/D) polymorphism of the ACE gene (II, lowest serum ACE; ID, intermediate; and DD, highest). Serum ACE activity has been positively associated with severe hypoglycemia rate in a prospective cohort study, and it has been proposed that this may be due to decreased cognitive "performance" during hypoglycemia (34). There was an association between DD genotype and earlier deterioration of cognitive dysfunction in the subgroup of HypoCOMPaSS participants who completed hyperinsulinemic-hypoglycemic clamp studies (35), but no association between ACE genotype and response group was observed in the current analysis.

A protective role of a residual β-cell functional mass including reduced risk of severe hypoglycemia has been demonstrated in the Diabetes Control and Complications Trial (DCCT) (36), and C-peptide negativity without highly sensitive assay or formal stimulation test was a HypoCOMPaSS inclusion criterion. Since study commencement, highly sensitive C-peptide assays have enabled detection of residual C-peptide microsecretion in up to 70% of people with long-standing type 1 diabetes (18), associated with reduced hypoglycemia severity (37). In mixed-meal tolerance tests performed after HypoCOMPaSS completion, only a minority were found to be C-peptide microsecretors. No incomplete responder had detectable fasting serum C-peptide or poststimulation urine C-peptide, but the majority of complete responders were also not C-peptide microsecretors. Thus, although absolute C-peptide negativity is a risk factor for severe hypoglycemia, it does not in itself preclude avoidance of severe hypoglycemia through multifactorial conventional intervention.

Study limitations include the requirement for complete severe hypoglycemia data at all study visits to classify a participant as a responder, whereas a single episode of severe hypoglycemia recorded at any point during the study designates the participant an incomplete responder. This may have led to underreporting of complete responders. There were more missing data at 24 months in the incomplete response group, but data at study entry were complete in virtually all participants, strengthening the primary analysis assessing baseline predictors of complete and incomplete response. Data for determination of associations between biochemical hypoglycemia, awareness, and severity were restricted to 7-day CGM profiles at baseline and 24 months, limiting conclusions regarding hypoglycemia exposure and other parameters of glycemic control/variability over the longer duration of the study (38). The freedom of the participants to switch between MDI and CSII therapy after the formal 24-week RCT when they returned to routine clinical care was a potential weakness in overall study design but should not unduly impact the current analysis seeking to determine factors associated with complete and incomplete response to an intervention primarily targeting hypoglycemia avoidance through a multifactorial intervention. It also strengthens conclusions regarding the potential for a complete response lasting at least 2 years despite the relatively short duration of the initial RCT. Although incomplete response was seen in comparable proportions randomized to RT-CGM and SMBG alone, the majority were no longer using RT-CGM at 24 months. It is likely that prevention of recurrent severe hypoglycemia in a greater proportion would now be attainable through updated RT-CGM technology with greater tolerability, utility, predictive low glucose alarms, and connectivity to suspend CSII insulin delivery.

In conclusion, a preplanned analysis of HypoCOMPaSS participants experiencing severe hypoglycemia over the year prior to study entry has confirmed that the majority experienced no further events over the 2 years following the trial intervention. Severe hypoglycemia rate was substantially reduced even in

incomplete responders. Incomplete response was associated not with a strong preference for or low concern about low glucose levels but with established diabetic neuropathy. This underlines the effectiveness of a structured psycho-educational intervention in parallel with optimized insulin delivery and glucose monitoring in preventing recurrent severe hypoglycemia in long-standing type 1 diabetes, even in those with a high baseline preference for high glucose avoidance. However, absolute C-peptide negativity and significant neuropathy may merit earlier consideration of sensor-augmented pump therapy to achieve "technological" hypoglycemia prevention or β-cell replacement therapy to achieve "biological" hypoglycemia prevention.

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