Multicenter Randomized Trial of Intermittently Scanned Continuous Glucose Monitoring Versus Self-Monitoring of Blood Glucose in Individuals With Type 2 Diabetes and Recent-Onset Acute Myocardial Infarction: Results of the LIBERATES Trial

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CARDIOVASCULAR AND METABOLIC RISK

OBJECTIVE

To analyze the impact of modern glucose-monitoring strategies on glycemic and patient-related outcomes in individuals with type 2 diabetes (T2D) and recent myocardial infarction (MI) and assess cost effectiveness.

RESEARCH DESIGN AND METHODS

LIBERATES was a multicenter two-arm randomized trial comparing self-monitoring of blood glucose (SMBG) with intermittently scanned continuous glucose monitoring (isCGM), also known as flash CGM, in individuals with T2D and recent MI, treated with insulin and/or a sulphonylurea before hospital admission. The primary outcome measure was time in range (TIR) (glucose 3.9–10 mmol/L/day) on days 76–90 post randomization. Secondary and exploratory outcomes included time in hypoglycemia, hemoglobin A_{1c} (HbA_{1c}), clinical outcome, quality of life (QOL), and cost effectiveness.

RESULTS

Of 141 participants randomly assigned (median age 63 years; interquartile range 53, 70), 73% of whom were men, isCGM was associated with increased TIR by 17 min/day (95% credible interval −105 to +153 min/day), with 59% probability of benefit. Users of isCGM showed lower hypoglycemic exposure (<3.9 mmol/L) at days 76–90 (−80 min/day; 95% CI −118, −43), also evident at days 16–30 (−28 min/day; 95% CI −92, 2). Compared with baseline, HbA_{1c} showed similar reductions of 7 mmol/mol at 3 months in both study arms. Combined glycemic emergencies and mortality occurred in four isCGM and seven SMBG study participants. QOL measures marginally favored isCGM, and the intervention proved to be cost effective.

CONCLUSIONS

Compared with SMBG, isCGM in T2D individuals with MI marginally increases TIR and significantly reduces hypoglycemic exposure while equally improving HbA_{1c}, explaining its cost effectiveness. Studies are required to understand whether these glycemic differences translate into longer-term clinical benefit.

Cardiovascular disease remains the main cause of mortality in patients with diabetes, and these individuals have worse prognosis after myocardial infarction (MI) than patients with normal glucose metabolism (1–3). The observed inferior clinical outcome in diabetes is particularly pronounced in insulin-treated patients (4).

After a coronary event, short- and medium-term glycemic targets in patients with diabetes are not clear, which was highlighted as a knowledge gap in both the 2015 and 2020 combined European Society of Cardiology/European Association for the Study of Diabetes guidelines (5,6). The more recent guideline further added the importance of avoiding hypoglycemia, while acknowledging that more work in this area is needed.

In patients with MI, hyperglycemia is associated with worse prognosis (7). The DIGAMI-1 (Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction-1) study demonstrated that intensive glucose control after acute coronary syndrome (ACS) is associated with reduction in hemoglobin A_{1c} (HbA_{1c}) and significantly lower mortality (8). However, DIGAMI-2, investigating different treatment regimens, failed to show significant differences between study arms (9). Although not statistically significant, there were numerically more deaths in the intervention arms, particularly in insulin-treated patients, raising an early concern over the potentially detrimental effect of hypoglycemia.

Glycemic outcome studies in MI patients have usually relied on HbA_{1c} for assessment of glycemic control, but hypoglycemia, which HbA_{1c} fails to detect, is also associated with adverse vascular outcome (10–12). Moreover, hypoglycemia can cause significant distress to patients, impairing quality of life (QOL) and compromising daily activities (13). Both hyperglycemia and hypoglycemia have shown associations with increased thrombosis potential, manifesting as impaired fibrinolysis (14,15), an important marker of adverse outcomes after ACS (16). These findings provide mechanistic explanations for the adverse clinical outcomes observed with extremes of blood glucose.

In order to optimize glycemic control in diabetes, individuals are asked to regularly perform self-monitoring of blood glucose (SMBG). However, this is inconvenient and may lead to anxiety and impaired QOL (17), particularly in the stressful post-MI period. Another approach to monitoring glycemia relies on continuous glucose monitoring (CGM), but the cost effectiveness of rolling this out across the entire type 2 diabetes (T2D) population has not been demonstrated (18).

We hypothesized that a modern glycemic-monitoring strategy optimizes glucose control in individuals with T2D after MI and improves QOL. Therefore, the LIBERATES (Improving Glucose Control in Patients With Diabetes Following Myocardial Infarction: Role of a Novel Glycaemic Monitoring Strategy) trial was designed to investigate the effects of intermittently scanned CGM (isCGM), also known as flash CGM, on glycemic control and QOL measures in patients with T2D after acute MI, while also analyzing the cost effectiveness of this strategy. Given the association between low glucose and adverse vascular outcome, T2D individuals at increased hypoglycemic risk were studied.

RESEARCH DESIGN AND METHODS

Details of the trial design and statistical plan were previously published in the trial protocol (19).

Study Design and Participants

LIBERATES was a phase 2 parallel-group open-label, randomized controlled trial investigating the role of isCGM compared with standard SMBG in glycemic control and QOL in individuals with acute MI and T2D who were already receiving therapies that may result in hypoglycemia. Favorable ethical approval for the trial was received in June 2017 (Integrated Research Application System 223768; Leeds East Research Ethics Committee, Leeds, U.K.). The study design was previously published (19). Briefly, inclusion criteria were: adult patients age ≥18 years, with preadmission diagnosis of T2D receiving treatment with a sulphonylurea and/or insulin (in addition to or without other hypoglycemic agents); MI was defined as symptoms of cardiac ischemia associated with a typical rise in troponin levels using the 99th percentile threshold (individuals with ST-elevation MI and non–ST-elevation MI were eligible). Exclusion criteria were active malignancy, other than localized squamous cell or basal cell skin carcinoma, known pregnancy, renal dialysis, inability to follow study instructions, or considered unsuitable for trial participation by the treating clinician/nurse. Patients with a permanent pacemaker were initially excluded but were subsequently allowed to participate after an ethics amendment (April 2019).

Randomization and Masking

Trial participants were randomly assigned at a one-to-one ratio to either isCGM (intervention) or standard SMBG (control) via an automated central telephone and web randomization service. Random allocation sequences were pregenerated by the trial statistician implementing the allocation rule of Soares and Wu (20) to minimize the risk of selection bias in an open-label design, stratified by site and baseline insulin use.

Procedures

Anthropometric measures, blood pressure data, and HbA_{1c} (determined using local hospital laboratories) were measured, and QOL questionnaires completed at baseline and on day 91.

In the intervention arm, participants were instructed to monitor glucose profile using isCGM sensor for a period of 90 days, replacing the sensor every 14 days. In the control arm, participants used SMBG to monitor glucose levels, and a Freestyle Libre-Pro blinded sensor was worn in the first month (two sensors) and on days 76–90 (third sensor).

A simplified protocol was used for changing insulin regimen or sulphonylurea therapies in the two groups (Supplementary Table 1), but final glycemic treatment decisions were left to the discretion of the research team at each center. Glucose control in both study arms was reviewed at days 15 ± 3, 30 ± 3, 76 ± 3, and 90 ± 3 postrandomization. After the glycemic assessment part of the study (first 3 months), individuals were followed up for a further median period of 10 months (interquartile range 6, 12) for the occurrence of clinical outcomes.

Outcome Measures

The primary outcome measure was time in range (TIR) of glucose between 3.9 and 10.0 mmol/L/day during the period of days 76–90 from randomization. The trial had a number of prespecified secondary measures, specifically 1) TIR per day during the period of days 16–30; 2) time in hypoglycemia per day during the period of days 76–90 and days 16–30 (analyzed as <3.9 and <3.0 mmol/L); 3) time in hyperglycemia per day during the period of days 76–90 and days 16–30 (analyzed as >10.0 mmol/L); 4) HbA_{1c} at

day 91; 5) QOL measures at day 91, including Diabetes Treatment Satisfaction Questionnaire (DTSQ), Euro Quality of Life 5 Dimension (EQ5D)–5L, and Audit of Diabetes-Dependent Quality of Life (ADD-QoL); 6) systolic and diastolic blood pressure at day 91; and 7) weight at day 91. Exploratory outcomes included 1) severe hypoglycemia and hospital admissions for diabetes-related complaints, 2) major adverse cardiovascular events (MACEs), and 3) death resulting from any cause during the follow-up period (up to 12 months).

Statistical Considerations

Given the absence of CGM studies in individuals with diabetes and recent MI, the LIBERATES trial adopted a probability-based likelihood, Bayesian approach (21,22), which allows decisions to be made based on prespecified levels of the probability of therapeutic activity. The probability that the mean difference in TIR per day (3.9–10.0 mmol/L) between isCGM and SMBG is greater than zero was calculated from the posterior probability distribution, under a prespecified range of prior distributions. A recommendation for isCGM was based on achieving at least 80% posterior probability, approved by members of the independent trial oversight committee.

Simulations assumed 9- and 14-day availability of complete data on patient/sensor, a mean TIR of 13.3 h in the control group, with intraclass correlation (ICC) of 0.75 for time per day within participants and within and between participant variances of 10.97 and 32.90, respectively, based mainly on previously published data in individuals with T2D with no recent MI (23). SEs of the treatment comparison and the mean of the posterior probabilities of a positive effect (conditional on a true increase of 1.5, 1, or 0.5 h in favor of the intervention) were obtained from multilevel random effects mixed models in 1,000 simulated data sets.

Simulations demonstrated that, with 75 participants per arm providing complete data, the expected posterior probability of the intervention arm being better than control would be 95.8%, under an uninformative prior. With 20% loss to follow-up, the expected posterior probability would be 93.9%, with the same distribution and assumed true difference.

Statistical analyses followed a prespecified analysis plan in line with published guidance (24). The primary outcome measure, TIR each day during days 76–90, was analyzed and interpreted within the Bayesian framework. The primary analysis used uninformative prior distributions for all parameters in the model, with sensitivity analyses considered a range of more informative priors, based on published data. The primary analysis was conducted on day measurements that had at least 80% of sensor readings complete (equivalent to 19 of 24 h recorded). Sensitivity analyses relaxed this to include day measurements with at least 65% of sensor readings (equivalent to 16 of 24 h recorded).

Analyses were conducted using a hierarchical longitudinal model, comprising random intercepts for participants and centers and random slopes for time, as well as fixed effects for intervention arm, insulin use, and time. The mean TIR for each patient was obtained and included in a linear regression model, adjusting for fixed effects of insulin and mean baseline glucose level and random intercept effects for randomizing center to allow comparison with other published trials using this approach.

For secondary glycemic outcome measures, including hypoglycemia (days 16–30 and 76–90) and TIR (days 16–30), hierarchical longitudinal linear regression models were constructed as detailed above. Analyses of secondary outcome measures based on a single measurement at day 91 (HbA$_{1c}$, blood pressure, weight, and patient-reported outcome measures) were analyzed by linear regression, adjusted for baseline values, randomizing center, and baseline insulin use. Safety outcomes were assessed using summary statistics because of the lower-than-expected frequency of events.

Cost-Effectiveness Analysis Plan

For estimation of long-term cost effectiveness, two different models were used. The first used the previously developed UKPDS (UK Prospective Diabetes Study) economic outcomes (25), which fail to take into account hypoglycemic exposure. Therefore, we also used the Markov model, which allows the inclusion of hypoglycemia; as per international guidance, a hypoglycemic event captures the impact of nonsevere hypoglycemia (level 1 [<3.9 mmol/L] and level 2 [<3.0 mmol/L]) as well as severe hypoglycemia requiring third-party intervention (26), in terms of cost and QOL.

Cost effectiveness was estimated by combining the UKPDS and Markov models.

In terms of expenditure, the UKPDS model estimates long-term costs of diabetes; costs of hypoglycemic events were obtained from Health and Social Care, including the Personal Social Services Research Unit, and device costs were provided by the manufacturer. Costs were updated to 2020 using the Office of National Statistics gross domestic product deflator index. The UKPDS model estimates long-term quality-adjusted life-years (QALYs) based on an initial utility value, estimated in the trial. Utility losses resulting from hypoglycemic events were obtained from the literature (27).

The base case scenario assumes that isCGM is used continuously during the first 3 months (trial duration), after which patients will use three sensors per year (one every 3 months) for life, while using SMBG testing outside these periods. Cost effectiveness was determined based on an assumption of £20,000 per QALY gained using 10,000 Monte Carlo iterations to account for the uncertainty of the parameter values and estimate the net monetary benefit (NMB) (NMB = QALYs * £20,000 in costs). Cost effectiveness was determined via the incremental cost-effectiveness ratio and the incremental NMB, with the latter being used when a particular intervention dominated (more effective and less costly).

RESULTS

Study Participants

Between November 2017 and November 2019, 141 participants were randomly assigned to SMBG (n = 72) or isCGM (n = 69). In total, 2,720 individuals were considered, of whom 2,341 were found to be ineligible and 189 did not consent, and the research teams were unable to approach the rest within the 5-day inclusion period (Supplementary Fig. 1).

Clinical characteristics and medications of the study participants were well balanced between the groups (Table 1). Almost half were receiving insulin treatment (49.6%), with a mean dose of 74.9 ± 48.6 and 58.7 ± 37.9 units/day for SMBG and isCGM groups, respectively. The remainder were receiving a sulphonylurea without insulin therapy (50.4%). The day-91 study visit was attended by 60 (83.3%) and 57

Table 1—Baseline characteristics of study participants

	Total (N = 141)	Control (SMBG) (n = 72)	Intervention (isCGM) (n = 69)
Age at randomization, years	63.0 (54.0, 70.0)	63.0 (53.0, 69.5)	62.0 (54.0, 71.0)
Sex			
Male	103 (73.0)	52 (72.2)	51 (73.9)
Female	38 (27.0)	20 (27.8)	18 (26.1)
Ethnicity			
White	127 (90.1)	62 (86.1)	65 (94.2)
South Asian	11 (7.8)	7 (9.1)	4 (5.7)
Black	2 (1.4)	2 (2.8)	0 (0)
Missing	1 (0.7)	1 (1.4)	0 (0)
Duration of diabetes, years	13.0 (7.0, 18.0)	11.0 (7.0, 17.0)	14.5 (9.0, 20.0)
Blood pressure, mmHg			
Systolic	126 (114, 140)	125 (114, 147)	128 (117, 137)
Diastolic	73 (65, 80)	75 (67, 80)	72 (65, 79)
Weight, kg	91.0 (81.9, 102.4)	90.0 (81.0, 107.9)	92.1 (82.0, 102.0)
BMI, kg/m^2	31.1 (27.9, 34.1)	30.4 (27.3, 34.2)	31.5 (28.1, 34.0)
Diabetes complications			
Coronary artery disease	38 (27.0)	21 (29.2)	17 (24.6)
Cerebrovascular disease	18 (12.8)	9 (12.5)	9 (13.0)
Peripheral artery disease	10 (7.1)	3 (4.2)	7 (10.1)
Heart failure	16 (11.3)	7 (9.7)	9 (13.0)
Nephropathy			
eGFR <60 mL/min/m^2	12 (8.5)	6 (8.3)	6 (8.7)
Albuminuria	48 (34.0)	22 (30.6)	26 (37.7)
Retinopathy	27 (19.1)	13 (18.1)	14 (20.3)
Neuropathy	28 (19.9)	12 (16.7)	16 (23.2)
Glycemic therapies			
Insulin	70 (49.6)	34 (47.2)	36 (52.2)
SU (no insulin)	71 (50.4)	38 (52.8)	33 (47.8)
Hypoglycemic agent other than insulin/SU	121 (85.8)	63 (87.5)	58 (84.1)
Metformin	106 (75.2)	56 (77.8)	50 (72.5)
DPP-4i	26 (18.4)	11 (15.3)	15 (21.7)
GLP1-RA	10 (7.1)	5 (6.9)	5 (7.2)
SGLT2i	22 (15.6)	15 (20.8)	7 (10.1)
Thiazolidinedione	2 (1.4)	0 (0.0)	2 (2.9)
Nonglycemic therapies			
Lipid lowering	131 (92.9)	66 (91.7)	65 (94.2)
Antiplatelet and/or anticoagulant	139 (98.6)	71 (98.6)	68 (98.6)
Antianginal/antihypertensive	137 (97.2)	69 (95.8)	68 (98.6)
Laboratory tests at baseline			
HbA$_{1c}$, mmol/mol	73.5 (61.0, 86.0)	73.0 (60.0, 93.0)	75.0 (62.0, 83.0)
HbA$_{1c}$, %	8.9 (7.7, 10.0)	8.8 (7.6, 10.7)	9.0 (7.8, 9.7)
Total cholesterol, mmol/L	4.1 (3.3, 4.9)	4.1 (3.4, 5.1)	4.0 (3.2, 4.9)
LDL cholesterol, mmol/L	2.3 (1.5, 2.9)	2.3 (1.7, 2.8)	2.2 (1.4, 3.0)
HDL cholesterol, mmol/L	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	1.0 (0.8, 1.1)
Triglycerides, mmol/L	2.0 (1.3, 2.9)	2.0 (1.3, 3.0)	2.1 (1.2, 2.8)

Data are presented as n (%) or median (interquartile range) for whole study group, SMBG control group, and isCGM intervention group. DPP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium glucose cotransporter 2 inhibitor; SU, sulphonylurea.

(82.6%) of control and isCGM participants, respectively.

Glucose Scanning Frequency

The median number of scans in the isCGM group was six per day, and this remained stable for 3 months (Supplementary Fig. 2).

Primary Outcome Measure

TIR (days 76–90)

Baseline TIRs (mean ± SD) in the SMBG and isCGM groups were well matched at 11.5 ± 6.1 and 11.3 ± 6.8 h/day. Primary analyses included data with sensor glucose coverage at >80% of the day. A 16.6-min increase (95% credible interval −105.1 to 153.1 min) in TIR per day with isCGM compared with SMBG was estimated (Fig. 1A). The posterior probability that the mean difference in TIR between isCGM and SMBG is greater than zero was 59% (Monte Carlo SE 3.8%) based
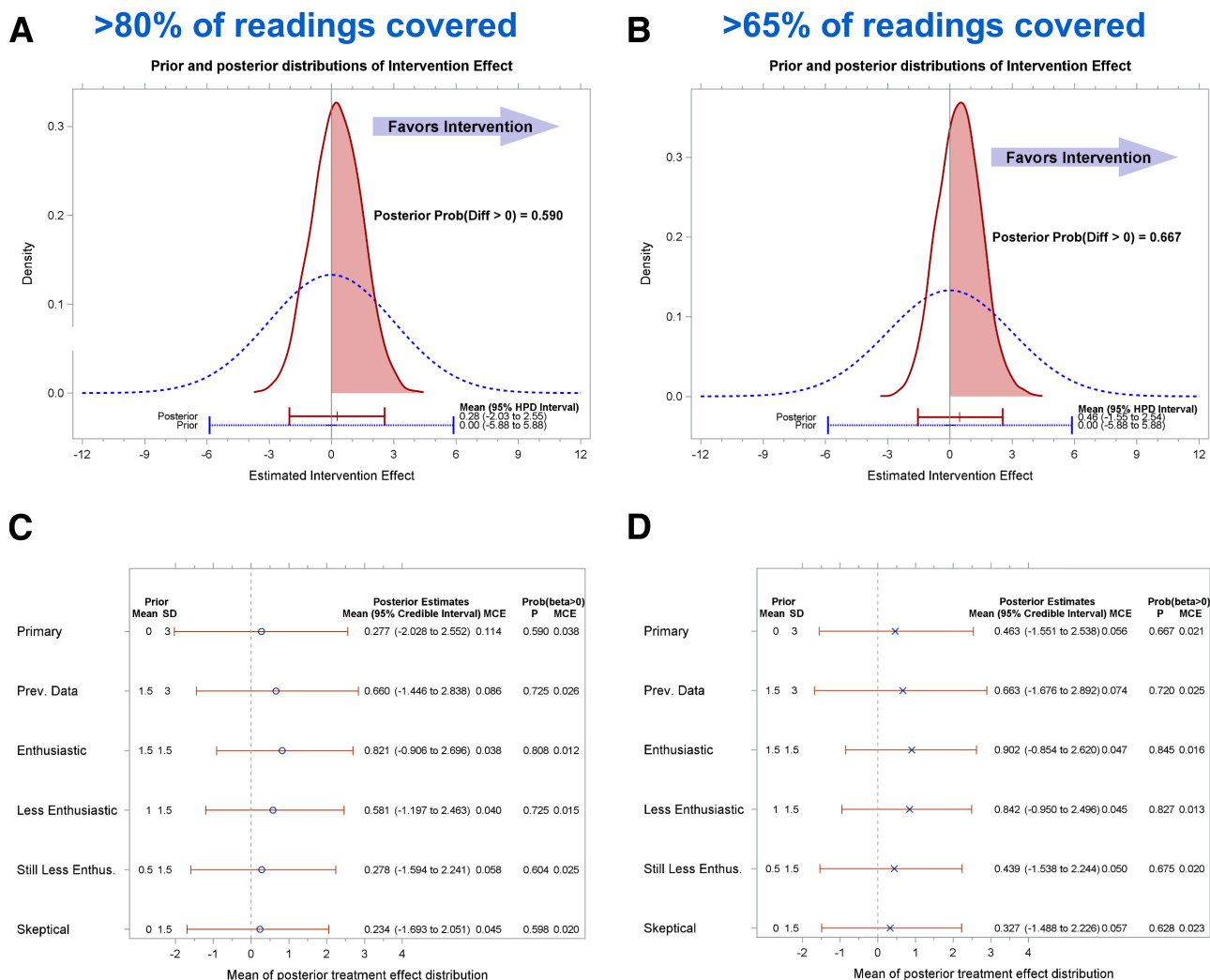
A   >80% of readings covered

Prior and posterior distributions of Intervention Effect

Favors Intervention

Posterior Prob(Diff > 0) = 0.590

	Mean (95% HPD Interval)
Posterior	0.28 (−2.03 to 2.55)
Prior	0.00 (−5.88 to 5.88)

Density — Estimated Intervention Effect (−12 to 12)

B   >65% of readings covered

Prior and posterior distributions of Intervention Effect

Favors Intervention

Posterior Prob(Diff > 0) = 0.667

	Mean (95% HPD Interval)
Posterior	0.46 (−1.95 to 2.94)
Prior	0.00 (−5.88 to 5.88)

Density — Estimated Intervention Effect (−12 to 12)

C

	Prior Mean	SD	Posterior Estimates Mean (95% Credible Interval)	MCE	Prob(beta>0) P	MCE
Primary	0	3	0.277 (−2.028 to 2.552)	0.114	0.590	0.038
Prev. Data	1.5	3	0.660 (−1.446 to 2.838)	0.086	0.725	0.026
Enthusiastic	1.5	1.5	0.821 (−0.906 to 2.696)	0.038	0.808	0.012
Less Enthusiastic	1	1.5	0.581 (−1.197 to 2.463)	0.040	0.725	0.015
Still Less Enthus.	0.5	1.5	0.278 (−1.594 to 2.241)	0.058	0.604	0.025
Skeptical	0	1.5	0.234 (−1.693 to 2.051)	0.045	0.598	0.020

Mean of posterior treatment effect distribution (−2 to 4)

D

	Prior Mean	SD	Posterior Estimates Mean (95% Credible Interval)	MCE	Prob(beta>0) P	MCE
Primary	0	3	0.463 (−1.551 to 2.538)	0.056	0.667	0.021
Prev. Data	1.5	3	0.663 (−1.676 to 2.892)	0.074	0.720	0.025
Enthusiastic	1.5	1.5	0.902 (−0.854 to 2.620)	0.047	0.845	0.016
Less Enthusiastic	1	1.5	0.842 (−0.950 to 2.496)	0.045	0.827	0.013
Still Less Enthus.	0.5	1.5	0.439 (−1.538 to 2.244)	0.050	0.675	0.020
Skeptical	0	1.5	0.327 (−1.488 to 2.226)	0.057	0.628	0.023

Mean of posterior treatment effect distribution (−2 to 4)

Figure 1—TIR (3.9–10.0 mmol/L) comparing two study groups at days 76–90 after randomization (Bayesian analysis). *A*: Comparison of isCGM with SMBG, analyzed with 80% of glucose data available per day. Based on uninformative prior, 17-min increase in TIR is evident in the isCGM group (posterior probability [prob] 0.590). *B*: Comparison of isCGM with SMBG, analyzed with 65% of glucose data available per day. Based on uninformative prior, 28-min increase in TIR is evident in the isCGM group (posterior probability 0.667). *C*: Sensitivity analyses using a range of priors with 80% of glucose data available per day. *D*: Sensitivity analyses using a range of priors with 65% of glucose data available per day. diff, difference; HPD, highest posterior density; MCE, Monte Carlo error; prev, previous.

on an uninformative prior. This failed to reach the prespecified 80% probability level. Sensitivity analyses based on alternative prior distributions showed the posterior probability that the mean difference in TIR between isCGM and SMBG is greater than zero ranged from 59 to 81% (Fig. 1*C*), depending on whether the prior estimate of effectiveness was uncertain or enthusiastic, respectively.

Sensitivity analyses, based on using sensor glucose coverage at >65% per day, estimated TIR was increased by 27.8 min/day (95% credible interval −93.1 to 152.3 min/day) with isCGM compared with SMBG (Fig. 1*B*). The posterior probability that the mean difference in TIR between isCGM and SMBG is greater than zero was

67% (Monte Carlo SE 2.1%), not reaching the prespecified 80% probability level. Sensitivity analyses based on alternative prior distributions were always greater than zero, ranging from 67 to 85% (Fig. 1*D*).

The ICC, important for the design of future cluster trials in this patient group, was 0.73.

Secondary and Exploratory Outcome Measures

Hypoglycemic Exposure

Baseline hypoglycemic exposures in the SMBG and isCGM groups were similar at 1.6 ± 2.9 and 1.5 ± 2.6 h/day. Participants randomly assigned to isCGM showed less hypoglycemia (<3.9 mmol/L) in days 16–30 (−45.5 min/day; 95% CI −137.9, 1.5;

ICC 0.60), a difference that became more pronounced in days 76–90 (−80.5 min; 95% CI −118, −42.8; ICC 0.42) (Fig. 2*A* and *B*). Findings were similar for hypoglycemic exposure at <3.0 mmol/L (Fig. 2*C* and *D*).

Early TIR (days 16–30)

Early TIR showed an estimated mean difference in TIR between isCGM and SMBG of 81.5 min (95% CI −49.6, 212.6; ICC 0.70) (Fig. 3*A*), with a numerically larger difference in baseline insulin patients (226.6 min; 95% CI −32.6, 485.8) (Fig. 3*A*).

HbA1c

Both study arms showed a similar reduction in HbA1c of 7 mmol/mol from baseline to day 91 (Fig. 3*B*). HbA1c difference at day 91 was 3.3 mmol/mol (95% CI

Hypoglycemic exposure (<3.9 mmol/l; <70 mg/dl)

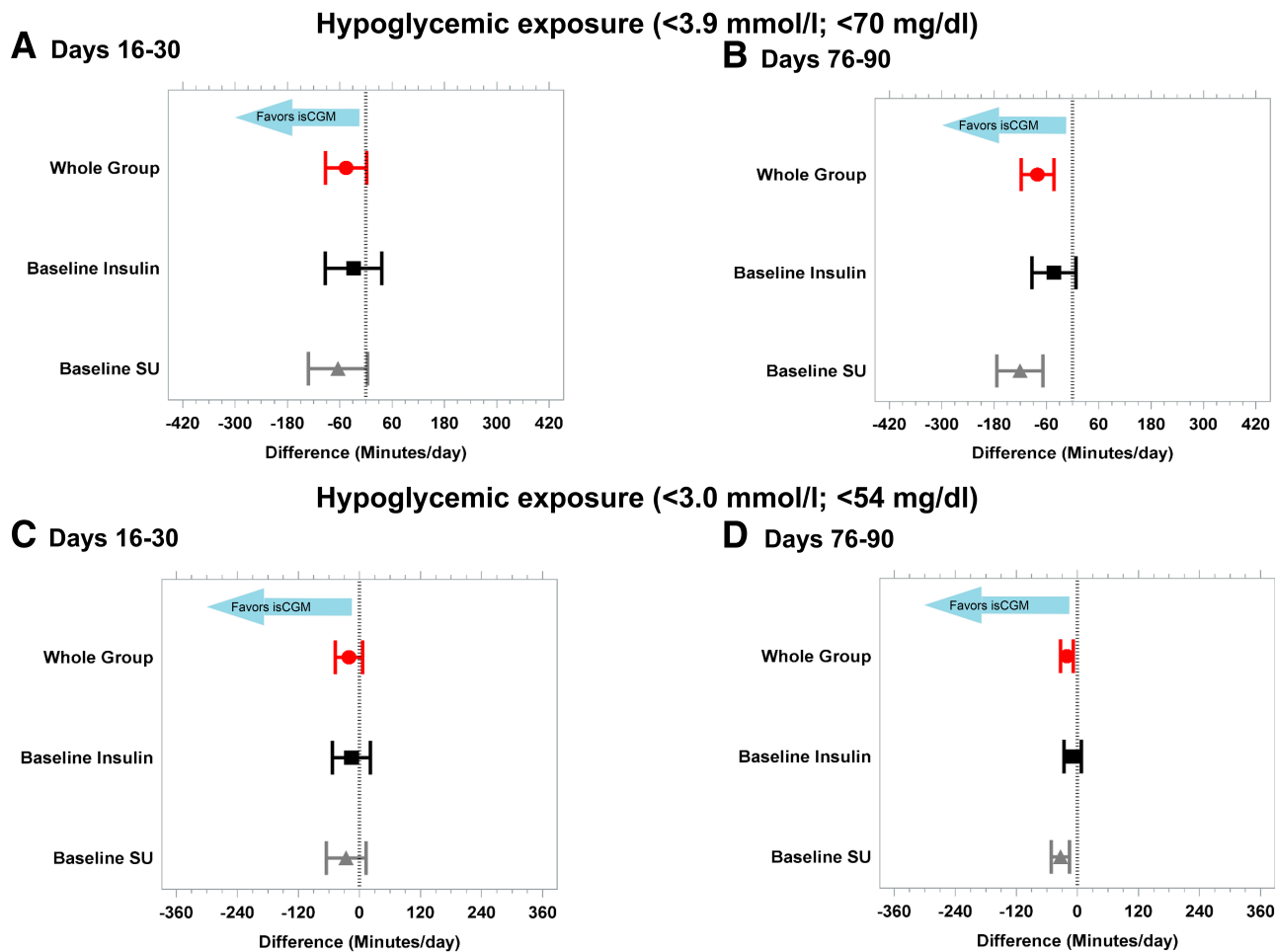## Hypoglycemic exposure (<3.0 mmol/l; <54 mg/dl)

Figure 2—Hypoglycemic exposure per day comparing two study groups. Analysis was performed for the whole group as well as for insulin and sulphonylurea (SU) users at baseline. A and B: Hypoglycemic exposure at <3.9 mmol/L (<70 mg/dL) at 16–30 (A) and 76–90 days (B). C and D: Hypoglycemic exposure at <3.0 mmol/L (<54 mg/dL) at 16–30 (C) and 76–90 days (D).

−0.8, 7.5) comparing isCGM with SMBG, after adjusting for baseline values.

Hyperglycemic Exposure
Participants randomly assigned to isCGM spent numerically less time in hyperglycemia (>10.0 mmol/L) in days 16–30 (−35.9 min/day; 95% CI −185.5, 113.6; ICC 0.77), with a numerical increase in days 76–90 (79.5 min/day; 95% CI −73.8, 232.8; ICC 0.77) (Supplementary Fig. 3A and B).

Patient-Related Outcome Measures
EQ5D-5L utility scores decreased between baseline and day 91 (Supplementary Fig. 4A). There was no difference between isCGM and SMBG in baseline-adjusted day-91 EQ5D-5L utility score (mean difference −0.004; 95% CI −0.076, 0.068).

In both arms, DTSQ scores improved between baseline and day 91 (Supplementary Fig. 4B). The mean difference between isCGM and SMBG in baseline-adjusted day-91 DTSQ score was 1.1

point (95% CI −0.7 to 2.9) (Supplementary Fig. 4B).

There was no overall difference in the ADDQoL score between isCGM and SMBG at day 91 (mean difference −0.02; 95% CI −0.24, 0.20); a 1-point difference in working life domain was observed in favor of isCGM (Supplementary Table 2).

Blood Pressure and Weight
Baseline-adjusted blood pressure was no different between isCGM and SMBG at day 91 (mean systolic difference −0.95 mmHg; 95% CI −7.5, 5.65); diastolic difference −1.88 mmHg; 95% CI −6.1, 2.35). There was no difference in weight (mean difference 0.4 kg; 95% CI −1.9, 2.7).

Glycemic Emergencies, MACEs, and Mortality
Severe hypoglycemia requiring third-party assistance occurred in two participants in the SMBG group and none in the isCGM group during the first 3 months. Hospital

admission for hyperglycemia occurred in one participant in the SMBG arm (day 268) and one participant in the isCGM arm (day 60). Hospital admission with hypoglycemia occurred in three participants in the SMBG arm (days 47–238) and in a single participant in the isCGM arm (day 235), when isCGM was no longer used.

In the first 3 months, MACEs were reported in one SMBG participant and six isCGM participants. A further 10 SMBG and 12 isCGM participants in each arm subsequently reported MACEs after 3 months.

Throughout the study, five participants died, three in the SMBG arm and two in the isCGM arm, with none of the deaths occurring in the first 3 months (all occurred at days 113–242). Coronary events occurred in seven SMBG and 10 isCGM participants (coronary artery bypass grafting/coronary artery intervention were required in three and one participants, respectively), cerebrovascular events
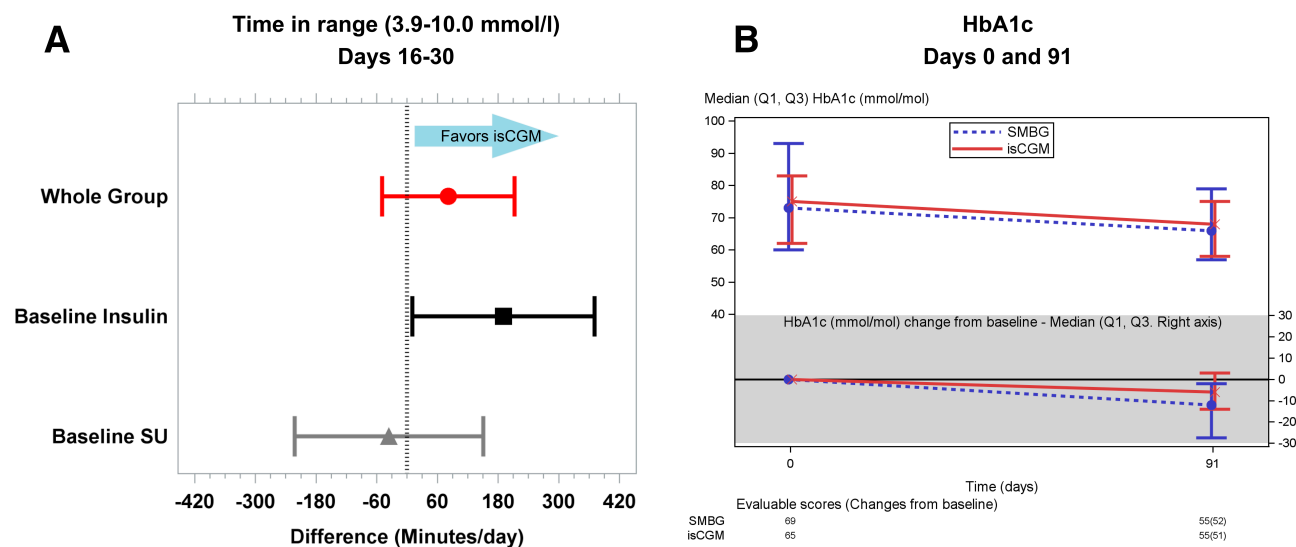
A
Time in range (3.9-10.0 mmol/l)
Days 16-30

B
HbA1c
Days 0 and 91

Figure 3—TIR (3.9–10.0 mmol/L) and HbA$_{1c}$. *A*: TIR with isCGM was compared with SMBG at 16–30 days after randomization (frequentist analysis) and presented for the whole group as well as for insulin and sulphonylurea (SU) users at baseline. *B*: HbA$_{1c}$ at baseline (randomization) and study end (day 91) in isCGM and SMBG users. Data are presented as median and interquartile range. Q, quartile.

occurred in one SMBG and three isCGM participants, and heart failure requiring hospital admission was documented in three isCGM participants.

Hypoglycemic Therapies
Changes in glucose-lowering therapies are summarized in Supplementary Table 3. Use of sulphonylureas decreased, particularly in the isCGM study arm, whereas use of cardioprotective agents increased in both study arms.

Sensor-Related Adverse Events
In the SMBG arm, seven sensor-related adverse events occurred in four patients, and none was severe (Supplementary Table 4). In the isCGM arm, 17 sensor-related adverse events occurred in 14 patients, and none was severe. Complaints included mild/moderate erythema, itching, bruising, and pain, but none was severe enough to warrant discontinuation of the sensor.

Cost-Effectiveness Analysis
By combining the UKPDS and hypoglycemia models, estimated costs for isCGM were £10,993 and QALYs were 8.497, whereas estimated SMBG costs were £11,258 and QALYs were 8.494. This indicates that isCGM is a cost-effective strategy, because it dominates SMBG, given the former is less costly and more effective. Further analysis using cost-effectiveness acceptability curves demonstrated that isCGM has 100% probability of being cost effective at a threshold of

£20,000/QALY, with an incremental NMB of £318.

CONCLUSIONS
This is the first multicenter randomized controlled trial to investigate an alternative glucose-testing strategy in individuals with T2D after acute MI. The planned analysis was novel because glucose traces were analyzed as individual patient-level daily readings, allowing for more detailed and robust analysis. The work shows that isCGM use was associated with a marginal increase in TIR compared with SMBG, mainly related to significantly lower hypoglycemic exposure. Both isCGM and SMBG were associated with a meaningful reduction in HbA$_{1c}$, but isCGM achieved this with less hypoglycemia both early and late after MI, explaining its cost effectiveness.

Despite the high stress level after ACS, our trial shows that patients with T2D and recent MI are ready to embrace new glycemic monitoring strategies, with a relatively high retention rate of 83%, which is close to previously published results in T2D without an acute medical illness (23). Moreover, there was a high level of engagement supported by good and consistent glucose scanning frequency, which was only marginally lower than that in the T2D group without a recent acute vascular event (23).

Using a stringent 80% coverage of glucose data per day, the primary outcome measure, TIR during days 76–90, showed an average 17-min difference between

the isCGM group and SMBG group. When criteria were relaxed to include glucose coverage of 65% per day, the difference between study arms increased to 28 min in favor of isCGM. Neither of these two planned analyses reached the predefined posterior probability cutoff of 80%, suggesting a marginal effect for the intervention on TIR. However, a prespecified secondary outcome, TIR at the earlier time point of 16–30 days, suggested an advantage of the intervention over standard SMBG, mainly seen in those receiving insulin therapy at baseline. Therefore, isCGM seems to offer the possibility of rapid improvement in glycemia after ACS, which may have two important clinical implications. First, evidence shows an association between elevated glucose level immediately after ACS and adverse clinical outcome (28–30). Therefore, early improvement in glycemia, particularly if hypoglycemia is avoided, has the potential advantage of improving outcomes in this high-risk population. Second, patients with ACS and diabetes who require surgical intervention for their coronary disease may benefit from isCGM to quickly optimize glycemia before surgery, with the potential to improve postsurgical outcomes (31).

Studies have linked hypoglycemia to adverse clinical outcomes (10–12,32–34), explaining the recent emphasis on avoidance of low-glucose levels, particularly in patients with diabetes at high vascular risk (6). We found a difference of >1 h/day in hypoglycemic exposure (defined as glucose

<3.9 mmol/L) comparing trial arms at days 76–90, which is highly likely to be clinically important (11)), particularly given guidance suggesting minimizing hypoglycemia in such populations to less than 15 min/day (35). This was also evident at days 16–30, and therefore, the beneficial effect of isCGM on hypoglycemia is both an early and sustained finding and applies to those receiving a sulphonylurea or insulin at enrollment.

Both groups showed a clinically meaningful absolute drop in HbA_{1c} of 7 mmol/mol comparing baseline with 3 months. Previous studies in insulin-treated patients with T2D and no recent history of vascular ischemia showed either a minor reduction in HbA_{1c} of 3 mmol/mol with isCGM over 6 months (An Evaluation of a Novel Glucose Sensing Technology in Type 2 Diabetes [REPLACE] trial) (23) or a more impressive reduction of 9 mmol/mol with isCGM over 2 months (36). However, our population included acutely unwell individuals receiving insulin and noninsulin therapies, which makes comparisons with the other two studies problematic.

Taken together, our trial data indicate that both isCGM and SMBG are effective at reducing HbA_{1c} in individuals with T2D and recent MI. Importantly, however, isCGM seems to reduce HbA_{1c} safely by minimizing hypoglycemic exposure, unlike SMBG. It should be noted that hypoglycemia creates a prothrombotic milieu, which can last up to 1 week after the hypoglycemic event (15), and is best avoided in an ACS population, particularly because hypoglycemic exposure is associated with high cardiovascular mortality (32).

Mortality in our trial population was low, and severe hypoglycemia and MACEs occurred in a minority. A much larger study will be required to draw conclusions on the effects of isCGM on MACEs. Reassuringly, the glucose sensor was well tolerated, with only mild to moderate local reactions, with none resulting in discontinuation. Also, the sensor had a positive effect on some QOL measures, although these did not always reach statistical significance, and therefore, the effects seem to be modest.

The economic evaluation combined two different models to account for both the hyperglycemic and hypoglycemic effects of glucose-monitoring strategies, and this showed isCGM to be cost effective if used

for 3 months after MI and intermittently thereafter (one sensor every 4 months).

The study has several strengths to be highlighted. This is the first randomized controlled trial investigating the use of isCGM in individuals with T2D and recent MI. Moreover, the trial included individuals receiving oral hypoglycemic agents and/or insulin therapies, broadening the clinical applicability of the work. Methodologically, the choice of randomization and analysis methods allowed unbiased estimates of the treatment effect (20). The analysis was planned to use longitudinal, individual daily glucose readings, avoiding simplification and averaging while also providing ICC, important for the design of future cluster trials. Moreover, data were analyzed using a combination of Bayesian and frequentist statistical methods, which has not been adopted previously in trials of glucose monitoring. There are, however, limitations to be acknowledged. The subgroup analysis of individuals receiving a sulphonylurea or insulin should be interpreted with caution and can only be regarded as preliminary. Furthermore, the duration of glycemic monitoring part of the trial was short at 3 months, and it is unclear hether a longer period would have had a greater effect, particularly because 6 months of isCGM may be required to show a difference in HbA_{1c} in non–insulin-treated individuals with T2D (37). Also, the majority of the population studied were Caucasian, and therefore, it is unclear whether the intervention has the same effect in other ethnic groups. Also, it remains unclear whether individuals with T2D and MI who are not receiving insulin and/or a sulphonyurea benefit from isCGM. Finally, as a glycemic, multicenter, randomized controlled trial, the work lacks power to investigate the effects of isCGM on vascular outcomes.

In summary, patients with T2D with recent ACS are receptive to the use of novel technology and alternative glucose-testing strategies. Our trial shows that isCGM is safe in this population, optimizes glycemia faster than SMBG, and results in clinically meaningful reduction in HbA_{1c} while limiting hypoglycemic exposure, in contrast to SMBG (Supplementary Table 5 summarizes main study findings). Large-scale longitudinal studies are warranted to investigate the effects of isCGM on long-term cardiac outcome

in individuals with diabetes and recent MI.

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