Received: 25 June 2021 | Revised: 9 September 2021 | Accepted: 24 September 2021

DOI: 10.1111/dom.14560

RESEARCH LETTER

WILEY

Underestimation of hypoglycaemia using patients' diaries compared with downloaded glucometer data: an ITAS post hoc analysis

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Funding information
Sanofi; Trial registration: EudraCT Number: 2015-001167-39

KEYWORDS: diary, glargine 300 U/mL, glucometer, hypoglycaemia, insulin, type 2 diabetes

INTRODUCTION

Minimizing hypoglycaemia when initiating basal insulin treatment in type 2 diabetes (T2D) is as important as assessing its efficacy in lowering HbA1c. Hypoglycaemic events are often under-reported by people treated with insulin, as indicated by studies comparing the occurrence of hypoglycaemia based on continuous glucose monitoring (CGM) with that based on less comprehensive self-monitored plasma glucose (SMPG).[1-3]

CGM is not yet routinely used for diabetes management because it is expensive and is not reimbursed in most countries.[4] In clinical practice, basal insulin titration is based on daily SMPG with analysis of data downloaded from glucometers. However, people with T2D still commonly present SMPG data that they have entered into their diaries themselves, rather than glucose values directly downloaded from a glucometer. In these circumstances, any retrospective analysis of plasma glucose values is based on data that may contain omissions and mistakes, which may lead to a misestimation of hypoglycaemic events. However, there are currently no reports comparing the incidence or rates of hypoglycaemia based on data downloaded from glucometers with that entered by patients into their diaries.

In the Italian Titration Approach Study (ITAS), insulin-naïve people with T2D were initiated to basal insulin treatment with glargine

300 U/mL (Gla-300).[5] Insulin was titrated either by the participants themselves, or by physicians using diary data, and resulted in similarly improved glycaemic control and low incidence and rate of hypoglycaemia.[5] In ITAS, hypoglycaemia was quantified based on self-reported data from patients' diaries in view of the pragmatic approach of the study.

In the current post hoc analysis, to assess whether patients' diaries under-report hypoglycaemia, hypoglycaemia incidence and rates in ITAS were compared using data downloaded from glucometers versus entries from participants' diaries.

METHODS

The study design and results of the primary analysis for ITAS have been published.[5,6] Briefly, ITAS was a multicentre, 24-week, pragmatic, phase 4, open-label, randomized (1:1) study (EudraCT Number: 2015-001167-39) conducted in Italy. ITAS included insulin-naïve adults with T2D aged 18 years or older with poor glycaemic control (HbA1c ≥7.5% to ≤10%) despite oral antihyperglycaemic drugs, with or without glucagon-like peptide-1 receptor agonists. Sulphonylureas or glinides were discontinued at inclusion. Participants were randomized 1:1 to initiation of once-daily Gla-300, titrated by either the participants themselves or their physicians.[5,6] All ITAS participants provided written, informed consent and the trial protocol was approved by the relevant local ethical committees.[5]

Following randomization, participants were instructed to measure prebreakfast SMPG daily until stable and until insulin titration was complete. Thereafter, fasting prebreakfast SMPG was mandatory on at least three consecutive days a week and seven-point SMPG (before and 2 hours after breakfast, lunch and dinner, and once at bedtime) was mandatory on at least one of the 3 days before each visit. SMPG was also measured when experiencing possible hypoglycaemia.[6] Participants were asked to record all plasma glucose (PG) data obtained with glucometers in the diaries, which were then used for the primary analysis. All hypoglycaemia episodes were recorded in the participant's diary or documented in the electronic case report form (eCRF).[5] Data from paper diaries were entered into the study database through OPIS double data entry, and glucometer data were downloaded locally to the MyStar Connect diabetologist database by the physician before being transferred to the study database.

In this post hoc analysis, the incidence of hypoglycaemia over 24 weeks and the annual rate of hypoglycaemia were analysed using PG data directly downloaded from glucometers versus data reported by the same participants in their diaries and/or by the investigator in the eCRF.

Hypoglycaemia was defined as events that were confirmed by an SMPG measurement (either ≤70 mg/dL [≤3.9 mmol/L] or <54 mg/dL [<3.0 mmol/L]) and/or that were classed as severe (requiring the assistance of another person to actively administer carbohydrate or glucagon, or to perform another resuscitative action), occurring either during the night (12:00 AM–05:59 AM), between 12:00 AM and prebreakfast (expanded nocturnal window), or at any time of day (24 hours).

Statistical analysis

The incidence and annual rate of hypoglycaemia were descriptively summarized overall and by patient- and physician-managed subgroups. Furthermore, the incidence and annual rate of hypoglycaemic episodes were compared between the different data sources (glucometer vs. diary) for all participants with available glucometer data using odds ratios and rate ratios, respectively, with two-sided 95% asymptotic Wald confidence intervals (CIs) using generalized linear models with a binomial distribution with a logit link function for the incidence endpoints, and with a negative binomial distribution with a logarithmic link of the time for comparison of the annual rates.

Demographics (i.e. sex), as well as baseline and change from baseline values of HbA1c and fasting plasma glucose (FPG), were descriptively summarized in the two groups (i.e. participants with and without glucometer data) and in the patient- and physician-managed subgroups. Results in those with and without glucometer data were compared using non-parametric tests (Chi-square for proportion and Wilcoxon test for continuous variables).

Because this was an exploratory analysis, nominal statistical significance at *P* less than .05 was reported, with no correction for multiple comparisons.

RESULTS

Baseline characteristics

Hypoglycaemia information from glucometers was unavailable for some participants owing to technical issues; this post hoc analysis was performed on a subgroup of 252 (71%) of the total 355 participants included in the intent to treat population for the ITAS study. Baseline characteristics of these participants (Table 1) were not different from those of the 103 participants without glucometer data, and were similar to those of the whole ITAS population (Table S1).

Incidence of confirmed and/or severe hypoglycaemia by data source

The proportion with confirmed (SMPG ≤70 mg/dL [≤3.9 mmol/L] or <54 mg/dL [<3.0 mmol/L]) and/or severe nocturnal (12:00 AM–05:59 AM), 12:00 AM-prebreakfast, or anytime (24 hours) hypoglycaemic events, were consistently higher when glucometer data were used versus data from the eCRF/diary, with odds ratios ranging from 2.0 to 3.5 (Figure 1A). These differences achieved nominal statistical significance for all confirmed and/or severe hypoglycaemia outcomes, except nocturnal (12:00 AM–05:59 AM) at the lower SMPG cut-off (<54 mg/dL [<3.0 mmol/L]), which showed the lowest number of events records.

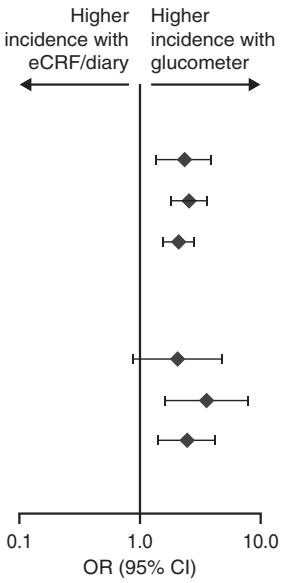
TABLE 1 Baseline patient demographic and clinical characteristics

	Patients with glucometer data		
	Total (n = 252)	Patient-managed (n = 126)	Physician-managed (n = 126)
Age (y), mean ± SD	64.1 ± 9.2	64.1 ± 9.3	64.0 ± 9.2
Male, n (%)	161 (63.9)	80 (63.5)	81 (64.3)
HbA1c (%), mean ± SD	8.80 ± 0.65	8.78 ± 0.67	8.82 ± 0.63
FPG (mg/dL), mean ± SD	173.5 ± 43.0	170.2 ± 39.6	176.9 ± 46.1

Abbreviations: FPG, fasting plasma glucose; ITAS, Italian Titration Approach Study; SD, standard deviation.

(A)

	Number of patients (%)		
	Glucometer data	eCRF/diary data	Odds ratio - glucometer versus eCRF/diary (95% CI)
Confirmed (≤70 mg/dL [≤3.9 mmol/L]) and/or severe hypoglycaemia			
Nocturnal (12:00 AM-05:59 AM)	28 (11.11)	13 (5.16)	2.30 (1.36, 3.89)
Nocturnal (12:00 AM-prebreakfast)	73 (28.97)	35 (13.89)	2.53 (1.78, 3.59)
Anytime (24 hours)	92 (36.51)	55 (21.83)	2.06 (1.52, 2.80)
Confirmed (<54 mg/dL [<3.0 mmol/L]) and/or severe hypoglycaemia			
Nocturnal (12:00 AM-05:59 AM)	10 (3.97)	5 (1.98)	2.04 (0.87, 4.79)
Nocturnal (12:00 AM-prebreakfast)	23 (9.13)	7 (2.78)	3.52 (1.60, 7.73)
Anytime (24 hours)	27 (10.71)	12 (4.76)	2.40 (1.38, 4.18)



(B)

	Number of events (annual rate)		
	Glucometer data	eCRF/diary data	Rate ratio - glucometer versus eCRF/diary (95% CI)
Confirmed (≤70 mg/dL [≤3.9 mmol/L]) and/or severe hypoglycaemia			
Nocturnal (12:00 AM-05:59 AM)	68 (0.536)	18 (0.142)	3.74 (2.52, 5.56)
Nocturnal (12:00 AM-prebreakfast)	272 (2.146)	106 (0.836)	2.55 (1.75, 3.72)
Anytime (24 hours)	377 (2.974)	164 (1.294)	2.29 (1.60, 3.27)
Confirmed (<54 mg/dL [<3.0 mmol/L]) and/or severe hypoglycaemia			
Nocturnal (12:00 AM-05:59 AM)	11 (0.087)	5 (0.039)	2.20 (1.40, 3.46)
Nocturnal (12:00 AM-prebreakfast)	40 (0.316)	7 (0.055)	5.71 (3.69, 8.83)
Anytime (24 hours)	49 (0.387)	18 (0.142)	2.72 (1.85, 4.00)

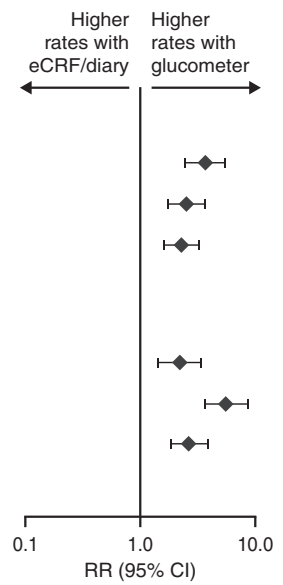


FIGURE 1 A, Incidence, and B, Annual rates of confirmed and/or severe hypoglycaemic events derived from glucometer versus eCRF/diary data. CI, confidence interval; eCRF, electronic case report form; OR, odds ratio; RR, rate ratio

Annual rate of confirmed and/or severe hypoglycaemia by data source

The annual rates of confirmed and/or severe hypoglycaemia, of any category and defined by either the SMPG equal to 70 mg/dL or less (≤3.9 mmol/L) or less than 54 mg/dL (<3.0 mmol/L) cut-offs, were nominally significantly higher when derived from glucometer data than when derived from eCRF/diary data, with rate ratios of 2.2–5.7 (Figure 1B).

Incidence and annual rate of confirmed and/or severe hypoglycaemia in patient- and physician-managed insulin titration groups, by data source

In the individual patient- and physician-managed groups, each comprising 126 participants, the incidence and rates of all definitions of hypoglycaemia assessed were similarly higher when derived from glucometer data than when derived from eCRF/diary data (Figures S1 and S2), as evidenced by overlapping 95% CIs around the point estimates.

Glycaemic control

Reductions in HbA1c and FPG from baseline to week 24 were similar in participants with and without glucometer data, in the overall ITAS population and in the patient- and physician-managed subgroups (Table S2).

DISCUSSION

The results of this post hoc analysis of the ITAS study[5] suggest that assessment of self-reported hypoglycaemia from patients' diaries underestimates the occurrence of hypoglycaemia (incidence by 2.0-3.5–fold and rate by 2.2-5.7–fold) in people with T2D who titrate basal insulin. Although hypoglycaemia was infrequent in ITAS,[5] patients' diaries still omit about 50% or more of the hypoglycaemia events, irrespective of the titration group (i.e. patient- or physician-managed). Therefore, the current analysis indicates the importance of evaluating hypoglycaemic events from glucometer data and not from patient diaries, regardless of whether titration is being managed by the patient or physician. Previous studies have emphasized the underestimation of hypoglycaemia calculated from SMPG in insulin-treated T2D, unmasked by CGM,[1-3] but surprisingly there are no observations comparing hypoglycaemia using SMPG data downloaded from glucometers with data entered by patients in diaries. The current post hoc analysis of ITAS fills this gap.

There is a range of evidence regarding suboptimal reporting of data in patient diaries. In a systematic review comparing glucometer and patient diary entries in 11 trials in type 1 diabetes, T2D, and gestational diabetes, the failure to record glucometer data (under-reporting) in diaries was the most common error and just over 50% of diaries were considered accurate/reliable.[7] Additional reporting faults identified included reporting a value that had not been measured (over-reporting) and incorrect recordings (poor concordance).[7] Another small study reported that up to two-thirds of people with diabetes will misreport hypoglycaemic or hyperglycaemic values to obscure periods of poor glucose control.[8] Hence, the common finding of the current study and previous reports is that patient diaries probably give incomplete information upon which to base therapeutic decisions. However, none of those previous studies actually quantified the impact of misreporting with patient diaries versus glucometer data on the accuracy of self-reported hypoglycaemia measurement, as performed in the present analysis.

In the present analysis, the incidence and/or rates of hypoglycaemia when evaluated by direct downloading of glucometer data were similar to those seen in the TAKE CONTROL randomized controlled trial (RCT), which investigated self- versus physician-managed titration of Gla-300 in a European population of insulin-naïve people with T2D,[9] and were slightly lower than those observed in the EDITION 3 RCT, which investigated the efficacy and safety of Gla-300 versus insulin glargine 100 U/mL in a global insulin-naïve T2D population.[10] ITAS was a pragmatic trial that tried to mimic real-life conditions, where hypoglycaemic events are typically reported through the use of patient diaries or electronic medical records, and not by independent glucose monitoring tools or detailed data review. Consequently, incomplete revision of glucometer data could have played a role in the underestimation of hypoglycaemia, as the physician may have focused on symptomatic rather than asymptomatic hypoglycaemia. While this represents a real-life situation for many individuals, it appears that these tools are unsuitable for the accurate detection of hypoglycaemic events in clinical practice. The present observation underscores the importance of directly downloading hypoglycaemia data from glucometers and/or its in-depth analysis to accurately estimate the incidence or rate of hypoglycaemia, both in experimental and real-life conditions.

The limitations of this study include that it was a post hoc, exploratory analysis and that it was performed in a subgroup of ITAS (71%) participants with glucometer data, although the demographic and clinical characteristics did not differ between those with and without glucometer data. Furthermore, it is not possible to determine whether knowledge that the glucometers store data may have impacted participants' willingness to record the same data in their diaries.

Based on data from this post hoc analysis of ITAS, in both experimental and clinical practice settings it is recommended to directly download and review glucometer data to accurately establish the incidence or rate of hypoglycaemia in patients on basal (and prandial) insulin, rather than relying on information from patient diaries.

ACKNOWLEDGEMENTS

The authors thank the study participants, trial staff, and investigators for their participation. The statistical analysis was performed by Veronica Pagano and Ilaria Pacchetti (OPIS s.r.l.). Editorial assistance with the preparation of this article was provided by Margarita Lens, PhD, of Fishawack Communications Ltd, part of Fishawack Health,

and support for this assistance was funded by Sanofi. This work was supported by Sanofi, Milan, Italy.

CONFLICT OF INTEREST

RB has received honoraria or consulting fees from Sanofi, Eli Lilly, AstraZeneca, Abbott, and Novo Nordisk. RCB has received honoraria or consulting fees from Sanofi, Merck Sharp & Dohme, Eli Lilly, Johnson & Johnson, Bristol-Myers Squibb, AstraZeneca, and Janssen. AG has received honoraria or consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, and Sanofi, and research funding from AstraZeneca. GP has received honoraria or consulting fees from Novo Nordisk, Sanofi, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Takeda, Abbott, Janssen, and Merck Sharp & Dohme. DC has received honoraria or consulting fees from Eli Lilly, Novo Nordisk, Roche Diagnostics, and Sanofi. CF has received honoraria or consulting fees from Sanofi and non-financial support from Menarini. AA has received honoraria or consulting fees from Novo Nordisk, Sanofi, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Takeda, and Servier, and research funding from AstraZeneca and Vifor Pharma. GA has received honoraria or consulting fees from Sanofi, AstraZeneca, IBSA Institut Biochimique, and Novartis, and research funding from Sanofi, AstraZeneca, and Novo Nordisk. ML is an employee of Sanofi and holds stocks/shares in Sanofi. IP is an employee of CRO (OPIS s.r.l.) contracted by Sanofi. GBB has received honoraria or consulting fees from Sanofi and Menarini, and research funding and speakers' bureau fees from Sanofi.

AUTHOR CONTRIBUTIONS

All authors contributed to the interpretation of data, drafting, and critical review of the manuscript, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14560.

DATA AVAILABILITY STATEMENT

Proposals relating to the data access should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Buzzetti R, Bonadonna RC, Giaccari A, et al. Underestimation of hypoglycaemia using patients' diaries compared with downloaded glucometer data: an ITAS post hoc analysis. *Diabetes Obes Metab*. 2021;1-5. doi: 10.1111/dom.14560