STRATUS study protocol

UNIVERSITY OF LEEDS

Long title: FreeSTyle LibRe and hospitAl admissions, morTality and qUality of life in high risk type 2 diabeteS patients

Short title: The STRATUS study

Study Protocol: V1.7

Investigators: R.A Ajjan, S.M Pearson, J Bailey and B Whittam

IRAS number: 273948

Funders reference number:

Signatory page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor
I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

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Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

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Study summary

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Sponsor	University of Leeds
Funder(s)	Abbott diabetes care
Key Protocol Contributors	Ramzi Ajjan Sam Pearson Julie Bailey

Study Title	FreeSTyle LibRe and hospitAl admissions, morTality and qUality of life in high risk type 2 diabeteS patients
Internal ref. no. (or short title)	STRATUS study
Study Design	Randomized controlled trial
Study Participants	Patients with type 2 diabetes whom have been recently treated by ambulance staff for hypoglycaemia
Planned Size of Sample (if applicable)	300
Follow up duration (if applicable)	6 months active involvement followed by a further 18 months of remote review of participants electronic medical records
Planned Study Period	April 2021 – April 2024

Role of study sponsor

The study sponsor, the University of Leeds, is responsible for the oversight of this work and ensuring the trial is run safely, in a timely manner and in full accordance with good clinical practice guidelines.

Role of study funder

The study funder, Abbott diabetes care, provided monitary support for this study but had no involvement in study design, study set up or the setting of the aims/objectives of the study. They will not be involved in data analysis or dissemination of results.

Introduction and preliminary data

The prevalence of diabetes continues to increase and is reaching epidemic proportions (http://www.who.int). Optimizing glycemic control is key to prevent microvascular complications and long-term macrovascular disease [1-4]. HbA1c is currently used as the gold standard for monitoring response to treatment but this glycemic marker fails to address hypoglycemia and glycemic variability, both of which have a role in determining clinical outcome [5]. Moreover, HbA1c shows a U-shaped correlation with mortality, indicating that lower glucose levels are not always better [6]. Indeed, a number of studies have shown that hypoglycemia is associated with increased cardiovascular mortality and we have demonstrated that severe hypoglycemia in the community is linked to increased mortality, particularly within the first 3 months of the event [7-10]. Moreover, hypoglycemia has a major economic impact on health resources, adding to the spiraling cost of managing diabetes [11]. Cardiac arrhythmias have been implicated as an important mechanism for the association between hypoglycemia and mortality [12]. However, there are some longer term effects of hypoglycemia as episodes of low blood glucose increase the inflammatory response and enhance the thrombotic environment contributing to the vascular pathology in diabetes, as we have shown [13].

Interestingly, our recent single center pilot study of 322 patients sustaining a severe hypoglycemic episode requiring ambulance services call out has shown that a 3 month structured nurse intervention in 150 type 2 diabetes patients (that includes regular glucose testing) reduces mortality over a follow up period of approximately 3 years. Mortality of type 2 diabetes patients in the standard arm of the study (managed as per local guidelines) was 45%, whereas in the interventional arm this fell to 28%. A third arm of the study (termed the observational arm) agreed to have their electronic data analyzed but did not wish to be randomized and the mortality in this group was 50% (figure 1).

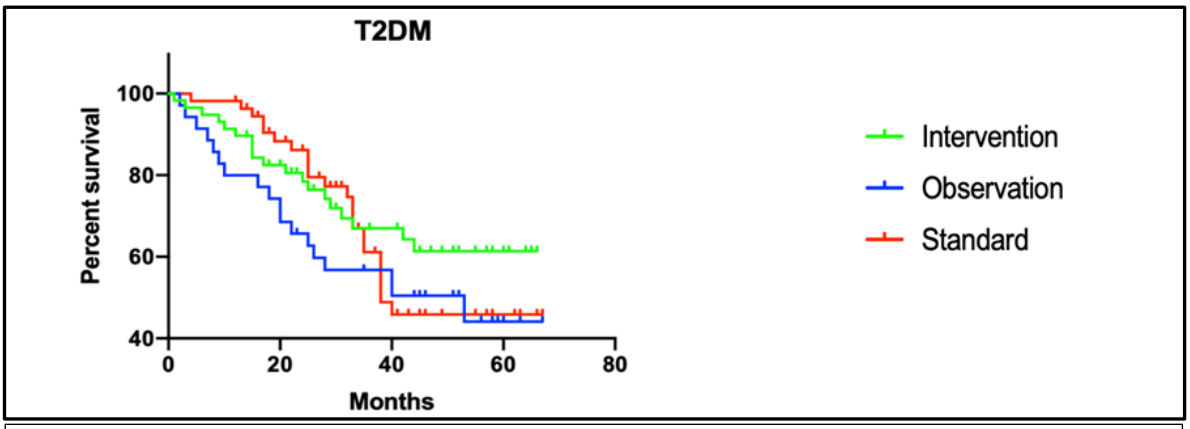

Figure 1: A kaplan Meier curve to show survival across the three study groups of the original study.

A key component of nurse intervention was encouragement to test glucose regularly followed by adjustment of hypoglycemic therapies as appropriate. Given that regular glucose testing can be difficult in older people, having a simple device to check glucose may prove to be crucial to improve the adverse clinical outcome in this population. These data indicate that the high mortality rate in patients with type 2 diabetes sustaining a severe hypoglycemic episode is potentially modifiable when appropriate glucose testing is undertaken and acted upon. Patients with type 1 diabetes (n=149) did not show a reduction in mortality in the intensive compared with the standard arm of the study (mortality was 10 and 9%, respectively; p>0.1), although the number of events was relatively small and the study lacked power to identify a difference in this group.

In addition to hyperglycemia and hypoglycemia, glycemic variability (GV) has been linked to an increased rate of both micro and macrovascular complications as well as higher mortality [14;15]. An increase in oxidative stress as a mechanism for enhanced vascular pathology has been proposed and this has shown an association with GV, in turn explaining the relationship between this glucose measure and adverse clinical outcome [16].

Patients with diabetes require self monitoring of blood glucose (SMBG) for safe and effective adjustment of glycemic therapy, particularly in insulin treated patients [17;18]. Previous work has shown that higher rate of glucose testing is associated with improved glycemic control [18;19]. However, repeated daily glucose checks are painful, inconvenient and can be difficult to maintain long-term. A UK-based analysis reported 2.1 glucose tests/day in insulin-treated patients [20], emphasizing the low rates of testing and providing one explanation for poor glycemic control in this population. Traditional continuous glucose monitoring (CGM) devices, and more recently the flash glucose monitor (Freestyle Libre), have made glucose checks easier with the ability to obtain a large number of glucose readings/day that is simply not possible with SMBG. A key advantage of the Freestyle Libre device is factory calibration, making it more convenient and eliminating potential inaccuracy encountered with CGM devices when calibration is not undertaken properly or frequently enough.

A recent study on freestyle Libre use in real-life settings has shown frequent glucose testing [21]. The number of glucose tests demonstrated an inverse correlation with time spent in hyperglycemia and hypoglycemia, emphasizing the importance of regular glucose checks for improving glycemic control. While these data are valuable, one of the main weaknesses is the inability to address hard end points, such as hospital admissions and quality of life measures, which would help to understand the full effects of this device on

patient management in real world settings; this would be particularly important in individuals at higher risk of dysglycemia. Therefore, more detailed patient data are required to understand the role of Freestyle Libre in altering quality of life and reducing emergency healthcare contacts in UK patients with type 2 diabetes.

Aims/objectives

Aim 1. Study the effects of Freestyle Libre on health care contact, hospital admissions and mortality in individuals with type 2 diabetes who have suffered an episode of severe hypoglycaemia

Using UK Hospital Episode Statistics (HES) data and GP records, we will establish the number of contacts with health care professionals over a period of 12 months before following starting Freestyle Libre. A comparator group receiving standard care will also have their health records analyzed. Moreover, the reason for the admission will be clarified and grouped into 4 categories: hyperglycemia (including ketoacidosis and hyperosmolar state), hypoglycemia, cardiovascular event and other. Mortality data will be collected in all patients with the effects of Freestyle Libre on survival analysed during a minimum anticipated median follow up period of 24 months. Cause of death will be analysed and grouped in the following manner: Cardiovascular cause, infection, renal disease, malignancy, glycaemic emergency, dementia/old age, other. This will allow for comparisons not only in mortality rates between groups but also differences in cause of death. In addition, data will be supplied by the Yorkshire ambulance service regarding number of contacts with emergency services in the year prior to the index event and the two years following this. This will be done by the study team contacting the ambulance service to update them as to whom consented to take part in the study and providing information regarding this using secure NHS email addresses.

In addition to hospital admission and mortality data, detailed glycaemic results will also be collected including glycated hemoglobin (HbA1c) at baseline and 6 months after start of Freestyle Libre use. Time spent in hypoglycemia in the first 3 days and full 14 days of sensor 1 use will be compared with sensor 6 and 12 (3 and 6 months). Data from Freestyle Libre will be acquired using the manufacturers (Abbott) secure software where possible to avoid in person clinical contact. If this is not possible then in-person review will take place. Similar analysis will be conducted on glucose variability, assessed as coefficient of variation (CoV) and standard deviation (SD), in the first 3 days and full 14 days of sensor 1, 6 and 12 use.

Aim 2. Analyze the effects of Freestyle Libre on quality of Life measures in type 2 diabetes patients

Asking the individual to undertake regular SMBG can be distressing and using flash glucose monitoring may help to decrease stress levels and improve quality of life. Indeed two RCTs in type 1 and type 2 diabetes

patients have shown that Freestyle Libre has a positive effect on QoL measures[22] but it is unclear whether the same applies in real life setting and in higher risk individuals. In the current proposal we will evaluate patient satisfaction with flash glucose monitoring by asking patients to complete a set of validated questionnaires including Diabetes Distress Scale (DSS), Diabetes Quality of Life (DoQL) questionnaire and Diabetes Treatment Satisfaction Questionnaire (DTSQ) [22-25]. Again, QOL measures will be compared between those using Freestyle libre and receiving intensive nurse led intervention and those receiving standard care. Comparison will be made between baseline and 6 months in the Libre study arm and we will also analyse difference between two study arms at 6 months in study cohort (adjusted for baseline).

Aim 3. Explore the role of Freestyle Libre as a substitute for laboratory HbA1c measurements

First, we will assess the value of estimated HbA1c (eHbA1c), provided by the device, at predicting laboratory HbA1c. We will use the mean value of eHbA1c over 3 months (6 sensors) and compare with laboratory hbA1c at 6 months. This will help to understand the clinical value of eHbA1c in the management of patients with diabetes. We will then move to understand the value of calculated HbA1c (cHbA1c), a new glycemic marker, in reflecting laboratory HbA1c. We have recently shown that cHbA1c accurately reflects laboratory HbA1c (manuscript in press). This glycaemic marker has the advantage of taking into account red blood cell glycation, generation and elimination thus making it person-specific. In the proposed work, we will have multiple laboratory HbA1c measurements and continuous glucose data that will further help to assess the accuracy of cHbA1c in predicting laboratory HbA1c. The value of cHbA1c will be calculated and subsequently used to assess correlation with laboratory HbA1c. This part of the work will be done in collaboration with personnel at Abbott who have the necessary experience in assessing cHbA1c and subsequently undertake the relevant analyses. Data provided will have important health economic and clinical implications in case cHbA1c shows enough accuracy to replace laboratory HbA1c.

Hypothesis

We propose to test 3 hypotheses:

1. Following a severe hypoglycemic episode, Freestyle Libre along with regular diabetes nurse contact reduces hospital admissions, health care contact and death (including from a cardiovascular cause) in type 2 diabetes patients.
2. Freestyle Libre improves quality of life type 2 diabetes patients at high risk of hypoglycemia.
3. Calculated HbA1c (cHbA1c), a glycemic marker derived from Freestyle Libre glucose data, closely reflects laboratory HbA1c, making glucose assessment more convenient to patients and offering healthcare savings.

Study design

Participant identification and recruitment

- The Yorkshire ambulance service (YAS) is a large emergency healthcare provided covering the areas in which the study will be conducted (Leeds, Bradford, Wakefield).
- When an ambulance crew attends to a patient whom is suffering from hypoglycaemia they provide appropriate treatment and when necessary transport the patient to hospital. An existing pathway is in place whereby the information surrounding the events is communicated to the ambulance administrative team.
- The YAS research team will contact patients recently treated for hypoglycaemia and ask if they would be willing to be contacted by the local diabetes research team for a study researching hypoglycaemia. If the treated patient responds yes, their details will be forwarded to the appropriate diabetes research nurse covering the local area.
- The diabetes research nurse will contact the patient within 7 days of the ambulance call out and, after introductions and explaining reasons for call, will outline the nature of the study and what it entails. If the patient is happy to receive further information a patient information sheet will be sent to them with more information.
- A follow up phone call will be made and if the patient is willing to participate in the study they will be offered to attend the relevant diabetes centre or be visited at their home.
- At this point, prospective participants will be given adequate time to ask questions about the study and any concerns they may have about taking part will be addressed. If they wish to continue in the enrolment process, written informed consent will be taken by the diabetes research nurse.

Inclusion and exclusion criteria

- Inclusion criteria: A known diagnosis of type 2 diabetes, sustained an episode of severe hypoglycaemia requiring ambulance call out, >18 years of age, able to give informed written consent.
- Exclusion criteria: A form of diabetes which is not type 2 or diagnosis is not clear, currently pregnant, receiving renal replacement therapy, unable to provide informed written consent.

Randomisation

- Following the taking of written informed consent participants will be randomised to one of two groups using a computerised telephone randomisation programme. Participants will be randomised into: i) A group who's care will be returned to their usual diabetes care provider but will be asked to wear a blinded glucose sensor for a period of two weeks at month 6 ii) A group receiving increased input from a diabetes research nurse with the addition of using Freestyle Libre 2 for a period of 6 months.

Methods

Day -14 to day 0.

- YAS research team contact patient recently treated for hypoglycaemia and ascertain if they are happy for their information to be passed to the hospital research nurses. If yes, information passed securely.
- Diabetes research nurse contacts prospective participant and explains trial. Screening questions asked to check eligibility for trial. If eligible and prospective participant is happy, trial information sent to patient.
- Patient contacted via telephone and if happy to proceed appointment made for baseline visit and consent to be obtained.

Day 0 (baseline)

- Written informed consent taken.
- Data capture form completed to document detailed past medical history, current medications and doses, diabetes complications and basic demographic data (age, height, weight, smoking status).
- Participant examined for lipohypertrophy.
- Donation of blood sample for HbA1c, U and E's, LFT's and lipid profile. Donation of urine sample for urine albumin:creatinine ratio (UACR).
- Both groups are asked to fill in questionnaires assessing diabetes distress (DQOL and DSS) and diabetes treatment satisfaction (DTSQ) as well as hypoglycaemic awareness (GOLD score).
- Those randomised to the freestyle libre arm have first sensor attached and are shown how to apply sensor and how to interpret data. Given dedicated contact details for diabetes research nurse in case of any issues and to discuss treatment of diabetes at any point.
- Those in the standard care arm are returned to their usual diabetes care provider.
- Letters sent to participants GP making them aware of participant trial enrolment.

Day 4

- Phone call to participants in Freestyle libre arm to ascertain if any issues with sensor and answer any questions.

Day 14

- Contact those in freestyle libre arm. Review glucose data and alter diabetes therapy as indicated.

Day 28

- Contact those in freestyle libre arm. Review glucose data and alter diabetes therapy as indicated.

Month 3

- Contact those in freestyle libre arm. Review glucose data and alter diabetes therapy as indicated.

Month 6

- Review of electronic patient data to ensure the participant is not deceased so as to not cause distress to friends/family by attempting to make contact in that eventuality.
- Both groups will attend an in-person meeting with the diabetes research nurse. Blood tests will be taken with consent for the same variables as at baseline (HbA1c, U and E's, LFT's, Lipids.) Urine for UACR collected.
- Questionnaires will be repeated.

- For those using the Freestyle Libre system the equipment will be returned.
- For those in the standard care arm, the blinded freestyle Libre device (Freestyle Libre pro) will applied and worn for a period of two weeks (facilities to return the sensor after this time will be provided.)
- This will mark the end of active participant involvement in the trial for both groups.
- Information will be sent to the participants primary care team alerting them that the participant has finished involvement in the trial.

Month 12

- All participants electronic records reviewed for unscheduled healthcare contacts, further ambulance call outs for hypoglycaemia, hospitalisations and death. If death has occurred, cause of death ascertained from death certificate.

Month 24

- All participants electronic records reviewed for unscheduled healthcare contacts, further ambulance call outs for hypoglycaemia, hospitalisations and death. If death has occurred, cause of death ascertained from death certificate.
- Data will be supplied by the ambulance service research department regarding number of emergency call outs in the year prior to enrolment and the two years following this.

A summary of trial design is shown in figure 2a and a summary of participant activities for the Freestyle Libre arm is shown in figure 2b.

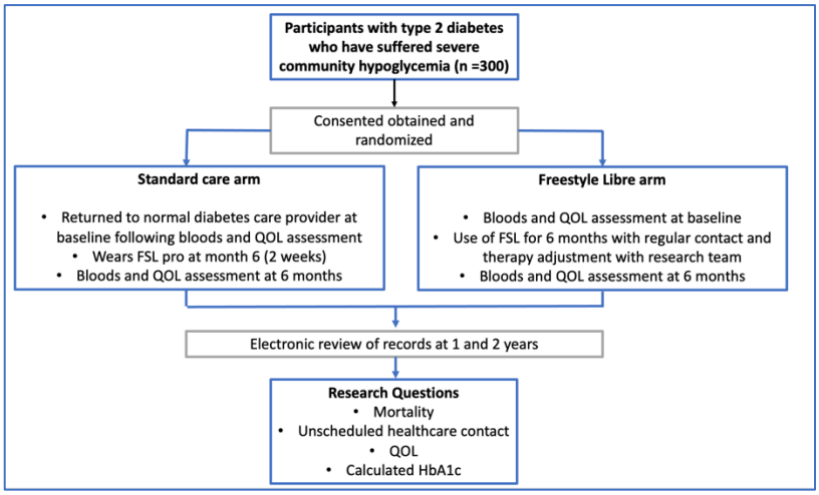

Figure 2a: A diagrammatic description of trial design

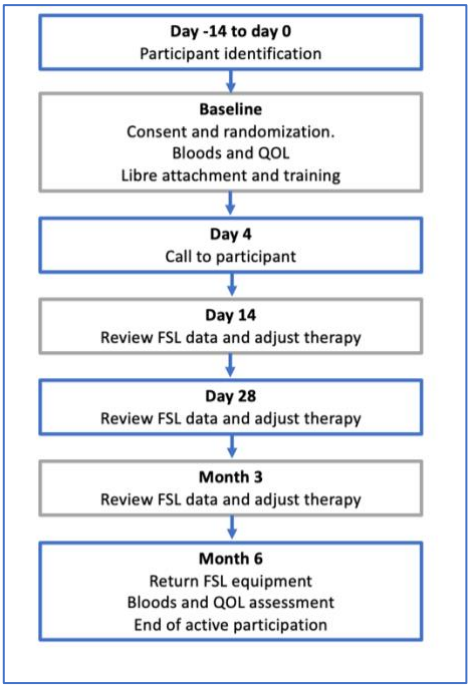

Figure 2b: A diagrammatic description of participant activities for Freestyle Libre arm

Primary end point

- Mortality at 2 years

Secondary end points

- All cause and cardiovascular mortality at 1 year and cardiovascular mortality at 2 years
- Number of unscheduled healthcare contacts between groups
- QOL measures between groups at 6 months
- Assess accuracy in calculated HbA1c compare to laboratory values at 6 months
- Assess HbA1c at 6 months in relation to baseline in both arms

Statistical analysis and feasibility

Results from our previous work [9] and the data presented above indicate that survival following severe hypoglycemia in type 2 diabetes patients over a median follow up period of 18 months is less than 80%. Assuming a conservative 28% reduction in mortality in the intervention compared with the standard arm during a median follow up of 18 months, 261 patients with type 2 diabetes will be required, powered at 90% with a significance level at $p<0.05$. Therefore, we will aim to recruit 300 patients with type 2 diabetes sustaining a severe hypoglycemic episode into the study.

We are unable to provide power calculations for hospital admissions or HCP contact of type 2 diabetes patients and therefore this part of the work will be exploratory.

Numbers of patients will be enough to show differences in quality of life measures given the data provided by a previous study in type 2 diabetes patients[22].

Our previous work on patients with severe hypoglycemia requiring ambulance services intervention has shown that a single centre is able to recruit over 90 patients/year. Therefore, we propose recruit the majority of participants from a single site (Leeds teaching hospitals) with separate sites in the local area also recruiting to this study. The number of sites may be expanded if recruitment goals are not met although based on our previous work this is not deemed likely.

COVID-19 precautions

- All efforts have been made for consultations to be remote wherever possible, with only 2 in-person healthcare contacts taking place.
- Participants will visit the diabetes research center at baseline and 6 months but the option will be given to attend at the participants home if they wish. The day prior to contact the patient will be contacted to ascertain if they or any close contact are suffering with symptoms of COVID-19 with the appointment rescheduled in that eventuality. On the day of appointment, screening questions will be repeated with a temperature taken on entering the diabetes research center.

Data management and ensuring the safety of patient identifiable data

All data will be recorded and stored in accordance with GCP. Electronic data will be stored on NHS computers/laptops which are encrypted and password protected. Information pertaining to participants medical records will be kept separately (electronically) from patient identifiable information (a separate spreadsheet will be used with a participant study number.) Paper records, namely the data capture form used at the baseline visit will be kept in a locked, secure area of the diabetes centre at the host institution.

Adverse event reporting

Adverse events will be reported to the study sponsor as soon as it is evident that such an event has taken place. It is not deemed likely, given the nature of the study, that this will occur frequently. Any serious and unexpected adverse event deemed related to the intervention will be reported to the NHS REC within 15 days.

Reference List

1. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. Kidney Int. 1995;47:1703-1720.
2. Coprogression of Cardiovascular Risk Factors in Type 1 Diabetes During 30 Years of Follow-up in the DCCT/EDIC Study. Diabetes Care 2016;39:1621-1630.
3. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-865.
4. Patel A, MacMahon S, Chalmers J et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N.Engl.J.Med. 2008;358:2560-2572.
5. Ajjan RA. How Can We Realize the Clinical Benefits of Continuous Glucose Monitoring? Diabetes Technol.Ther. 2017;19:S27-S36.
6. Currie CJ, Peters JR, Tynan A et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481-489.
7. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care 2011;34 Suppl 2:S132-S137.
8. Hsu PF, Sung SH, Cheng HM et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. Diabetes Care 2013;36:894-900.
9. Elwen FR, Huskinson A, Clapham L et al. An observational study of patient characteristics and mortality following hypoglycemia in the community. BMJ Open Diabetes Res.Care 2015;3:e000094.
10. Khunti K, Davies M, Majeed A et al. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. Diabetes Care 2015;38:316-322.
11. Foos V, Varol N, Curtis BH et al. Economic impact of severe and non-severe hypoglycemia in patients with Type 1 and Type 2 diabetes in the United States. J.Med.Econ. 2015;18:420-432.
12. Chow E, Bernjak A, Williams S et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738-1747.
13. Chow E, Iqbal A, Phoenix F, Heller SR, Ajjan RA. Hypoglycaemia promotes thrombosis and inflammation for at least one week in patients with type 2 diabetes. Diabetologia 2013;56:S243.
14. Lin CC, Li CI, Yang SY et al. Variation of fasting plasma glucose: a predictor of mortality in patients with type 2 diabetes. Am.J.Med. 2012;125:416-418.
15. Gorst C, Kwok CS, Aslam S et al. Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis. Diabetes Care 2015;38:2354-2369.
16. Cavalot F. Do data in the literature indicate that glycaemic variability is a clinical problem? Glycaemic variability and vascular complications of diabetes. Diabetes Obes.Metab 2013;15 Suppl 2:3-8.
17. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140-149.

18. Miller KM, Beck RW, Bergenstal RM et al. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. Diabetes Care 2013;36:2009-2014.
19. Schutt M, Kern W, Krause U et al. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. Exp.Clin.Endocrinol.Diabetes 2006;114:384-388.
20. Lee WC, Smith E, Chubb B, Wolden ML. Frequency of blood glucose testing among insulin-treated diabetes mellitus patients in the United Kingdom. J.Med.Econ. 2014;17:167-175.
21. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes Res.Clin.Pract. 2018;137:37-46.
22. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254-2263.
23. Haak T, Hanaire H, Ajjan R et al. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial. Diabetes Ther. 2016
24. Polonsky WH, Fisher L, Earles J et al. Assessing psychosocial distress in diabetes: development of the diabetes distress scale. Diabetes Care 2005;28:626-631.
25. Bradley C, Speight J. Patient perceptions of diabetes and diabetes therapy: assessing quality of life. Diabetes Metab Res.Rev. 2002;18 Suppl 3:S64-S69.