Nurse-led Intervention Improves Survival Following Severe Hypoglycaemia in Type 2 Diabetes Irrespective of Baseline Risk Characteristics.

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Abstract

Background

Recent evidence suggests severe hypoglycaemia may pose a risk of premature mortality to individuals with type 2 diabetes. Evidence surrounding strategies to mitigate this risk is currently lacking as is evidence regarding risk stratification of such patients.

Methods

We performed a post-hoc analysis from a previously published RCT studying the impact of a structured nurse led intervention following severe hypoglycaemia. A Cox regression model was used to identify baseline characteristics associated with increased mortality and to adjust for differences between study groups. Kaplan Meier (KM) curves were created to demonstrate differences in outcome between study groups across a number of variables.

Results

124 participants (mean age 75, 57% male) were included in analysis. Diabetes severity score, age and insulin use were found to correlate with mortality, while other variables including HbA1c and presence of established cardiovascular disease showed no correlations. When comparing KM curves between study groups, the intervention appeared to be beneficial irrespective of glycaemic control, presence of vascular disease, diabetes severity score or age.

Conclusion

In this analysis, only diabetes severity score, age and insulin use were significantly associated with death following severe hypoglycaemia in the community. A structured nurse-led intervention appears to reduce the risk of death irrespective of age, co-morbidities or type of treatment.

Trial registration

Data is taken from a previously published randomised controlled trial with trial registration NCT04422145.

Background

Type 2 diabetes (T2D) is characterised by chronic hyperglycaemia resulting in increased risk of vascular complications and reduced life expectancy[1]. Treatment intensification which aims to reduce hyperglycaemia decreases risk of microvascular complications[2] and long-term macrovascular risk[3]. However, intensification of glycaemic treatment increases hypoglycaemic exposure, which is believed to be associated with an increased risk of cardiovascular event[4,5,6]. As such, guidelines suggest individualising HbA1c targets while also focusing on hypoglycaemic avoidance[7]. However, evidence

surrounding interventions to improve outcome in T2D following severe hypoglycaemia is sparce and preliminary.

Recently, we conducted a randomised controlled trial (RCT) investigating the impact of a structured nurse-led intervention on mortality in people with T2D following severe hypoglycaemia. The intervention, which focused on patient education, initiation of self-monitoring of blood glucose, and pragmatic medication changes resulted in a reduction in all-cause mortality. Mean baseline HbA1c tended to be higher in those who survived till study completion compared with patients who died at any point, suggesting that outcome can be influenced by pre-treatment patient characteristics. However, the use of individual metrics in isolation, such as HbA1c, fails to capture the complexity of T2D and have limited application for risk stratification and predicting clinical outcome. Conversely, tools that combine routine clinical metrics to better capture global comorbidity and overall diabetes severity have been shown to yield greater predictive value than individual proxy indicators, including HbA1c[8].

Therefore, the aim of this exploratory post-hoc analysis was to understand risk factors for mortality following severe hypoglycaemia in T2D and investigate possible heterogeneity in response to the intervention. This information may help to identify subgroups of patients who show enhanced, or reduced, benefits from nurse-led support.

Methods

We performed an exploratory post-hoc analysis using data from a previously published RCT[9] (clinical trial registration NCT04422145). The RCT received ethical approval from the UK National Health Service Health Research Authority (reference 100244) and all participants gave written informed consent. Detailed information about study procedures have been published previously. In brief, patients with diabetes who suffered an episode of severe community hypoglycaemia requiring the assistance of emergency services in the area surrounding Leeds, UK, were randomised to either standard care or a structured nurse-led intervention. The Intervention centred on the initiation of self-monitoring of blood glucose, education surrounding the avoidance of hypoglycaemia and adjustment of glycaemic medication, as appropriate. The main intervention took place in the three months following recruitment with further limited involvement of the research nurse for a further 9 months. Data surrounding mortality were collected using electronic records and death, including cause, was confirmed using death certificates, a statutory requirement in the UK. In the present analysis, we included patients with T2D randomised to standard care and intervention arms, given that the intervention failed to show an effect on those with type 1 diabetes.

Participants were stratified into subgroups using an established diabetes severity score which has previously been shown to associate with mortality and healthcare costs[10]. The severity score is a composite of hard clinical endpoints and biochemical variables and represents an assessment of existing, as well as risk of developing, diabetes-related complications. Scores range from 1-4 with 4

categorised as the greatest degree of diabetes severity. Scores were then compressed to provide dichotomous variables (groups 1+2 and 3+4).

Statistical analysis

Data analysis was performed using SPSS version 27 (IBM corporation, USA) and assessed for normality. Continuous variables are reported as mean±SD, and categorical variables reported as frequency (%). Differences between dichotomised variables were assessed using independent t-tests or chi-square test. We employed a Cox-regression model to identify factors associated with an increased risk of mortality. Statistical significance was determined as $p<0.05$ for all analyses. Graphpad (Prism 9) USA, was used to construct Kaplan Meier curves comparing survival between groups.

Results

Baseline characteristics

A summary of baseline characteristics is shown in Table 1.

Table 1: A summary of baseline characteristics. Continuous variables displayed as mean±SD and categorical as number (percentage.) Independent T-test used for comparisons between means of continuous variables and chi-squared or Fishers exact test for comparison between categorical variables. Insufficient data was available for severity score calculation for 3 participants, 1 in the intervention group and 2 in standard of care.

	Intensive (n = 60)	*Standard (n = 64)*	*Difference between groups (p value)*
Male (%)	33 (55)	37 (57.8)	0.75
Age (years)	74.2 ± 10.7	74.84 ± 10.2	0.82
Presenting capillary glucose (mmol/L)	2.3 ± 0.7	2.3 ± 0.8	0.94
HbA1c (mmol/mol)	58.5 ± 13.4	60.0 ± 16.2	0.59
Duration of Diabetes (years)	21.4 ± 11.3	20.2 ± 11.1	0.55
Established cardiovascular disease (%)	21 (35)	30 (46.9)	0.18
Antiplatelet use (%)	30 (50)	29 (45.3)	0.73
Lipid lowering therapy use (%)	50 (83.3)	47 (73.4)	0.18
Anti-hypertensive use (%)	50 (83.3)	53 (82.8)	0.94
Severity score 1 (%)	8 (13.3)	3 (4.7)	0.09
Severity score 2 (%)	21 (35)	19 (29.7)	0.53
Severity score 3 (%)	9 (15)	8 (12.5)	0.69
Severity score 4 (%)	21 (35)	32 (50)	0.09
Using insulin therapy (%)	48 (80)	53 (82.8)	0.97

Baseline factors affecting mortality

In order to ascertain which baseline characteristics were impactful on mortality, variables were added individually to a Cox regression model with HR, 95% CI and p-values calculated. Diabetes severity score, insulin use, and age were found to significantly impact on mortality, whereas established cardiovascular disease at baseline, duration of diabetes, baseline HbA1c, presenting capillary blood glucose, anti-platelet, anti-hypertensive and statin therapies failed to show an effect. Data are displayed in Table 2.

Table 2: The impact of baseline characteristics on mortality following severe community hypoglycaemia. Data in bold represent significant differences.

Variable	Hazard Ratio (HR) and 95% Confidence Interval (CI)	P-value
Gender (male)	1.11 (0.64–1.91)	0.71
Age	**1.04 (1.01 -1 .07)**	**< 0.01**
Presenting capillary blood glucose	0.85 (0.56–0.28)	0.43
HbA1c	1.01 (0.99–1.03)	0.59
Duration of diabetes	1.01 (0.99–1.03)	0.45
Prescence of established cardiovascular disease	1.32 (0.77–2.28)	0.31
Anti-platelet use	1.25 (0.61–2.58)	0.54
Lipid lowering therapy use	1.30 (0.65–2.58)	0.46
Anti-hypertensive use	1.34 (0.61–2.98)	0.47
Diabetes severity score (groups 1 + 2 vs 3 + 4)	**0.23 (0.17–0.47)**	**< 0.001**
Insulin use	**2.43 (1.04–5.71)**	**0.04**

Comparison between study groups

Overall, mortality rate was 1.5-fold greater in the standard care arm as compared to the intervention arm with 32 (50%) and 20 (33%) deaths occurring, respectively. The leading cause of death in the intervention arm of the study was infection, which occurred at a similar rate in two study arms, while cardiovascular disease was the major contributor to mortality in the standard care arm with a clear difference observed comparing study arms. Using a Cox-regression model, a comparison between groups was made after adjustment for factors shown to correlate with mortality (age, diabetes severity score and insulin use), with HR 0.67 (95% CI; 0.38-1.19) in favour of the intervention. After adjustment for additional covariates HR was largely unchanged at 0.71 (95% CI; 0.35 to 1.43).

We also attempted to demonstrate the benefit of the intervention in subgroups of participants. Four variables were selected (baseline HbA1c, baseline diabetes severity score, presence of established cardiovascular disease at baseline and age at baseline) and Kaplan Meier curves were constructed to assess differences in mortality between study groups. Due to the architecture of the data diabetes severity scores 1+2 and 3+4 were grouped together as were quartiles of age and baseline HbA1c. A logrank test was used to compare trends between curves with significance shown for severity score, HbA1c quartile and age quartile; data are displayed in figure 1.

Discussion

Severe hypoglycaemia in those with type 2 diabetes necessitating the assistance of emergency services results in high mortality, which can be modulated following a simple and pragmatic intervention focussed on patient education, glucose monitoring, and medication review. From this exploratory analysis, we show that some pre-treatment characteristics influence mortality following severe hypoglycaemia yet the studied intervention was beneficial even following adjustment for such variables. Overall, single variables do not adequately predict which patients may benefit from intervention with classical markers of risk, such as HbA1c and the presence of established cardiovascular disease, failing to provide significant impact on mortality, albeit in a relatively small sample size. The strongest predictors of mortality were a composite diabetes severity score which incorporates hard clinical endpoints and biochemical data from individuals and age.

These results highlight the significant risk to those with type 2 diabetes following severe hypoglycaemia, the benefit of a relatively straightforward and non-invasive intervention and raise the question as to whether diabetes severity score, calculated through a validated scoring system, should be incorporated into the management of such patients, prioritising higher risk individuals. Our findings extend recent work investigating the impact of multimorbidity on hypoglycaemia risk[11] and suggests the potential utility of severe hypoglycaemia risk stratification for assessing treatment response to subsequent intervention.

Importantly, this exploratory analysis suggests that the intervention is beneficial in all study participants, regardless of baseline characteristics and indicates that in healthcare systems with adequate funding and resources it could be considered for all patients suffering from severe community hypoglycaemia.

A strength of this study is the uniformity of patient care, the completeness of data regarding baseline characteristics and the simplicity of study intervention. There are a number of drawbacks that should be acknowledged. Notably, our relatively small sample size from a single centre study, limits generalisation to different healthcare systems and different ethnic groups. Therefore, larger multi-centre studies are urgently needed to confirm our initial findings and provide more robust data that can be incorporated into national guidelines to improve outcome in this high-risk group of patients with severe hypoglycaemia.

Conclusions

For patients with T2D sustaining an episode of severe hypoglycaemia in the community, a structured intervention appears to be helpful in all patients regardless of their baseline risk factors and diabetes severity score. However, those with higher diabetes severity score appear to be at particular risk and may require prioritisation of the intervention. A large multicentre randomised controlled trial is urgently needed to provide conclusive data that a similar intervention should be part of routine clinical practice.

Declarations

Ethical approvals

Ethical approval was gained from the UK National Health Service Health Research Authority (reference 100244) and informed written consent was obtained from all study participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The funding for the original study was allocated by Lifescan inc who had no impact on study design or data analysis.

Authors contribution

S.M.P was the main writer of the manuscript and performed statistical analysis. B.W and N.K were involved in manuscript appraisal and the editing process. R.B was involved in the manuscript review process and assessed for suitability of statistical methods used. M.D.C formulated the idea for the manuscript and was involved in critical manuscript editing. R.A.A has overall responsibility for the trial and critically reviewed the manuscript.

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Not applicable

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Figures

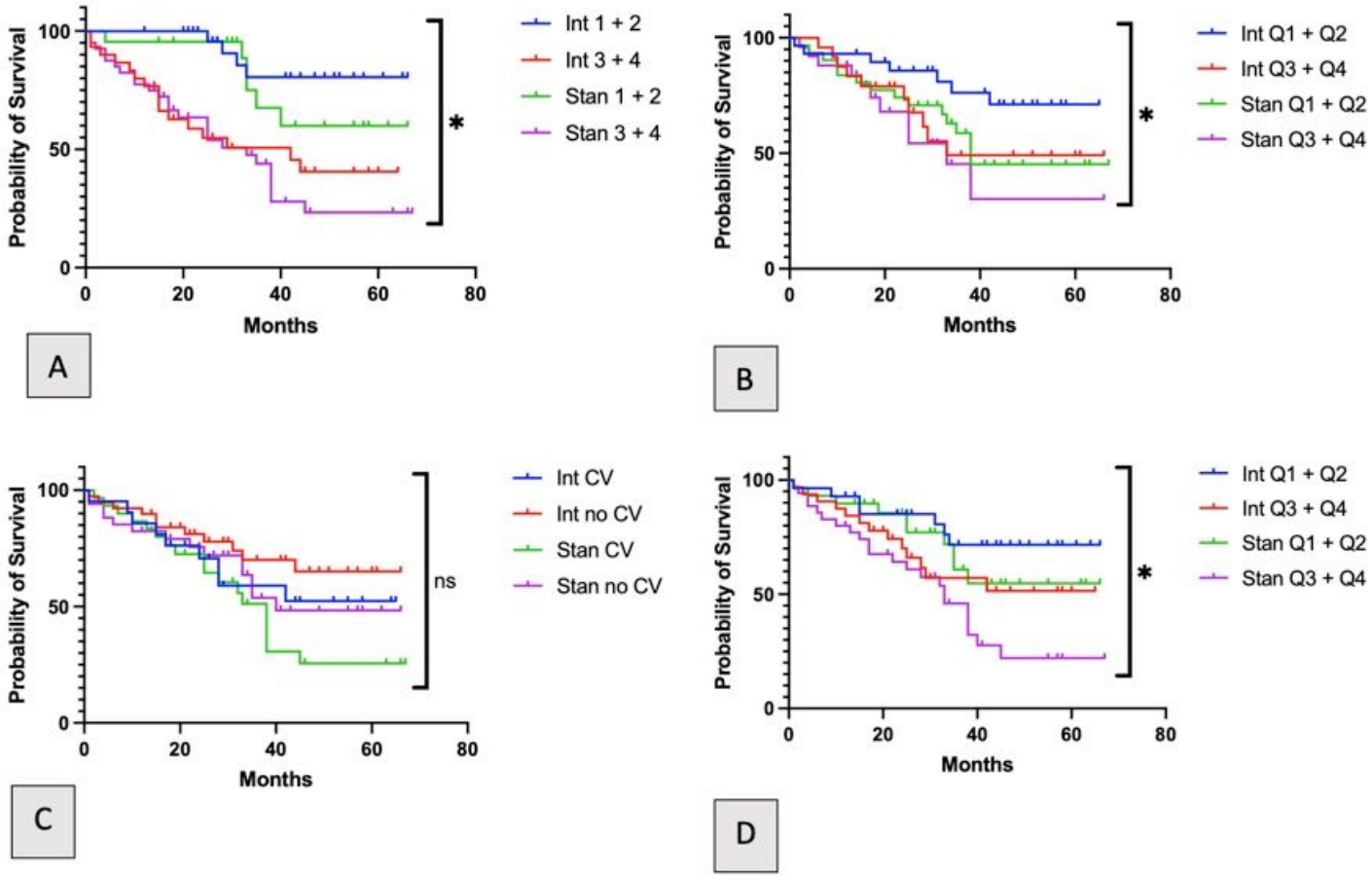

Figure 1

Survival curves comparing different groups. a) Spilt by diabetes severity score, b) Split by baseline HbA1c quartiles, c) Split by presence of established cardiovascular disease (CV) at baseline and d) Split by age quartile. Int=intervention; Stan=standard. * denotes p = <0.05 for logrank test for trend.