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ARTICLE

Outcomes of people with severe hypoglycaemia requiring prehospital emergency medical services management: a prospective study

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Abstract

Aims/hypothesis The aim of this work was to investigate clinical outcomes following severe hypoglycaemia requiring prehospital emergency medical services (EMS) management.

Methods We carried out a prospective, observational study of adults with diabetes attended by prehospital EMS for management of severe hypoglycaemia between April 2016 and July 2017. Information on precipitants, hospitalisation, length of hospital stay and recurrence was collected at 1 and 3 months following the episode of severe hypoglycaemia. Median and logistic regression models examined predictive factors.

Results Five hundred and five adults (61% male, median age 67 years) participated in the study. Fifty-two per cent had type 1 diabetes, 43% type 2 diabetes and 5% were unsure of their diabetes type. Following EMS management of the index episode of severe hypoglycaemia, 50.3% were transported to hospital. Of those transported, 41.3% were admitted to hospital for ongoing management (20.8% of all participants). The following factors predicted hospital admission: older age (OR 1.28 [95% CI 1.02, 1.60] per 10 years), greater number of comorbidities (OR 1.27 [95% CI 1.08, 1.48] per morbidity), moderate–severe injury accompanying the hypoglycaemia (OR 5.24 [95% CI 1.07, 25.8] compared with nil–mild injury) and unknown cause of hypoglycaemia (OR 2.21 [95% CI 1.24, 3.94] compared with known cause). The median (interquartile range) length of hospital stay was 4 (2–7) days. During follow-up, recurrent severe hypoglycaemia attended by prehospital EMS was experienced by 10.7% of participants. Predictive factors of recurrent severe hypoglycaemia in 3 months were decreased HbA_{1c} (OR 1.97 [95% CI 1.27, 3.06] per 10 mmol/mol decrease) and a greater number of antecedent severe hypoglycaemia episodes (OR 1.12 [95% CI 1.03, 1.23] per episode).

Conclusions/interpretation Following an episode of severe hypoglycaemia managed by EMS, one-fifth of participants required hospital admission, more likely in those with advancing age, increasing comorbidities and injury and one-tenth required EMS again for severe hypoglycaemia in a 3 month period, more likely in those with a greater number of antecedent episodes and lower HbA_{1c}. Knowledge of these factors associated with admission and recurrence provides an opportunity for development of targeted strategies aimed at prevention of severe hypoglycaemia in those most vulnerable.

Keywords Diabetes · Diabetic emergency · Emergency medical services · Outcome · Prehospital · Severe hypoglycaemia

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-019-4933-y) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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Research in context

What is already known about this subject?

- Few studies have examined the patient trajectory following severe hypoglycaemia managed by emergency medical services (EMS), including hospital admission, length of stay and recurrent severe hypoglycaemia in the months following the initial episode, when an individual may be particularly vulnerable to recurrence as well as adverse clinical outcomes

What is the key question?

- What are the clinical outcomes for individuals with severe hypoglycaemia requiring EMS management and what factors are associated with these outcomes?

What are the new findings?

- Following an episode of severe hypoglycaemia requiring EMS management and transport to the emergency department, approximately 40% were admitted to hospital; admission was associated with older age, a greater number of comorbidities, substantial injury at time of hypoglycaemia and unknown cause of hypoglycaemia
- The median length of hospital stay was 4 days and this was increased among individuals with type 2 diabetes and heart disease
- Recurrent severe hypoglycaemia requiring EMS management within 3 months occurred in over 10% of individuals and was more likely among those with a lower HbA_{1c} and those reporting a greater number of previous episodes of severe hypoglycaemia

How might this impact on clinical practice in the foreseeable future?

- Prevention-focused interventions targeting individuals at greatest risk, such as those with type 2 diabetes, heart disease, lower HbA_{1c} or history of antecedent episodes, could be developed to improve patient safety and reduce EMS and hospital burden

Abbreviations

EMS Emergency medical services
IQR Interquartile range

Introduction

Hypoglycaemia among those with diabetes is a common and potentially avoidable complication of therapy [1]. When cognitive impairment necessitates external assistance for treatment, the hypoglycaemia is classified as severe [2] and may require the assistance of prehospital emergency medical services (EMS). Following immediate treatment by EMS in the community, individuals may be transported to a hospital for further care, from where they may be discharged or admitted to a ward. While immediate attendance to a hospital emergency department may not be necessary, medical review of the treatment regimen is advised for all patients [3]. In the weeks following occurrence of the severe hypoglycaemia, a period of relaxed glucose targets may be recommended, in order to reduce risk of recurrence and to restore symptoms and hypoglycaemia awareness [2].

Studies following individuals for up to 3 days after an episode of severe hypoglycaemia have suggested that many of them may remain safely at home after acute treatment [4–9], with minimal difference in symptom recurrence between those who are and are not transported to hospital. However, the detailed patient trajectory following the transport decision, including length of hospital stay and recurrence in the months following, when the individual may be particularly vulnerable to adverse clinical outcomes, has not been well studied.

The primary aims of this study were to investigate factors associated with hospitalisation, length of hospital stay and recurrence in the 3 months following the index episode of severe hypoglycaemia managed by prehospital EMS. Secondary aims were to describe precipitants and prior care management of severe hypoglycaemia managed by prehospital EMS as well as behaviours of follow-up medical review. By understanding the common precipitants and the clinical outcomes following an episode of severe hypoglycaemia, as they relate to predisposing factors, high-risk populations can be identified and strategies to reduce and/or improve use of EMS for management of severe hypoglycaemia can be developed.

Methods

Study design We carried out a prospective, observational study of adults (aged >17 years) with diabetes mellitus (type 1 or type 2) experiencing an episode of severe hypoglycaemia

managed by Ambulance Victoria between April 2016 and July 2017 (approximately 15 months). Following an episode of severe hypoglycaemia, potential participants were identified through Ambulance Victoria's electronic data warehouse. Exclusion criteria were age ≤17 years, nil diagnosis of type 1 or type 2 diabetes and living in a residential care facility. Ambulance Victoria's Clinical Practice Guidelines specify a blood glucose level of <4 mmol/l, with associated symptoms, as the treatment threshold for hypoglycaemia [10]. This study was approved by Monash University Human Research Ethics Committee (project no. CF15/3091 – 2015001303) prior to data collection.

Setting This study was conducted in the state of Victoria, Australia, which had a population of 6.29 million at March 2017 [11]. Victoria is serviced by Ambulance Victoria, a two-tiered prehospital EMS system, which deploys Advanced Life Support and Intensive Care paramedics and deals with over 500,000 emergency cases annually [12]. Approximately 1% of cases attended by Ambulance Victoria are classified as hypoglycaemia [13].

Data sources and recruitment An electronic patient care record is completed for every individual attended by Ambulance Victoria, by the paramedic, during the episode of care. Clinical data from the electronic patient care record and operational data from the computer-aided dispatch system are uploaded to the Ambulance Victoria electronic data warehouse. Potential participants were identified weekly through the Ambulance Victoria electronic database and were sent a letter of invitation. Telephone contact was initiated approximately 4 weeks following the index episode and consenting participants were surveyed over the phone with regards to general and diabetes-related health and management practices. Prior to participation in this study, participants gave informed consent. Participants were surveyed again at 3 months after the index episode in order to collect information regarding health and clinical outcomes. A pre-calculated sample size was chosen to capture the experiences of individuals with diabetes from a range of demographic situations, ages and locations. Recruitment commenced on 24 April 2016 and continued for 15 months until the desired sample size was reached on 25 July 2017.

Outcome variables The main outcome variables were as follows: (1) hospital admission (yes, if participant attended hospital within 24 h following the episode and was admitted); (2) length of stay (days, if admitted) and (3) recurrence (yes, if participant experienced at least one episode of severe hypoglycaemic managed by EMS within the 3 months of index episode). Hospital admission and length of stay were self-reported and data on recurrence were obtained from the Ambulance Victoria data warehouse. Other outcome variables were as follows: (1) the main precipitant of hypoglycaemia, classified as related to food, exercise or activity, insulin, other medication, intercurrent illness or other or unknown; (2) prior treatment attempted (either by the participant or others at scene), classified as oral carbohydrate, glucagon or neither oral carbohydrate or glucagon and (3) attendance to medical review (general practitioner, endocrinologist or diabetes educator) within 7 days of episode or within 7 days of hospital discharge in those who attended hospital.

Predictor variables The predictor variables were pre-specified and were self-reported, except where extracted from the electronic patient care record, as stated. Basic demographic variables were sex, age in years, location of residence (classified as metropolitan or regional as per the Regional Development Victoria Geography Structure [14]) and living situation (alone or with others). The country of birth was classified as Australia or overseas. Employment status, classified as employed, unemployed or retired and recipient of government benefit status, was ascertained. Prehospital EMS care in the state of Victoria is provided free of charge for government benefit recipients.

Diabetes-related variables were diabetes type (type 1, type 2 or unknown), diabetes duration (years), treatment with insulin, sulfonylurea use, the estimated number of severe hypoglycaemia episodes in the 12 months prior to index episode (any episode requiring assistance of others) and HbA_{1c} result if known by participants and measured within the last 3 months. HbA_{1c} was self-reported and collected in percentage units, as this was the measurement most participants were familiar with, and was converted to mmol/mol for analysis. Diabetes medical care provider was classified as general practitioner only, specialist practitioner (endocrinologist) only, both general practitioner and specialist care or neither. The self-reported frequency of attendance to a physician for diabetes (either general practitioner or endocrinologist) was classified as follows: monthly or more frequently; less than monthly to 3 monthly; less than 3 monthly to 6 monthly and less frequent than 6 monthly. The number of comorbidities (additional to diabetes) was recorded from the electronic patient care record. Diagnosis of specific medical conditions, including heart disease, renal disease, cerebrovascular disease (including stroke and transient ischaemic attack), depression and anxiety, was ascertained. In addition, the specific medical diagnoses to allow the calculation of the Charlson Comorbidity Index, a measure of prognostic comorbidity that assigns weighted scores from 22 comorbid conditions and predicts 1 year mortality risk [15], were collected. Interpretation of these scores is described in detail elsewhere [15].

The following variables related to the index episode of hypoglycaemia were extracted from the paramedic electronic patient care record: time of day of index episode (00:00 hours to before 08:00 hours, 08:00 hours to before 16:00 hours,

16:00 hours to before 00:00 hours); the Glasgow Coma Score and blood glucose level (mmol/l) on presentation (initial) and following hypoglycaemia treatment (final); the prehospital EMS treatment provided (oral treatment only [glucose paste or complex carbohydrate] or parenteral treatment [intramuscular glucagon or intravenous glucose]) and whether hospital transport was provided by EMS. Self-reported, episode-related variables were the presence of intercurrent illness and self-rated injury (classified as none–mild or moderate–severe).

Statistical methods Summary results were presented as percentage for categorical variables and as median with interquartile range (IQR) for continuous variables; Spearman ρ was reported where both the predictor and outcome variables were continuous (such as in length of stay). To assess representation of the sample against eligible non-participants, differences in sex, age, location of residence, diabetes type and treatment with insulin were compared, using χ^2 test or Mann–Whitney *U* test, as appropriate.

Precipitants of hypoglycaemia, prior treatment attempted and follow-up medical review were presented descriptively. Multivariable analysis was performed with the main outcome variables hospital admission, length of stay and 3 month recurrent episode. Factors associated with hospital admission (yes/no) and 3 month recurrent episode (yes/no) were analysed using mixed effects logistic regression. The mixed models were chosen to account for clustering of participants within the same postcode. The hospital length of stay was noted to have a positively skewed distribution, so regression of the median with robust standard error was used to analyse factors associated with admission length of stay. Univariable analysis was initially performed. Multivariable models were constructed in a stepwise manner. Starting from the most significant variables, variables identified to yield a p value <0.05 in the univariable analysis were consecutively added to the model. Following the addition of each variable, a likelihood ratio test was performed and the variable was retained in the model where the likelihood ratio yielded a p value <0.05 and was thus deemed to improve the model. Given the importance of age and diabetes type, these variables were forced into the models in the initial stages of the multivariable modelling process. Where data were missing, every effort was made to contact participants for rectification. Missing data were minimal and no imputation of missing data was performed. Participants with missing data for a particular variable were not included in the analysis pertaining to that particular variable but were not excluded from other analyses where relevant data were available. All analyses were performed using Stata Statistical Software (StataCorp, College Station, TX, USA) version 14.0.

Results

Ambulance Victoria managed 4510 episodes of severe hypoglycaemia among 3479 adults, of which a sample of 505 were prospectively studied during the 15 month study period (see electronic supplementary material [ESM] Fig. 1). Initial surveys were completed at a median (IQR) of 28 (24, 33) days following the index severe hypoglycaemia event. Most of the cohort (88.3%, $n = 446$) were contactable at 3 months (final survey), with a median (IQR) follow-up of 99 (93–109) days after the index severe hypoglycaemia event. The following reasons for incomplete follow-up were reported: decline (2.2%, $n = 11$); moved to residential care facility (0.6%, $n = 3$); deceased (1.2%, $n = 6$) and unable to contact (7.7%, $n = 39$).

Study population characteristics Participant characteristics, overall and by diabetes type, are presented in Table 1. Over half (51.9%) the participants had type 1 diabetes, 42.8% had type 2 diabetes and 5.3% were unsure of their diabetes type. The median (IQR) age of participants was 67 (56–77) years, 60.6% were men and 68.7% resided in a metropolitan location. Over 80% of participants had at least one comorbidity in addition to diabetes, with a median (IQR) of 2 (1–3) comorbidities and a median (IQR) Charlson Comorbidity Index score of 4 (2–6). Most (65.3%) of participants were retired, 24.6% were employed and 10.1% were unemployed. Overall, 70.9% were recipients of a government benefit. Participants born in a country outside Australia made up 28.1%. Compared with eligible non-participants, the sample was of similar sex ($p = 0.496$), diabetes type ($p = 0.361$) and location of residence (metropolitan/regional, $p = 0.109$). However, participants were older, by a median of 6 years ($p < 0.001$), and a greater proportion were treated with insulin compared with non-participants (91% vs 54%, $p < 0.001$) (ESM Table 1).

Precipitants of severe hypoglycaemia and prior management The self-reported primary precipitant of severe hypoglycaemia included food (28.9%), insulin (17.3%), exercise/activity (8.3%), intercurrent illness (5.5%), other medications (4.5%) and other cause (5.4%). Almost one-third of participants (30.1%) were unsure of the reason for development of hypoglycaemia. In 60.8% of the episodes, hypoglycaemia treatment was attempted prior to prehospital EMS arrival; 55.1% were given oral carbohydrate and 5.7% were given intramuscular glucagon (with or without oral carbohydrate). Where prior treatment was not attempted, the following reasons were given: participant was unconscious (including seizure) (64.1%); hypoglycaemia was not recognised as such (including suspected stroke/cardiac problems) (21.7%); uncertainty of what to do (6.1%); no treatment was available (1.5%) and other reasons (6.6%).

Table 1 Study population characteristics

Characteristic	Total population	Type 1 diabetes	Type 2 diabetes	Unknown diabetes type
No. of participants	505	262 (51.9)	216 (42.8)	27 (5.3)
Male sex	306 (60.6)	161 (61.5)	133 (61.6)	12 (44.4)
Age	67 (56–77)	60 (47–69)	74 (66.5–81.5)	78 (68–82)
Location of residence				
Metropolitan	347 (68.7)	181 (69.1)	151 (69.9)	15 (55.6)
Regional/rural	158 (31.3)	81 (30.9)	65 (30.1)	12 (44.4)
Duration of diabetes, years	27 (17–38)	32 (22.5–41)	21.5 (14–30)	25 (20–34)
Insulin treated	458 (90.7)	262 (100)	172 (79.6)	24 (88.9)
Sulfonylurea treated	57 (11.3)	0 (0)	56 (25.9)	1 (3.7)
Annual antecedent severe hypoglycaemia[a]				
0	222 (45.5)	81 (32.4)	133 (62.7)	8 (30.8)
1–3	187 (38.3)	116 (46.4)	59 (27.8)	12 (46.2)
4–6	43 (8.8)	32 (12.8)	8 (3.8)	3 (11.5)
7–12	22 (4.5)	11 (4.4)	8 (3.8)	3 (11.5)
12+	14 (2.9)	10 (4.0)	4 (1.9)	0 (0)
HbA_{1c}, mmol/mol[b]	54 (48–63)	54 (48–63)	53 (48.5–61.5)	63 (49.5–75)
HbA_{1c}, %[b]	7.1 (6.5–7.9)	7.2 (6.5–7.9)	7.0 (6.6–7.8)	8.0 (6.7–9.1)
Overseas born	142 (28.1)	59 (22.5)	78 (36.1)	5 (18.5)
Living situation				
Alone	115 (22.8)	47 (17.9)	63 (29.2)	5 (18.5)
With others	390 (77.2)	215 (82.1)	153 (70.8)	22 (81.5)
Employment status				
Employed	124 (24.6)	101 (38.5)	21 (9.7)	2 (7.4)
Unemployed	51 (10.1)	41 (15.5)	8 (3.7)	2 (7.4)
Retired	330 (65.3)	120 (45.8)	187 (86.6)	23 (85.2)
Government benefit recipient	358 (70.9)	149 (56.9)	184 (85.2)	25 (92.6)
Charlson Comorbidity Index	4 (2–6)	3 (2–5)	5 (3–6)	4 (3–7)
No. of comorbidities	2 (1–3)	1 (0–3)	2.5 (1–4)	3 (1–4)
Heart disease	158 (31.3)	58 (22.1)	88 (40.7)	12 (44.4)
Renal disease	104 (20.6)	44 (16.8)	54 (25.0)	6 (22.2)
Cerebrovascular disease	60 (11.9)	19 (7.3)	38 (17.6)	3 (11.1)
Depression	137 (27.1)	73 (27.9)	55 (25.6)	9 (33.3)
Anxiety	73 (14.5)	39 (14.9)	29 (13.4)	5 (18.5)

Data are presented as *n* (%) or as median (IQR)

[a] Self-reported no. of episodes of severe hypoglycaemia prior to index episode, in previous 12 months

[b] Where result reported is within previous 3 months

Predictors of hospital admission Of the 505 participants, 50.3% ($n = 254$) were transported to the emergency department within 24 h (249 immediately by paramedics or private car and 5 later by private car). Of these, 58.7% ($n = 149$) were discharged from the emergency department and 41.3% ($n = 105$) were admitted to a hospital ward, representing 20.8% of the whole cohort. Factors associated with hospital admission are presented in Table 2. Hospital admission was predicted by increased age (OR 1.28 [95% CI 1.02, 1.60]), increasing number of comorbidities (OR 1.27 [95% CI 1.08, 1.48]), moderate–severe injury sustained with severe hypoglycaemia (OR 5.24 [95% CI 1.07, 25.8]) and unknown cause of hypoglycaemia (OR 2.21 [95% CI 1.24, 3.94]).

Length of hospital stay For the 105 participants admitted to a hospital ward following an episode of severe hypoglycaemia, the median (IQR) length of stay was 4 (2–7) days (ESM Fig. 2). Independent predictors of length of hospital stay (Table 3) were type 2 diabetes and heart disease. Type 2 diabetes was associated with an increase in the median length of stay of 2 (95% CI 0.11, 3.89) days, compared with type 1 diabetes, and a history of heart disease was associated with an increase in

Table 2 Factors associated with hospital admission following prehospital EMS attendance for severe hypoglycaemia

Factor	Hospital admission	No hospital admission	Univariable OR (95% CI)	*p* value	Multivariable OR (95% CI)	*p* value
Overall	105 (41.3)	149 (58.7)				
Sex						
Male	56 (53.3)	90 (60.4)	Reference			
Female	49 (46.7)	59 (39.6)	1.34 (0.81, 2.21)	0.262		
Age, years[a]	74 (67–82)	68 (57–78)	1.37 (1.13, 1.65)	0.001	1.28 (1.02, 1.60)	0.032
Living situation						
With others	73 (69.5)	111 (74.5)	Reference			
Alone	32 (30.5)	38 (25.5)	1.28 (0.73, 2.23)	0.383		
Diabetes type						
Type 1	36 (34.3)	67 (45.0)	Reference		Reference	
Type 2	63 (60.0)	72 (48.3)	1.63 (0.96, 2.76)	0.070	0.96 (0.51, 1.82)	0.911
Unknown	6 (5.7)	10 (6.7)	1.12 (0.38, 3.32)	0.843	0.47 (0.14, 1.65)	0.242
Diabetes duration, years[a]	26.5 (17–40)	23 (15–34)	1.13 (0.94, 1.34)	0.189		
Insulin treated	84 (80.0)	132 (88.6)	0.52 (0.26, 1.03)	0.062		
Sulfonylurea treated	19 (18.1)	19 (12.8)	1.51 (0.76, 3.02)	0.242		
Annual antecedent severe hypoglycaemia[b]	1 (0–2)	0 (0–2)	0.99 (0.96, 1.02)	0.623		
HbA_{1c}, mmol/mol[c,d]	56 (53–63)	53 (48–63)	1.00 (0.71, 1.40)	0.980		
HbA_{1c}, %[c]	7.5 (7.0–8.0)	7.0 (6.5–7.9)				
No. of comorbidities	3 (2–4)	2 (1–3)	1.28 (1.11, 1.48)	0.001	1.27 (1.08, 1.48)	0.003
Time of severe hypoglycaemia occurrence						
00:00 to <08:00 hours	22 (21.0)	34 (22.8)	Reference			
08:00 to <16:00 hours	48 (45.7)	63 (42.3)	1.12 (0.61, 2.27)	0.625		
16:00 to 00:00 hours	35 (33.3)	52 (34.9)	1.04 (0.52, 2.07)	0.910		
Reason for severe hypoglycaemia unknown	45 (42.9)	39 (26.2)	2.12 (1.24, 3.60)	0.006	2.21 (1.24, 3.94)	0.007
Intercurrent illness	9 (8.6)	10 (6.7)	1.30 (0.51, 3.33)	0.580		
Moderate–severe injury	7 (6.7)	2 (1.3)	5.25 (1.07, 25.8)	0.041	5.24 (1.07, 25.8)	0.038
Initial Glasgow Coma Score	14 (9–15)	14 (10–15)	0.98 (0.91, 1.05)	0.571		
Final Glasgow Coma Score	15 (15–15)	15 (15–15)	0.74 (0.48, 1.13)	0.164		
Initial BGL (mmol/l)	1.8 (1.0–2.7)	1.7 (1.0–2.7)	1.03 (0.89, 1.20)	0.630		
Final BGL (mmol/l)	6.1 (4.6–8.4)	5.7 (4.2–7.6)	1.06 (0.98, 1.16)	0.124		
EMS treatment						
Oral	39 (37.1)	68 (45.6)	Reference			
Parenteral	66 (62.9)	81 (54.4)	1.42 (0.85, 2.37)	0.178		

Data for hospital admissions are presented as *n* (%) or as median (IQR)

Previous history of heart disease, renal disease, cerebrovascular disease, depression and anxiety were examined in univariable analysis and found not to be associated with hospital admission (not shown in table); multivariable model included adjustments for age, diabetes type (forced), number of comorbidities, unknown reason for severe hypoglycaemia and moderate–severe injury

[a] OR per 10 year increase

[b] Self-reported no. of episodes of severe hypoglycaemia prior to index episode, in previous 12 months

[c] Where result reported is within previous 3 months

[d] OR per 10 mmol/mol decrease

BGL, blood glucose level

the median length of stay of 2 (95% CI 0.36, 3.64) days compared with no history of heart disease. There was a suggestion of an increasing length of stay among those treated with sulfonylureas (7 days vs 4 days, $p = 0.083$) compared with those not treated with this medication.

Predictors of recurrent severe hypoglycaemia requiring prehospital EMS Of the 505 participants, 10.7% ($n = 54$) had one or more recurrent episodes of severe hypoglycaemia requiring EMS in the 3 months following the index episode, generating a total of 602 occurrences during follow-up. The

Table 3 Factors associated with length of hospital stay following prehospital EMS attendance for hypoglycaemia

Factor	Length of hospital stay (days)	Univariable difference in medians (95% CI)	*p* value	Multivariable difference in medians (95% CI)	*p* value
Overall	4 (2–7)				
Sex					
Male	3 (2–6.5)	Reference			
Female	5 (3–7)	2.00 (0.12, 3.88)	0.038		
Age, years[a]	0.121	0.41 (−0.12, 0.95)	0.126	0.00 (−0.07, 0.07)	1.000
Living situation					
With others	4 (2–7)	Reference			
Alone	5 (2–7)	1.00 (−1.41, 3.41)	0.412		
Diabetes type					
Type 1	3 (2–4.5)	Reference		Reference	
Type 2	5 (2–7)	2.00 (0.54, 3.45)	0.008	2.00 (0.11, 3.89)	0.039
Unknown	5 (4–10)	3.00 (−2.95, 8.95)	0.320	2.00 (−1.70, 5.70)	0.286
Diabetes duration, years[a]	0.020	0.00 (−0.18, 0.17)	1.000		
Insulin treated					
No	7 (4–14)	Reference			
Yes	4 (2–6)	−3.00 (−6.24, 0.24)	0.070		
Sulfonylurea treated					
No	4 (2–6)	Reference			
Yes	7 (3–14)	3.00 (−0.40, 6.40)	0.083		
Annual antecedent severe hypoglycaemia[b]	−0.181	−0.08 (−0.3, 0.14)	0.481		
HbA_{1c}, mmol/mol[c,d]	0.481	0.4 (−0.76, 1.56)	0.484		
No. of comorbidities	0.171	0.50 (0.04, 0.96)	0.034		
Heart disease	5 (2.5–7)	2.00 (0.27, 3.63)	0.023	2.00 (0.36, 3.64)	0.018
Depression	3 (2–5)	−2.00 (−3.67, −0.33)	0.019		
Unknown reason for severe hypoglycaemia					
No	4 (2–7)	Reference			
Yes	4 (2–7)	0.00 (−2.11, 2.11)	1.000		
Intercurrent illness					
No	4 (2–7)	Reference			
Yes	5 (3–7)	1.00 (−2.4, 4.4)	0.565		
Injury					
None–mild	4 (2–7)	Reference			
Moderate–severe	3 (2–14)	−1.00 (−2.5, 0.52)	0.195		
Initial Glasgow Coma Score	0.090	0.00 (−0.25, 0.25)	1.000		
Final Glasgow Coma Score	−0.134	0.00 (−1.60, 1.60)	1.000		
Initial BGL	−0.032	0.00 (−0.49, 0.49)	1.000		
Final BGL	−0.085	−0.10 (−0.32, 0.13)	0.406		
EMS treatment					
Oral	4 (2–7)	Reference			
Parenteral	4 (2.5–7)	0.00 (−2.12, 2.12)	1.000		

Length of stay is presented as median (IQR) for categorical variables or as Spearman ρ for continuous variables

Previous history of renal disease, cerebrovascular disease and anxiety were examined in univariable analysis and found not to be associated with hospital admission (not shown in table); multivariable model included adjustments for age, diabetes type and heart disease

[a] Difference in medians per 10 year increase

[b] Self-reported number of episodes of severe hypoglycaemia prior to index episode, in previous 12 months

[c] Where result reported is within previous 3 months

[d] Difference in medians per 10 mmol/mol decrease

BGL, blood glucose level

median (IQR) number of recurrent episodes was 2 (2–3) and the median (IQR) time between episodes was 28 (8–50) days. Predictors of recurrent severe hypoglycaemia are presented in Table 4. Recurrent severe hypoglycaemia was independently associated with lower HbA_{1c} (OR 1.97 [95% CI 1.27, 3.06] for every 10 mmol/mol decrease) and a greater number of antecedent severe hypoglycaemia episodes (OR 1.12 [95% CI 1.03, 1.23] per increase by one episode).

Table 4 Factors associated with recurrent severe hypoglycaemia attended by prehospital EMS within 3 months

Factor	Single episode	Recurrent episode	Univariable OR (95% CI)	*p* value	Multivariable OR (95% CI)	*p* value
Overall	451 (89.3)	54 (10.7)				
Sex						
Male	273 (60.5)	33 (61.1)	Reference			
Female	178 (39.5)	21 (38.9)	0.97 (0.55, 1.74)	0.935		
Age[a]	68 (57–78)	59.5 (49–72)	0.77 (0.65, 0.91)	0.003	0.99 (0.72, 1.35)	0.926
Diabetes type						
Type 1	226 (50.1)	36 (66.6)	Reference			
Type 2	203 (45.0)	13 (24.1)	0.40 (0.21, 0.78)	0.007	0.66 (0.20, 2.19)	0.493
Unknown	22 (4.9)	5 (9.3)	1.42 (0.51, 4.01)	0.500	3.25 (0.25, 42.5)	0.368
Living situation						
With others	345 (76.5)	45 (83.3)	Reference			
Alone	106 (23.5)	9 (16.7)	0.65 (0.31, 1.37)	0.261		
Diabetes duration[a]	26 (16–38)	31 (20–40)	1.14 (0.94, 1.37)	0.181		
HbA_{1c} (mmol/mol)[b,c]	54 (50–64)	49 (40–54.5)	2.01 (1.35, 2.99)	0.001	1.97 (1.27, 3.06)	0.002
HbA_{1c} (%)[b]	7.1 (6.7–8.0)	6.6 (5.8–7.2)				
Insulin treated	406 (90.0)	52 (96.3)	2.88 (0.68, 12.2)	0.151		
Sulfonylurea treated	55 (12.2)	2 (3.7)	0.27 (0.07, 1.17)	0.081		
No. of comorbidities	2 (1–3)	1 (0–3)	0.79 (0.65, 0.95)	0.012		
Heart disease	149 (33.0)	9 (16.7)	0.41 (0.19, 0.85)	0.017		
Annual antecedent severe hypoglycaemia[d]	0.5 (0–2)	2 (1–6)	1.12 (1.06, 1.19)	<0.001	1.12 (1.03, 1.23)	0.011
Diabetes care provider						
General practitioner	127 (28.2)	14 (25.9)	Reference			
Endocrinologist	106 (23.5)	13 (24.1)	1.11 (0.51, 2.47)	0.793		
General practitioner & endocrinologist	213 (47.2)	27 (50.0)	1.14 (0.58, 2.27)	0.688		
Neither	5 (1.1)	0 (0)	–	–		
Medical appointment						
Monthly or more	123 (27.3)	18 (33.3)	Reference			
<1–3 monthly	193 (42.8)	22 (40.7)	0.78 (0.40, 1.51)	0.460		
<3–6 monthly	112 (24.8)	9 (16.7)	0.55 (0.24, 1.27)	0.162		
>6 monthly	23 (5.1)	5 (9.3)	1.48 (0.50, 4.40)	0.475		
Attended ED	229 (50.8)	20 (37.0)	0.57 (0.32, 1.02)	0.059		
Did not attend ED or review appointment[e]	103 (22.8)	17 (31.5)	1.55 (0.84, 2.87)	0.161		

Data for single/recurrent episode of severe hypoglycaemia are presented as *n* (%) or as median (IQR)

Previous history of renal disease, cerebrovascular disease, depression and anxiety were examined in univariable analysis and found not to be associated with hospital admission (not shown in table); multivariable model included adjustments for diabetes type, age, no. of episodes of severe hypoglycaemia in previous 12 months and HbA_{1c}

[a] OR per 10 year increase

[b] Where result reported is within previous 3 months

[c] OR per 10 mmol/mol decrease

[d] Self-reported no. of episodes of severe hypoglycaemia prior to index episode, in previous 12 months; OR per increase by 1 episode

[e] Within 7 days following index episode

ED, emergency department

Follow-up review with primary diabetes care provider Overall, 56.2% ($n = 284$) of participants attended a diabetes review appointment (involving a general practitioner, endocrinologist or diabetes educator) within 7 days of the episode or hospital discharge (where admission had occurred). Of those who attended a review, over half (52.1% [$n = 148$]) reported a change to their diabetes medication or management. Of those who did not attend an emergency department following EMS management of severe hypoglycaemia, approximately half (52.2% [$n = 131$]) attended a diabetes review appointment within 7 days. Overall, 23.8% ($n = 120$) did not attend an emergency department or a diabetes review appointment within 7 days following the episode. Non-attendance at an emergency department or a diabetes medical review within 7 days was not associated with the risk of recurrent severe hypoglycaemia within 3 months of initial episode (OR 1.55 [95% CI 0.84, 2.87], $p = 0.161$) (Table 4).

Discussion

This is the largest prospective study of short- and medium-term outcomes of people with diabetes following an episode of severe hypoglycaemia managed by prehospital EMS. Following an episode of severe hypoglycaemia, one-fifth of the participants required hospital admission predicted by advancing age, increasing number of comorbidities, injury associated with hypoglycaemia and unknown cause of hypoglycaemia. The median (IQR) length of hospital stay was 4 (2–7) days, increased in those with a history of type 2 diabetes or heart disease. Within 3 months of the index severe hypoglycaemia episode, 10% experienced another episode requiring EMS management, predicted by a lower HbA_{1c} and greater number of antecedent severe hypoglycaemia episodes.

Of note, many participants were able to recognise the major precipitant for their severe hypoglycaemia. The reasons provided were generally consistent with those described by other studies [16–18] with most participants reporting reduced food intake or increased insulin administration. However, about 30% were unsure of the cause, suggesting that some participants may have impaired awareness of hypoglycaemia or not have sufficient knowledge of precipitants or risk factors for hypoglycaemia. Accordingly, strategies to educate people on the prevention of hypoglycaemia are required to reduce future burden for EMS care.

Attempts to treat the hypoglycaemia prior to EMS arrival occurred in approximately 60% of the episodes, less than 6% involving use of glucagon. Where no treatment was attempted, a large proportion of participants reported this was due to an altered level of consciousness. In addition, hypoglycaemia was not recognised as such in a substantial proportion of conscious individuals. This suggests that targeted education to assist individuals with diabetes and their family with earlier recognition and treatment of symptoms as soon as they are feeling unwell, prior to loss of consciousness, as well as appropriate use of glucagon, may reduce the need for prehospital EMS care. Indeed, greater prescription and use of glucagon may be of particular benefit to those with impaired awareness of hypoglycaemia.

Following an episode of severe hypoglycaemia, over 40% of participants who attended an emergency department required hospital admission. This is within the wide range of admission rates reported in previous studies [5, 6, 19–21]. Predictors of hospital admission were older age, number of comorbidities, injury associated with severe hypoglycaemia and unknown cause of severe hypoglycaemia. Knowledge of these factors may be used by paramedics and emergency clinicians to risk-stratify individuals to identify those requiring hospital transfer and/or those most vulnerable to adverse outcomes.

The median (IQR) length of hospital stay was 4 (2–7) days and a diagnosis of heart disease or type 2 diabetes independently predicted longer length of hospital stay. These results are especially important in light of the increasing prevalence of both diseases in an ageing population. Education regarding hypoglycaemia avoidance especially for people with type 2 diabetes and/or heart disease must clearly be a high priority for health systems and may be of particular interest to those involved in diabetes education. Our analysis pointed to an increased length of hospital stay in those treated with sulfonylureas (7 days vs 4 days, $p = 0.083$). This is consistent with previous literature reporting that patients with sulfonylurea-related hypoglycaemia require a long hospital stay and are at risk of recurrent in-hospital hypoglycaemia and recurrent hospital admission [22] and supports the recommendations for admission of individuals with hypoglycaemia caused by a sulfonylurea drug [23].

Medical review with a diabetes care professional is recommended following an episode of severe hypoglycaemia, to allow examination of treatment targets, make necessary adjustments and improve understanding of precipitants [24]. Frequency of medical review following an episode of severe hypoglycaemia reported in the literature varies from 34% to 60% [4, 7, 9, 18, 25] and our finding (56.2%) is consistent with this. Of those who did not attend a medical review appointment (43.8% [$n = 221$]), about half ($n = 101$) had attended an emergency department and may have considered a separate medical review appointment unnecessary. Nonetheless, the 23.8% who did not attend an emergency department or a diabetes review appointment following the episode may be of concern. Severe hypoglycaemia requiring hospitalisation has previously been shown to be associated with increased mortality rate in older adults [26]. However, the authors of this paper and others [27, 28] point to hypoglycaemia being a marker of vulnerability to adverse events rather than it being a contributing factor. Thus, medical

review following an episode of severe hypoglycaemia is paramount and may be as important as preventative strategies. Although medical review following an episode of severe hypoglycaemia was not found to reduce future episodes in this study, it serves as an opportunity for a general health assessment with a focus on frailty, falls risk, polypharmacy and an opportunity to optimise the management of comorbidities and reassess blood glucose targets.

Previous studies [29, 30] have evaluated interventions following the use of EMS for severe hypoglycaemia. Individuals who remained at home following EMS treatment for hypoglycaemia were given an information leaflet [29] or prompt card [30] and were later contacted by phone for a follow-up medical appointment. Both studies reported high levels of patient satisfaction and confidence in the ability to prevent future episodes [29]. Where an appointment was offered, almost 80% of individuals attended the appointment [29]. Given the high proportion of individuals who did not have medical contact following an episode in the current study, future research could examine the feasibility of more proactive paramedic-led interventions in the local setting.

Over a 3 month follow-up, 10% of the participants in our study had at least one recurrent episode of severe hypoglycaemia; recurrence was more likely in those with a lower HbA_{1c} and a greater number of antecedent episodes. Our results are consistent with previous literature showing increased risk of hypoglycaemia in those with tightly controlled type 2 diabetes [31, 32] and those with prior episodes of hypoglycaemia [33, 34]. Our study further adds that these factors extend to the prehospital EMS setting and highlights the need for consideration of relaxed glucose targets and increased preventative measures, such as sensor technology, in those most vulnerable.

Our study is comparable with previous research [21] examining the use of emergency health services for severe hypoglycaemia in Tayside, Scotland. This study found that people who had an episode of severe hypoglycaemia requiring emergency treatment (including from prehospital emergency services, hospital emergency departments and primary care) were older, had a longer duration of diabetes and a higher HbA_{1c}, than those who did not. An association between lower socioeconomic status and increased incidence of emergency treatment for severe hypoglycaemia was also reported in the same study cohort [35]. Our study expands on this by examining factors associated with later hospital admission, length of stay and recurrence outcomes and finds similar themes, where admission is associated with older age and recurrence is associated with HbA_{1c}, but not socioeconomic status.

This is the first study to link prehospital EMS factors with later hospital outcomes and is strengthened by its large sample size and prospective design. Results are generalisable to other developed countries with extensive prehospital EMS systems. This study has some limitations. Our sample was largely a retired cohort, who were older and more likely to be treated with insulin, and this may affect the generalisability of results. Self-reported data are used in this study and may be subject to interpretation and memory. However, with regards to severe hypoglycaemia at least, self-reports are said to be reliable for up to 12 months [36]. Of the 2540 individuals eligible for the study, 20% ($n = 505$) participated. As this was a phone-based survey, and there were a large number of people for whom a telephone number was not provided on the electronic patient care record, this may have contributed to the resultant response rate.

Furthermore, it should be noted that only individuals who contacted prehospital EMS were examined in this study and those who attended hospital emergency departments directly were not included. Previous research suggests those who attend hospital emergency departments directly form a minority of those who require emergency assistance [21] and may form a distinct subgroup with a different profile.

Conclusion This large prospective study has identified common precipitants and prior management of severe hypoglycaemia, as well as studied the patient trajectory from transport to an emergency department, hospital admission and recurrent requirement of EMS in the following months. Our findings regarding poor recognition of precipitants and treatment of early warning signs of hypoglycaemia in some, will be of interest to those involved in diabetes education. Following management by EMS, approximately 20% of participants required hospital admission, for a median (IQR) of 4 (2–7) days, predicted by older age, greater number of comorbidities, injury sustained with severe hypoglycaemia and unknown cause of severe hypoglycaemia. These data serve to inform EMS clinicians, attending at the scene, of those most vulnerable and may assist in transport decision. Furthermore, the finding that almost one-quarter of participants did not attend an emergency department or a diabetes review appointment is of concern and investigation of strategies to increase the rate of medical follow-up are warranted. Finally, those with lower HbA_{1c} and increased number of antecedent episodes of severe hypoglycaemia were at greatest risk of a recurrent episode requiring EMS, and this finding supports interventions such as education and use of sensor technology to improve patient safety. The results of this study will assist those caring for people at risk of hypoglycaemia to promote increased vigilance and awareness of strategies aimed at reducing this life-threatening but preventable diabetic complication.

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Data availability The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

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