

## Accepted Manuscript

A new integrated care pathway for Ambulance attended severe hypoglycaemia in the East of England: the Eastern Academic Health Science Network (EAHSN) model

Michael Sampson, Marcus Bailey, John Clark, Mark L Evans, Rebekah Fong, Helen Hall, Clare Hambling, Martin Hadley–Brown, Nick Morrish, Helen Murphy, Gerry A Rayman, Karunakaran Vithian, Peter Winocour, Amanda Harries

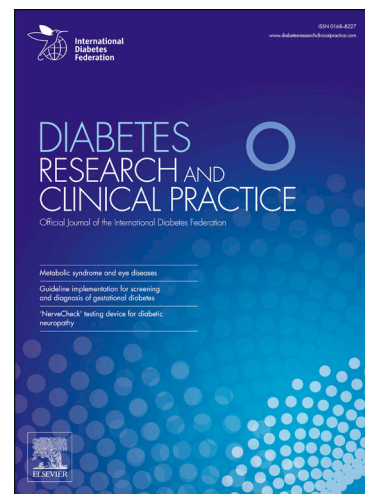
PII: S0168-8227(17)31166-X  
DOI: <http://dx.doi.org/10.1016/j.diabres.2017.08.017>  
Reference: DIAB 7064

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 18 July 2017  
Revised Date: 14 August 2017  
Accepted Date: 22 August 2017

Please cite this article as: M. Sampson, M. Bailey, J. Clark, M.L. Evans, R. Fong, H. Hall, C. Hambling, M. Hadley–Brown, N. Morrish, H. Murphy, G.A. Rayman, K. Vithian, P. Winocour, A. Harries, A new integrated care pathway for Ambulance attended severe hypoglycaemia in the East of England: the Eastern Academic Health Science Network (EAHSN) model, *Diabetes Research and Clinical Practice* (2017), doi: <http://dx.doi.org/10.1016/j.diabres.2017.08.017>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**Michael Sampson<sup>a</sup>, Marcus Bailey<sup>b</sup>, John Clark<sup>c</sup>, Mark L Evans<sup>d</sup>, Rebekah Fong<sup>e</sup>  
Helen Hall<sup>b</sup>, Clare Hambling<sup>f</sup>, Martin Hadley – Brown<sup>g</sup>, Nick Morrish<sup>h</sup>, Helen Murphy<sup>a</sup>  
Gerry A Rayman<sup>i</sup>, Karunakaran Vithian<sup>j</sup>, Peter Winocour<sup>k</sup>, Amanda Harries<sup>a</sup>**

<sup>a</sup> Department of Diabetes and Endocrinology, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK. mike.sampson@nnuh.nhs.uk

<sup>b</sup> East of England Ambulance Trust, Melbourn, UK. marcus.bailey@eastamb.nhs.uk

<sup>c</sup> Department of Diabetes and Endocrinology, West Suffolk Hospital NHS Trust, Bury St. Edmunds, UK. John.Clark@wsh.nhs.uk

<sup>d</sup> Institute of Metabolic Science, University of Cambridge, Cambridge, UK. mle24@cam.ac.uk

<sup>e</sup> Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, UK. R.Fong-Soe-Khioe@uea.ac.uk

<sup>f</sup> Bridge Street Surgery, Downham Market, UK. c.hambling@nhs.net

<sup>g</sup> School Lane Surgery, Thetford, UK. mh@nhs.net

<sup>h</sup> Department of Diabetes and Endocrinology, Bedford Hospital NHS Trust, Bedford, UK.

Nick.Morrish@bedfordhospital.nhs.uk

<sup>a</sup> Department Diabetes and Endocrinology, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK. Helen.murphy@nnuh.nhs.uk

<sup>i</sup> The Ipswich Diabetes Centre, Ipswich General Hospital NHS Trust, Ipswich, UK.

gerry.rayman@ipswichhospital.nhs.uk

<sup>j</sup> Colchester Hospital NHS Trust, Colchester, UK. Karunakaran.Vithian@colchesterhospital.nhs.uk

<sup>k</sup> ENHIDE, East and North Hertfordshire NHS Trust, Herts, UK. peter.winocour@nhs.net

**Correspondence to:** Professor Mike Sampson, Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich, NR4 7UY 0044 (0)1603 287094.  
mike.sampson@nnuh.nhs.uk

**ABSTRACT**

**Aims** We developed a new clinical integrated pathway linking a regional Ambulance Trust with a severe hypoglycaemia (SH) prevention team. We present clinical data from the first 2,000 emergency calls taken through this new clinical pathway in the East of England.

**Methods** SH patients attended by Ambulance crew receive written information on SH avoidance, and are contacted for further education through a new regional SH prevention team. All patients are contacted unless they actively decline.

**Results** Median age (IQR) was 67 (50 - 80) years, 23.6% of calls were for patients over 80 years old, and patients more than 90 years old were more common than 20 - 25 year olds in this population. Most calls were for patients (84.9%) who were insulin treated, even those over 80 years (75%). One - third of patients attended after a call were unconscious on attendance. 5.6% of patients in this call population had 3 or more ambulance call outs, and they generated 17.6% of all calls. In total, 728 episodes (36.4%) were repeat calls. Insulin related events were clinically more severe than oral hypoglycaemic related events. Patients conveyed to hospitals (13.8%) were significantly older, with poorer recovery in biochemical hypoglycaemia after ambulance crew attendance. Only 19 (1 %) opted out of further contact. Patients were contacted by the SH prevention team after a median 3 (0 - 6) days. The most common patient self - reported cause for their SH episode was related to perceived errors in insulin management (31.4%).

**Conclusions** This new clinical service is simple, acceptable to patients, and a translatable model for prevention of recurrent SH in this largely elderly insulin treated SH population.

**Key words** Severe Hypoglycaemia  
Ambulance  
Diabetes  
Insulin  
Emergency

**1 INTRODUCTION.** Severe hypoglycaemia (SH), defined as an episode severe enough to require external assistance in treatment and recovery, is a frequent and distressing experience for people with diabetes, and is due to insulin therapy or to some oral hypoglycaemics [1,2]. The significant direct and indirect costs related to ambulance attendance, hospital transfers and admissions, and lost productivity due to SH, are well described [2 – 4]. The impact of SH on quality of life, the fear of hypoglycaemia, and a determination to avoid SH often influences efforts to reach reasonable glycaemic targets [5, 6].

More than 90% of the UK diabetes population have Type 2 diabetes, and recent large meta-analysis of hypoglycaemia outcomes in Type 2 diabetes [7], estimated that insulin treated Type 2 diabetes patients experience a mean of 1.05 (95% CI 0.0 – 3.69) SH episodes per annum. The equivalent data for sulphonylurea treated patients and SH was 0.01 (95% CI 0 to 0.55). Elderly patients with insulin treated Type 2 diabetes and co-morbidities such as cognitive impairment, dementia, or renal impairment are more likely to experience SH [8 -10], and have higher mortality and morbidity following SH [11, 12]. Robust glycaemic targets in diabetes management guidelines, or in UK primary care diabetes quality frameworks, do not give enough weight to the risk of SH in the frail elderly, or promote clinically sensible targets relevant to the frail elderly [13, 14].

Ambulance Trusts are the main provider in the UK of first contact emergency medical services for people experiencing SH, and may be attending up to 100,000 emergency calls for SH episodes per annum [15]. Effective management of SH is one of the key performance indicators for UK Ambulance Trusts (16) and they operate effective ‘see and treat’ policies for SH, where Ambulance Crew manage the episode at the scene, with few patients carried onwards to a local emergency department or admitted [17,18]. The weakness of this model is that SH patients managed successfully by Ambulance Crew do not then receive any additional education triggered by the SH event, and the patient’s normal primary or secondary care diabetes team often remain unaware of these episodes. In one large UK population more than half of ambulance attended SH patients either declined further treatment or were only advised to seek further advice at their discretion [18]. This is important, as many patients with SH make multiple calls about SH to emergency services, describe multiple previous SH episodes, and have had little advice or education on SH avoidance. The risk of further SH episodes can be reduced with enhanced diabetes education and support [1, 2, 8, 17 – 19]. Many patients are also

reluctant to identify themselves as having had an SH episode, as they understand the risk to then holding a driving licence [6].

We developed a regional integrated SH management team for a population of 4.4 million in the East of England based around a single point of contact (SPOC) model between Ambulance Trust and primary and secondary care, with an associated mass SH education programme for patients and health care teams. We describe this model, and the first 2,000 SH episodes we have taken through this pathway.

**2 METHODS** The East of England Ambulance Trust (EEAAT; [www.eastamb.nhs.uk](http://www.eastamb.nhs.uk)) provides emergency services to a population of 5.8 million in the East of England. The Ambulance service covers an area of 7,500 square miles, supports 17 Acute Trusts and 19 primary care Clinical Commissioning Groups (CCG) covering the counties of Norfolk, Suffolk, Cambridgeshire, Bedfordshire, Hertfordshire, and Essex. The Eastern Academic Health Science network (EAHSN; [www.eahsn.org](http://www.eahsn.org)) is one of 15 academic health science networks in England, established by NHS England in 2013 to spread innovative services at scale and pace and connect academic and NHS organisations and local authorities to improve outcomes, and variance in outcomes, for patients. The EAHSN covers a population of 4.45 million within the EEAAT area, with an estimated 271,000 people, and an average adult diabetes prevalence of 6.1% [20]. In 2014, before the current programme commenced, this Ambulance Trust recorded 9,374 emergency calls to people with a primary diagnosis of diabetes, overwhelmingly due to severe hypoglycaemia, an estimated 80% being SH; as elsewhere in the UK, there was no structured pathway to provide further care for these patients, or to identify causes of SH, or to link these recorded incidents with the patients existing primary or secondary care team. We developed a regional collaborative group of diabetes specialists from primary and secondary care, and secured significant funding from the EAHSN to develop a new pathway with the East of England Ambulance Trust to improve outcomes for SH patients. We developed a single point of contact model (SPOC) where Ambulance Crew attending an SH emergency, call through the patient details to the SPOC office after appropriate SH treatment. Attending Ambulance Crew also give every attended patient written information on SH avoidance, causes of SH and driving license implications (see supplementary material A and [www.eahsn.org](http://www.eahsn.org)); the model we developed is an 'opt out' model, where patients with SH have to actively *opt out* of further contact from

ACCEPTED MANUSCRIPT

educators by calling SPOC within 3 working days, and all patients are given this number. We then appointed and trained 12 part time clinical educators and project managers across the East of England, based in large Acute Trusts, to service this workload. The patients details are called through to SPOC, and after 3 days these clinical details are passed to the relevant project managers in that area. These project managers or EAHSN educators then contact the patient to arrange further education and SH advice and support, given either directly in a one to one consultation, or by phone, or arranged through patients normal care team in primary or specialist care. In all areas, the intervention was standardised, but the method of delivery was adapted to local service models. We also undertook a mass education programme for all of the 2,800 Ambulance Crew in the EAHSN area, invited and arranged access for all 458 GP practices to online education on SH through the Cambridge Diabetes education programme ([www.cdep.org](http://www.cdep.org)), and developed a model where all pharmacies in the East of England gave a standardised written leaflet on SH to patients collecting an insulin or oral hypoglycaemic prescription (see supplementary material B and [www.eahsn.org](http://www.eahsn.org)).

This programme was not developed as a research programme, but as a new clinical service model in the East of England. The data in this paper are summary outcomes data from this clinical service, and all data analysis was undertaken on anonymised summary data, and analysis of routine clinical service data did not require research ethical approval. Patient clinical consent to refer to this new clinical service is gained by the crew at the time of referral, and patients can opt out of further clinical contact within 3 working days using a contact telephone number in the provided hypoglycaemia avoidance leaflet. Patient data is passed over a confidential and secure nhs.net pathway after 3 working days to the appropriate locality team for further contact. The data in this service was collected in real time prospectively after programme launch, with a pre specified decision to analyse clinical outcome data from the first consecutive 2,000 calls received through SPOC within the EAHSN area.

The EAHSN education programme has developed rapidly, and more than 50% of ambulance crew are now referring into this programme. However, during the development of this programme it would have been possible for a patient to have an Ambulance attended SH episode without referral to the programme, making accurate estimates of any overall population level intervention effect difficult.

Patients attended by Ambulance crew were defined as unconscious (and analysed in this paper as unconscious) by crew if they met the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) criteria

ACCEPTED MANUSCRIPT

derived from the Glasgow Coma Scale for coma or impaired consciousness [21]. The JRCALC (21) guidelines are used by the EEAAT crew to determine the treatment pathway of SH, and the definition of SH, and for transferring the patient to an Acute Hospital. These criteria [21] include transferring patients who have had a similar SH episode in the previous 48 hours, and patients who have not returned to a normal mental status within 10 minutes of intravenous glucose.

In this analysis, blood glucose data is derived from a capillary blood glucose test undertaken by Ambulance crew before treatment and after treatment as part of routine clinical care. The after treatment blood glucose measurement is taken by Ambulance crew at a time that depends on the intervention and speed of recovery, but JRCALC guidelines [21] suggest reassessment after 10 minutes and Ambulance crew would not normally leave a patient at home unless capillary blood glucose is recorded as  $> 5.0$  mmol/L. Basic clinical data (such as medication use and self - reported previous SH episodes) are collected from the patient by crew after recovery, although more detailed data (type of medication , duration of diabetes, or if patient had Type 1 or insulin treated Type 2 diabetes for example) are not collected in this acute situation. .Data is shown as mean (one standard deviation), or median and ( interquartile range). Comparisons between group variables were assessed by unpaired t test or Wilcoxon signed - rank test as appropriate.

### 3 RESULTS

**3.1 Baseline data** (Table 1). The first 2,000 calls in the EAHSN area were generated between 1.12.14 and 15.4.16 and referral activity into the programme is currently a mean of 62 per week across the East of England (March 2016). Of these 2,000 calls, only 19 (1%) declined further contact. SH attended patients either self - identified themselves as being under the care of their GP for diabetes management (1131; 56.6%) or under a local secondary care team (769; 38.5%) or were unsure (100; 5.0%).

The median age of this call population ( $n = 2,000$ ) was 67 years (interquartile range IQR 50 - 80), with 472 calls (23.6%) from people over 80 years old; there were more callers aged  $> 90$  yrs ( $n = 77$ ) vs than those aged 20 – 25 years old. The overwhelming majority of these 2,000 calls were from people treated with insulin (1,697; 84.9%), rather than with oral agents (251; 12.6%); a small number of calls (52; 2.6%) were from people with SH who were unaware if they were receiving oral hypoglycaemics.



Overall one - third of callers were unconscious, or had reduced consciousness, on attendance, one - half had a glucose level < 2.5 mmol/L when attended by crew, and about one - half needed parenteral therapy (intramuscular glucagon or intravenous glucose). In addition, about one – third of callers described having had a similar SH episode in the previous month that needed third party assistance, including previous ambulance attendances in the previous month (Table 1) The Ambulance service was highly effective at treating these 2,000 SH calls with only 276 (13.8%) requiring transfer to an Acute Hospital, and when the Ambulance Crew left the scene, nearly all subjects (1,933; 96.7%) had a capillary blood glucose (CBG) measured by Ambulance crew of > 4 mmol/L, with median CBG of 6.4 mmol/L (5.4 – 8.1).

**3.2 Treatment category by age band** (Table 2). Nearly all SH episodes in callers under 70 years old (n = 1,094) were insulin treated (n = 997; 91.1 %), and even for callers over 80 years old (n = 472), most (n = 354; 75%) were insulin treated (Table 2). The data collected by Ambulance Crew do not distinguish between those with Type 1 diabetes, with insulin treated Type 2 diabetes, or those receiving combined insulin and oral hypoglycaemics.

**3.3 Group differences by treatment category, age band, and transfer to Acute Hospital** (Tables 3 - 5). The insulin treated SH callers (n = 1,697) had significantly more severe clinical hypoglycaemia than the oral hypoglycaemic treated SH group, that is they were almost twice as likely to be unconscious on attendance, to need intramuscular glucagon, and have a significantly more severe biochemical hypoglycaemia (Table 3). Despite this, they responded to Ambulance crew treatment as well as those on oral hypoglycaemic agents, and this younger group were then significantly *less* likely to be transferred to an Acute Hospital than the older group treated with oral agents (Table 3). The younger predominantly insulin treated group (under 70 years) were also significantly more likely to be unconscious on attendance and to have a more severe clinical and biochemical SH episode (Table 4). Most of these calls were managed successfully by Ambulance crew at the scene, with only 276 (13.8 %) callers transferred by crew to an Acute Hospital for further treatment. The callers who were transferred to an Acute Hospital did not differ from those not transferred in initial median blood glucose or frequency of glucose < 2.5 mmol/L (Table 5), but were significantly older, with higher rates of unconsciousness and glucagon requirements, and had responded less well to therapy at the scene in terms of hypoglycaemia recovery (Table 5).



Of these 2,000 calls, 700 (35%) self - reported at the time of crew attendance that they had had a similar SH episode in the previous month. These subjects with a self - reported SH episode were significantly more likely to be insulin treated, to be unconscious and to have more severe hypoglycaemia when attended by Ambulance crew than those without any antecedent self - reported episode in the previous month. In addition, 372(18.6%) callers self - reported at the time of crew attendance that they had both a similar SH episode in the previous month, and an ambulance call out in the previous month - this group (Table 7) were particularly high risk with 36.8 % unconscious on attendance and 60.8 % having a glucose on attendance of < 2.5 mmol/L. These 2,000 calls were generated by 1,546 individuals, of whom 1,272 (82.3%) made only one call. There were 728 calls (36.4%) made by 275 individuals (17.7%) who called more than once in this time period. In addition, 87 individuals (5.6 %) made > 3 calls during this time period, and accounted for 352 of all calls (17.6%).

### **3.5 Clinical education and contact with SH callers.**

All 2,000 SH calls led to contact by the education team, and 1442 (72.1%) then had direct face to face or telephone contact education on SH management and avoidance, largely delivered by the dedicated team of educators working in primary care. The median time between SPOC contact in the Ambulance Trust and the education team being made aware was 1 (0 – 4) days, between the team being informed and first contact with the caller was 3 days (0 – 6 days), and median time between SPOC referral and educational contact was 5 (1 - 11) days.

Of the 2,000 calls, 558 (27.9%) callers had no *immediate* direct contact by the education team, as they missed an initial education appointment (111; 5.6%), declined an appointment (36; 1.8%), had died (21; 1.2 %), were in hospital (8 ; 0.4%), or were waiting for an appointment (27 ; 1.4%). In addition, a further 238 (11.9%) did not respond to contact, although in all these subjects (and all those who missed appointments) the usual primary care or specialist team were made aware of the SH episode and Ambulance contact, and the need for further clinical input.

### **3.6 Crew, GP and Pharmacy education**

There are an estimated 2,800 ambulance crew and paramedics in EAAAT ([www.eastamb.nhs.uk](http://www.eastamb.nhs.uk)). Between 1.12.14 and 15.4.16, 1,214 (43.3%) of all crew in the EAHSN area attended 6 large regional events, 35 Ambulance station events, or received e - mail correspondence and materials on the pathway and relevant updates. These events were to highlight the causes, prevention and future care of SH patients, and to introduce the pathway. As of 15.4.16, 1200 (41%) crew had referred at least one SH patient. Of the 458 GP practices in the EAHSN area, 174 practices had one staff member complete online training in SH management and avoidance. Lastly, all 742 community pharmacies in the EAHSN area have been given SH avoidance leaflets to distribute to all patients receiving an insulin or SH prescription and 75,000 of these leaflets have been printed. During education sessions, we undertook a structured survey to collect the views of participants on the causes of their SH episode. In total, 1051 patients, gave one or more reasons (n = 1,771 total ) for the emergency Ambulance SH contact, the commonest being insulin dose error or related to current insulin usage (556; 31.4%), missed or delayed meals (297 ; 16.8%), intercurrent illness (199; 11.2%), hypoglycaemia unawareness (189 ; 10.7%), or 'too few carbohydrates' (169 ; 9.5%). Exercise, excess alcohol, or problems with injection techniques each were each reported by approximately 5% of all patients.as causes of SH.

#### **4 DISCUSSION**

The clinical and health economic impacts of severe hypoglycaemia (SH) are well described [1, 2, 19]. In the UK, most emergency clinical contact for SH is managed by Ambulance crew attending after a 999 emergency call(16). However, there is no systematic whole system pathway in a large population for the further management of these ambulance attended SH patients that links ambulance crew with primary care or specialist diabetes services, or which undertakes a mass education programme of SH patients and health care professionals. The current model provides an integrated service for a population of 4.4 million and a diabetes population of 271,000 based around a single point of contact (SPOC) model, with SH patients having to actively opt out of further contact, and with linkage to further education and support from the patients usual diabetes team, or from programme educators. An important element of this programme is that patients with a

SH episode were given 3 working days to opt out of further contact, but only 1% chose to, and the model of guaranteed further clinical contact after an SH event is acceptable to the great majority of patients.

One of the most obvious features of this SH population is the age distribution, with 23.6 % of callers over 80 years and 43.8 % over 70 years old. Other SH population studies have described similar age distributions in the UK and Europe [3,8,11, 22], but it is striking that there are more people over 90 years old having SH events than 20 – 25 year olds in our population. The SH events in the elderly were largely associated with insulin use and this clearly raises questions about glycaemic targets and therapy in this older population. In the UK general practices have operated under a performance management and reimbursement scheme called the Quality and Outcomes Framework (QOF) since 2004, with various achievement thresholds at a practice level set at HbA1c targets of 59, 64, or 75 mmol/mol [23]. There is limited evidence of benefit for frail very elderly patients with diabetes managed within this framework for these glycaemic targets, and a strong evidence base for immediate harm with robust glycaemic targets in this population [8 – 12, 14]. The very high risk of SH in elderly patients with multiple comorbidities, cognitive impairment, and high frailty scores in primary care is increasingly well recognised [24], along with a recognition of the need for more sensible tailored glycaemic targets in these patients [13,14].

In UK populations, ambulance attended and community based populations with SH have had a median plasma glucose of 2.3 (IQR 1.7 – 3.4) mmol/L (18), or 1.85 (IQR 0.72) mmol/L (11), which are broadly similar to the data in the current larger population. Ambulance Crew 'see and treat' policies appear to be an effective model for the treatment of an acute event, with the majority (96.7 %) in this series having a blood glucose of > 4 mmol/L when crew departed, and a median blood glucose of 6.4mmol/L. This model also appears to be effective at limiting the number of SH patients conveyed onwards to local emergency departments. Only 13.8 % of Ambulance attended patients were conveyed onwards, and this group were significantly older, more likely to be unconscious, and to live alone which suggest some of the clinical triggers for conveyance to further emergency care. The conveyed patients were not significantly different from those managed by crew alone in terms of initial median blood glucose levels, but responded significantly less well to treatment when the decision was taken to transfer. In the East of England, there was however a wide variance between clinical commissioning group (CGG) areas in rates of transfer (range 9 – 22%) to local Emergency Departments. This

may reflect geographical differences in skill mix among Ambulance crew, distance from local Emergency Departments (and therefore Ambulance turnaround times), and the views of Ambulance crew on pressures in local Emergency Depts. The conveyance rate to Emergency Department in this series (13.8 %) is relatively low in relation to the majority of Ambulance attended European and UK SH populations, where transportation rates have been recorded as 21% [3], 27 % [17], and 35.3% [18], although closer to more recent UK populations at 7 % (11). This low rate may be an underestimate, and may reflect a tendency in Ambulance crew conveying patients to emergency hospital care not to pass patient details through to the SPOC pathway. Recent analysis of hospital admissions for severe hypoglycaemia [25] in England based on Hospital Episode Statistics (HES) data suggested a decline in admission rates for SH between 2011 and 2014 adjusted for diabetes prevalence. Ambulance transport rates to emergency departments must be a key factor in admission rates, but it is unknown if the decline in SH admissions [26] reflects enhanced Ambulance crew performance and lower transport rates. The current data adds to literature on the safety of Ambulance crew provided 'see and treat' policies in the UK [16-18] with 96.7% of all attended episodes having a capillary blood glucose > 4mmol/l before crew left the patient.

About one - third of callers self - reported to crew that they had experienced a 'similar severe episode in the previous month' although not all of these episodes were managed by Ambulance crew. These self - reported recurring SH patients had significantly more severe hypoglycaemia clinically and biochemically, and were more likely to be insulin treated. As well as self - reported antecedent SH in the previous month, 36.4 % of the calls in this pathway were made by people who made multiple calls to ambulance crew, with a small minority generating a large number of calls (> 3 each) accounting for nearly 18% of all calls, In other SH populations 31% [3], 37 % [11], or 12.7 % [18] of emergency SH ambulance contacts have been generated by repeat calls from the same patient(s), often relatively soon after the initial call, and up to 11% of patients have a further episode within 14 days [27]. These data suggest that while UK Ambulance Crew 'see and treat' policies are highly effective at treating individual SH events, and at keeping patients at home following SH treatment, they are treating and identifying a population with very high rates of recurrent SH events and repeat contact with emergency services. This is important, as simple modelling based on ambulance call out rates in the UK and the prevalence of SH calls, suggests there are between 48,400 and 98,736 SH Ambulance call outs per annum [15,27] in the UK, and the scale of this activity has been apparent for some time (15). If we

assume that perhaps one - third of these calls are from repeat callers [3,11], then there are perhaps up to 33,000 Ambulance SH calls per annum generated by repeat callers.

As far as we are aware, the programme we describe here is the first published large at scale attempt to link Ambulance SH events with enhanced structured education and support on SH avoidance from primary and secondary diabetes teams for all emergency SH patients, linked to a mass patient and healthcare education programme [28]. The majority of patients experiencing a SH episode attended by Ambulance Crew in the UK do not have evidence of further contact with primary or secondary care diabetes services [18,27]. Many SH patients feel they have had only limited education in hypoglycaemia avoidance and management [1] and the lack of further education and support means patients do not have an opportunity to have an individualised glycaemic target reviewed (29), or access education and advice on hypoglycaemia avoidance [1,2,29 – 31]. There may also be reluctance on the part of patients to let their normal diabetes team know about SH events, in case they feel clinical teams will be critical, or that it may effect holding a driving license [6]. Patients may under report SH episodes because of this risk, and people who under report in this way are more likely to have further SH episodes [6].

This programme covers a population of 4.4 million with an estimated 271,000 people with diabetes, and the total recurring salary and operational costs for the clinical programme is an estimated £190,114 per annum for 9 hospitals and 10 primary care clinical commissioning group areas. An upper cost for 'see and treat' SH in these data is £159, for an SH patient carried on to an Acute Hospital is reported at £314 (without admission), and health economic modelling of indirect costs of SH on lost productivity has been estimated at £60 per episode [32]. These estimates suggest a total tariff cost incurred by this activity (Table 1) of £359,722 just with the first 2,000 cases in this pathway, of which £125,902 was generated by patients who made repeat calls. In 2014, the EEAAT made 9,374 attendances with 'diabetes emergency' as a primary cause of call in an area of 5.8 million, and adjusting for the smaller EAHSN population (4.4 million), and an estimated 80% of these calls being SH) suggests an estimated 5,753 SH call outs per annum in the EAHSN area, at an estimated tariff cost in total of £1.035 million per annum. To generate tariff savings to cover all the salary and operational costs of this network of educators and project managers would require a 20.3 % reduction in overall SH call rates. Further analysis of outcome data at a population level is required to demonstrate cost

efficacy. It should be noted that the current cost of this programme does not include modelling for the costs and time of Ambulance crew and primary care staff to attend SH training.

There are weaknesses in the current analysis, which reflect the fact that this large regional programme only started on 1.1.15, that different areas within the region entered the programme at different points early in 2015, and that not all SH calls are yet referred into the pathway. We estimate in the last year that we have contacted all Ambulance crew, that about one - half have attended face to face training days, and all relevant crew received the educational materials, and are now actively referring. This would be concordant with current mean referral rates of 62 per week (projected 3,224 per annum), with an estimated potential maximum 5,573 SH calls per annum and while referrals and referring teams are increasing, this could clearly contribute to sample bias. In addition, it is possible that there is a bias in referral to the SPOC pathway, with less referral of those seen as 'less severe' in terms of social circumstances, treatment and SH severity by Ambulance crew, and that we are managing the 'more severe' or highest risk cases referred by Ambulance Crew. There are also some weaknesses in the education programme we offered. Firstly, the education in SH prevention was largely directed at the patients, and in this frail elderly population a wider approach to include carers and family members might be more suitable. Secondly, the education programme for SH patients could perhaps have been stratified by risk of further SH, and offered more intense support and follow up for those with 2 or more episodes. Lastly, we feel that current pressures on primary care staff may have limited uptake to the online education programme in SH avoidance that we offered.

This paper describes the first year of a new integrated SH pathway, and there remains significant work to be done on developing evidence of improved outcomes and sustainability in terms of improved patient satisfaction, reduced SH risk, reduced SH impact on Ambulance call outs and Emergency Departments, and linkage with other diabetes process measures through NHS number and database linkage. However, the model has strong patient acceptability with low opt out rates and effective management of SH is a UK Ambulance Trust priority (16). There is a need to undertake significant population level analysis of these data over the next few years to examine the impact of this programme on age and diabetes population adjusted SH rates in the intervention areas, and benchmark this against national SH data and SH rates in areas without this model. This paper adds to the growing literature on the adverse impact of SH in a largely elderly insulin

ACCEPTED MANUSCRIPT

treated diabetes population, highlights the high rate of repeat calls for SH episodes, and describes a new, effective, and translatable model linking the emergency SH event attended by Ambulance crew, with an SH treatment and prevention team in a population of 4 million.

### **Permissions and funding**

The programme was funded by the Eastern Academic Health Science Network (EAHSN) who played no part in the collection, analysis, or in the publication of these data, or in the writing of this manuscript.

### **COI**

There are no conflicts of interest in this work or in the submission of this manuscript from the authorship group.

### **Acknowledgements**

We are grateful to Professor David Simmons and Sister Candice Ward (both Addenbrookes Hospital, Cambridge) for their help with this programme start up and with the Cambridge Diabetes Education Programme. We are grateful to Jim Bibby and Carol Roberts (both EAHSN) for their help with this programme, and grateful also to the crew and staff of the East of England Ambulance Trust. We would like to thank the EAHSN educators and project managers who have worked on this programme (Heidi Cobb, Angela Young, Lynn Dorsett, Helen Swarbrick, Jenni Curtis, Karen Moore - Haines, Sarah Woodley, Emma Page, Sadie Cooper, Anne Scott Deborah Hughes, Alice Rowley Lisa Newdick, Angela Young, and Emma Birbeck), and all the Ambulance Crew in the East of England Ambulance Trust for their support.

### **Submission declaration and verification**

This work described has not been published previously is not under consideration for publication elsewhere, that its publication is approved by all authors, who have read and approved the final version of this manuscript, and explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be



published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. Each author declares their individual contribution to the article and all authors materially participated in the research, in the development of this service, and in article preparation and approval. All authors have approved the final article.

## References

- 1 Frier B.M. (2014). Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat. Rev. Endocrinol.*, **10**, 711 – 22.
- 2 Heller, S., Amiel, S., Khunti, K. (2015). Hypoglycaemia, a global cause for concern. *Diabetes Res. Clin. Pract.* , **110**, 229 – 32.
- 3 Barranco R.J., Gomez – Peralta, F., Abreu, C. et al. (2015). Incidence and care related costs of severe hypoglycaemia requiring emergency treatment in Andalusia (Spain) : the PAUEPAD project. *Diabet Med* , **32** ,1520 – 26.
- 4 Parekh, W.A., Ashley, D., Chubb, B., Gillies, H., Evans, M. (2015) Approach to assessing the economic impact of insulin related hypoglycaemia using the novel Local Impact of Hypoglycaemia Tool. *Diabetic Med* , **32**, 1156 – 66.
- 5 Evans, M., Khunti, K., Mamdani, M. et al. (2013) Health related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade off survey in 5 countries. *Health Qual. Life Outcomes*, **11**, 90.
- 6 Domgaard M, Bagger M, Rhee NR, Burton CM, Thorsteinsson B. (2015) Individual and societal consequences of hypoglycaemia: a cross - sectional survey. *Postgrad Med* 2015; **127**: 438 - 45
- 7 Edridge, C.L., Dunkley, A.J., Bodicoat, D.H. et al. (2015) Prevalence and incidence of hypoglycaemia in 532,542 people with Type 2 diabetes on oral therapies and insulin.: A systematic review and meta analysis of population based studies. *PLoS One*, Jun 10;10(6):e0126427. doi: 10.1371.

- 8 Prinz, N., Stingl, J., Dapp, A. et al. (2016) High rate of hypoglycaemia in 6770 diabetes patients with comorbid dementia : a multicenter cohort study on 215,832 patients from the German /Austrian diabetes registry. *Diabetes Research and Clinical Practice* , 112, 73-81.
- 9 Davis, T.M.E., Brown, S.G.A., Jacobs, I.G., Bulsara, M., Bruce. D.G., Davis, W.A. (2010). Determinants of severe hypoglycaemia complicating Type 2 diabetes: The Fremantle Diabetes Study. *J Clin. Endocrin. Metab*, **95**, 2240 – 47.
- 10 Bruce, D.G., Davis, W.A., Casey, G.P., et al. (2009). Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. *Diabetologia* , 52, 1808 – 15.
- 11 Elwen, F.R., Huskinson A, Clapham L et al. (2015). An observational study of patient characteristics and mortality following hypoglycaemia in the community. *BMJ Open Diabetes Res Care* 2015; 3(1):e000094. doi: 10.1136/bmjdr-2015-000094.
- 12 Lu, C., Hsu, P., Shen, H., Chang, Y., Chen, H., Li, C. (2015). Association between history of severe hypoglycaemia and risk of falls in younger and older patients with diabetes. *Medicine*, 94:1 – 5.
- 13 International Diabetes Federation. Global Guideline: Managing Older People with Type 2 Diabetes [Internet]. Brussels: IDF; 2013. Available from: <http://www.idf.org/sites/default/files/IDF-Guideline-for-older-people-T2D.pdf>
- 14 Rodriguez – Gutierrez, R., Lipska, K.J., McCoy, R.G. et al. (2016). Hypoglycaemia as an indicator of good diabetes care. *BMJ* , 352, i1084. doi: 10.1136/bmj.i1084.
- 15 Joint British Diabetes Societies for Inpatient Care. Admissions avoidance and diabetes: guidance for clinical commissioning groups and clinical teams. [www.diabetologists-abcd.org.uk/JBDS-IP-admissions-avoidance-diabetes.pdf](http://www.diabetologists-abcd.org.uk/JBDS-IP-admissions-avoidance-diabetes.pdf). Accessed June 2016
- 16 Siriwardena, A.N., Shaw, D., Donohoe, R., Black, S., Stephenson, (2010). *J Emerg Med*, 27, 317 –31.
- 17 Brackenridge, A., Wallbank, H., Lawrenson, R.A., Russell – Jones, D. (2006). Emergency management of diabetes and hypoglycaemia. *Emerg. Med J* , 23m 183 - 85
- 18 Farmer, A.J., Brookbank, K.J., Keech, M.L., England, E.J., Deakin, C.D. (2012). Incidence and costs of severe hypoglycaemia requiring attendance by the emergency medical services in South Central England. *Diabet. Med* , 29,1447 – 50.

- 19 International Hypoglycaemia Study Group. (2015). Minimizing Hypoglycaemia in Diabetes. *Diabetes Care* , 38, 1583 – 91.
- 20 Diabetes Prevalence. Public Health England Diabetes prevalence <https://fingertips.phe.org.uk/diabetes> (2015). Last accessed 30<sup>th</sup> November 2016
- 21 Joint Royal Colleges Ambulance Liaison Committee (JRCALC 2016) <http://www.jrcalc.org.uk/guidelines/> Last accessed 30<sup>th</sup> November 2016
- 22 Leese, G.P., Wang, J., Broomhall, J. et al. (2003). Frequency of severe hypoglycaemia requiring emergency treatment in Type 1 and Type 2 diabetes. *Diabetes Care* , 26, 1176 -80.
- 23 Summary of QOF Indicators – Gov.uk. [www.gov.uk/government/uploads/system/. Summary of QOF indicators.pdf](http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/41216/summary_of_qof_indicators.pdf). Last accessed 4.12.16
- 24 Hambling, C.E., Seidu, S., Khunti, K. (2013) Elderly people with Type 2 diabetes and dementia are managed to similar glycaemic targets as those without dementia. *Diab Med* , Abstract P364.
- 25 Zaccardi, F., Davies, M., Dhalwani, N.N. et al. (2016). Trends in hospital admissions for hypoglycaemia in England: a retrospective, observational study. *Lancet* , Online 09 June 2016; doi: 10.1016/S2213-8587(16)30091-2.
- 26 Fitzpatrick D, Duncan EAS. Hypoglycaemic emergencies attended by the Scottish Ambulance service : a multiple methods investigation. PhD thesis. University of Stirling (2015) <http://hdl.handle.net/1893/21854>(last accessed 19.3.16).
- 27 Duncan, E.A.S., Fitzpatrick, D. (2016) Improving self - referral for diabetes care following hypoglycaemic emergencies : a feasibility study with linked patients data analysis. *BMC Emerg. Med*, 2016, **16**,13.
- 28 Mathur, S., Zammit, N.N., Frier, B.M. (2015). Optimal glycaemic control in elderly people with Type 2 diabetes: what does the evidence say ? *Drug Safety* , **38**,17 – 32.
- 29 Yeoh, H., Choudhary, P., Nwokolo, M., Avis, S., Amiel, S.A. (2015). Interventions that restore awareness of hypoglycaemia in adults with type 1 diabetes: a systematic review and meta – analysis. *Diabetes Care*, 38, 1592 – 09.
- 30 Cox, D.J., Gonder – Frederick, F., Ritterband, L., Clarke, W., Kovatchev, B.P. (2007). Prediction of severe hypoglycaemia. *Diabetes Care* , 30, 1370 – 73.
- 31 Seaquist, E.R., Anderson, J., Childs, B. et al. (2013). Hypoglycaemia and diabetes: a report of a working group of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 36 ;1384-95.

32 Khunti, K., Fisher, H., Iqbal, M., Davies, M.J., Siriwardena, A.N. (2013). Severe hypoglycaemia requiring emergency medical assistance in the East Midlands: a retrospective study. *Primary Care Diabetes*, 7, 159

- 65

ACCEPTED MANUSCRIPT

**Table 1. Clinical details for the first 2,000 severe hypoglycaemia (SH) episodes attended by Ambulance crew and managed through the integrated single point of contact (SPOC) pathway.**

n	2,000
m:f	1129 : 871
Age (yrs)	67 (50 – 80)
> 70 years	876 (43.8%)
> 80 years	472 (23.6%)
Insulin treated *	1697 (84.9%)
Oral hypoglycaemic treated **	251 (12.6%)
Diet alone	44 (2.2%)
'Not diabetes'	8 (0.4%)
Unconscious on attendance ***	645 (32.3 %)
Similar episode in previous month	700 (35.0%)
Lives alone	578 (28.9 %)
Under primary care management	1130 (56.5 %)
Transferred to Acute Hospital	276 (13.8 %)
Glucose level on attendance (mmol/L)	2.3 (1.9 – 2.9)
Glucose level < 2.5mmol/L on attendance	1117 (55.9%)
Treated with im glucagon or ivglucose	904 (45.2 %)
Treated with oral carbohydrate or oral glucose	1086 (54.3%)
Other treatment	7 (0.35%)
No treatment	3 (0.15%)
Glucose level after treatment (mmol/L)	6.4 (5.4 – 8.1)
Glucose level > 4 mmol/L after treatment ****	1933 (96.7%)

Data shown as n (%), or mean (one standard deviation) or median (interquartile range x - y)

- \* Does not preclude concurrent oral hypoglycaemic therapy (in all Tables)
- \*\* Oral hypoglycaemic therapy alone without insulin (in all Tables)
- \*\*\* Patients unconscious, or with reduced level of consciousness (in all Tables)
- \*\*\*\* Data not available for n = 67 (3.3%)

**Table 2 Treatment categories for 2,000 episodes of severe acute hypoglycaemia (SH) attended by Ambulance crew and managed through the integrated single point of contact (SPOC) pathway by age band.**

	Age		
	< 70 yrs	70 – 80 yrs	> 80 yrs
<b>n</b>	1094	434	472
<b>Insulin</b>	997(91.1 %)	346 (79.7%)	354 (75%)
<b>Oral hypoglycaemics</b>	70 (6.4%)	80 (18.4%)	101 (21.4%)
<b>Diet</b>	25 (2.3%)	8 (1.8%)	11 (2.3%)
<b>Not known to have diabetes</b>	2 (0.2%)	0 (0%)	6 (1.3%)

Data as n (%) for each age category

'No diabetes' or 'Diet' recorded as patient response to Ambulance crew

**Table 3. Clinical characteristics by treatment category for 2,000 severe acute hypoglycaemia episodes attended by Ambulance crew and managed through the integrated single point of contact (SPOC) pathway.**

	Oral hypoglycaemic	Insulin
n	303	1697
Age (yrs)	77 (65 – 85)	64 (48 -78)**
Unconscious on attendance	55 (18.2%)	590 (34.8%) **
Similar SH episode in previous month <sup>a</sup>	65 (21.5 %)	635 (37.4%) **
Lives alone	117 (38.6 %)	461 (27.2%) **
Transferred to Acute Hospital	61 (20.1 %)	215 (12.7%) *
Glucose level on attendance (mmol/L)	2.6( 2.2 – 3.2 )	2.3 (1.8 – 2.9) **
Glucose level < 2.5mmol/L on attendance	124 (40.9 %)	993 (58.5 %) **
Treated with im glucagon or iv glucose	89 (29.4%)	815 (48.0 %) **
Treated with oral carbohydrate or oral glucose	213 (70.3%)	873 (51.4 %) **
Treated with other	1 (0.3%)	6 (0.4 %)
No Treatment	0 (0.0%)	3 (0.2%)
Glucose level after treatment (mmol/L)	6.1 (5.3 – 7.4)	6.4 (5.4 – 8.2) *
Glucose level > 4.0 mmol/L after treatment	292 (96.4%)	1641 (96.7 %)

<sup>a</sup> Self described severe hypoglycaemic episode in previous month reported to Ambulance crew by patient

Data shown as n (%), or or median (interquartile range x - y).

Oral hypoglycaemic group (n = 304) includes those self - identifying as 'diet alone' or those unaware of a diabetes diagnosis, on the assumption that documented SH was due to oral agents and patient was unclear about medication.

\* p < 0.01 \*\* p < 0.0001



**Table 4. Clinical characteristics by age band for 2,000 severe acute hypoglycaemia episodes attended by Ambulance crew and managed through the integrated single point of contact (SPOC) pathway.**

	< 70 years	> 70 years
n	1124	876
Unconscious on attendance	437 (38.9%)	208 (23.7 %) ***
Similar SH episode in previous month	422 (37.5%)	278 (31.7%)*
Lives alone	265 (23.6%)	313 (35.7%) ***
Transferred to Acute Hospital	135 (12.0%)	141 (16.1%) *
Glucose level on attendance (mmol/L)	2.2 (1.8 – 2.9)	2.5 (2 – 2.9) ***
Glucose level < 2.5mmol/L on attendance	686 (61.0%)	431 (49.2%) ***
Treated with im glucagon or iv glucose	528 (47.0%)	376 (42.9%)
Treated with oral carbohydrate	591 (52.6%)	495 (56.5%)
Treated with other	3 (0.3%)	4 (0.5 %)
No Treatment	2 (0.2%)	1 (0.5 %)
Glucose level after treatment (mmol/L)	6.6 (5.4 – 8.4)	6.3 (5.4 – 7.7)*
Glucose level > 4.0 mmol/L after treatment	1086 (96.6 %)	847 (96.7%)

Data shown as n (%), or median (interquartile range x - y)

\* p < 0.05      \*\*\* p < 0.0001

**Table 5. Clinical characteristics of SH episodes managed by Ambulance Crew at scene, or conveyed to an Acute Hospital<sup>a</sup>**

	Not conveyed	Conveyed <sup>a</sup>
n	1724	276
Age (yrs)	66 (49 – 80)	72 (55 – 82) **
Unconscious on attendance	521 (30.2 %)	124 (44.9 %) ***
Similar SH episode in previous month	608 (35.3 %)	92 (33.3 %)
Lives alone	475 (27.6%)	103 (37.3 %) **
Insulin	1482 (85.9 %)	215 (77.9 %) **
Oral hypoglycaemic	198 (11.5 %)	53 (19.2 %) ***
Glucose level on attendance (mmol/L)	2.4 (1.9 – 2.9)	2.3 (1.8 – 2.8)
Glucose level < 2.5mmol/L on attendance	956 (55.5%)	161 (58.3 %)
Treated with im glucagon or iv glucose	750 (43.5 %)	154 (55.8 %) ***
Treated with oral carbohydrate or Oral Glucose	965 (56.0%)	121 (43.8%) ***
Treated with other	6 (0.4%)	1 (0.4%)
No Treatment	3 (0.2%)	0 (0.0%)
Glucose level after treatment (mmol/L)	6.4 (5.4 – 8.1)	5.9 (4.9 - 8) ***
Glucose level > 4.0 mmol/L after treatment	1689 (98.0 %)	244 (88.4%) ***

Data shown as n (%), or median (interquartile range x - y)

Oral hypoglycaemic group (n = 304) includes those self - identifying as 'diet alone' or those unaware of a diabetes diagnosis, on the assumption that documented SH was due to oral agents and patient was unclear about medication.

<sup>a</sup> Please note these data for transferred patients are derived only from those whose details were referred to the SPOC pathway.

\* p < 0.05      \*\* p < 0.005      \*\*\* p < 0.0001

**Table 6 Clinical and treatment characteristics of callers with, or without, self - reported severe hypoglycaemic (SH) episode in the previous month**

	No previous SH	Recurrent SH episode
n	1300	700
Age (yrs)	68 (50 – 80)	64 (49 – 79)
Unconscious on attendance	392 (30.2%)	253 (36.1 %) *
Lives alone	350 (26.9 %)	228 (32.6 %) *
Transferred to Acute Hospital	184 (14.2 %)	92 (13.1 %)
Insulin	1062 (81.7%)	635 (90.7 %) ***
Oral hypoglycaemic	193 (14.9%)	58 (8.3 %) ***
Glucose level on attendance (mmol/L)	2.40 (1.9 – 3.0)	2.30 (1.8 – 2.8) **
Glucose level < 2.5mmol/L on attendance	700 (53.9%)	417 (59.6%)
Treated with im glucagon or iv glucose	569 (43.8%)	335 (47.9 %)
Treated with oral carbohydrate	724 (55.7%)	362 (51.7 %)
Treated with other	5 (0.4 %)	2 (0.3 %)
No Treatment	2 (0.2%)	1 (0.1 %)
Glucose level after treatment (mmol/L)	6.40 (5.4 – 8)	6.50 (5.4 – 8.2)
Glucose level > 4.0 mmol/L after treatment	1261 (97%)	672 (96%)

Data shown as n (%), or median (interquartile range x - y)

\* p < 0.01      \*\* p < 0.005      \*\*\* p < 0.0001

**Table 7 Clinical and treatment characteristics where callers self - reported no recent severe episode or ambulance call out (A) in previous month, or a severe episode without a 999 call in the previous month (B), or with both a severe episode *and* an ambulance call (C) in the previous month**

	A	B	C
n	1235	295	372
Age (years)	68 (50 – 80)	64 (48 - 79)	64 (51 - 80)
Unconscious on attendance	366 (29.64%)	104 (35.25 %)	137 (36.83%) *
Lives alone	334 (27.04%)	89 (30.17%)	130 (34.95%)*
Transferred to Acute Hospital	178 (14.41%)	41 (13.9%)	49 (13.17%)
Insulin treated	1012 (81.94 %)	272 (92.20%)	336 (90.32%) **
Oral Hypoglycaemic treatment	181 (14.66 %)	22 (7.46%)	33 (8.87 %) **
Glucose on attendance (mmol/L)	2.40 (1.9 -3)	2.30 (1.8 – 2.9)	2.3 (1.8 – 2.7)*
Glucose < 2.5mmol/L	662 (53.6%)	175 (59.32%)	226 (60.75%)
Treated with IM Glucagon	539 (43.64%)	133 (45.08%)	189 (50.81%)
Treated with Oral Carbohydrates	689 (55.79%)	162 (54.92%)	180 (48.39%)*
Treated with Other	5 (0.4%)	0 (0%)	2 (0.54%)
No Treatment	2 (0.16%)	0 (0%)	1 (0.27%)
Glucose after treatment (mmol/L)	6.4 (5.4 – 8.0)	6.4 (5.4 - 8.2)	6.7 (5.4 - 8.2)
Glucose level > 4.0 mmol/L post treatment	1196 (96.84%)	287 (97.29%)	354 (95.16%)

By ANOVA across groups

\* p < 0,05 \*\* p < 0.001

Note: 98 patients did not report ambulance call out outcomes