# Frequency of Severe Hypoglycemia Requiring Emergency Treatment in Type 1 and Type 2 Diabetes

## A population-based study of health service resource use

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**OBJECTIVE** — To determine the incidence, predisposing factors, and costs of emergency treatment of severe hypoglycemia in people with type 1 and type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — Over a 12-month period, routinely collected datasets were analyzed in a population of 367,051 people, including 8,655 people with diabetes, to measure the incidence of severe hypoglycemia that required emergency assistance from Ninewells Hospital and Medical School (NHS) personnel including those in primary care, ambulance services, hospital accident and emergency departments, and inpatient care. Associated costs with these episodes were calculated.

**RESULTS** — A total of 244 episodes of severe hypoglycemia were recorded in 160 patients, comprising 69 (7.1%) people with type 1 diabetes, 66 (7.3%) with type 2 diabetes treated with insulin, and 23 (0.8%) with type 2 diabetes treated with sulfonylurea tablets. Incidence rates were 11.5 and 11.8 events per 100 patient-years for type 1 and type 2 patients treated with insulin, respectively. Age, duration, and socioeconomic status were identified as risk factors for severe hypoglycemia. One in three cases were treated solely by the ambulance service with no other contact from health care professionals. The total estimated cost of emergency treatment of severe hypoglycemia was ≤£92,078 in one year.

**CONCLUSIONS** — Hypoglycemia requiring emergency assistance from health service personnel is as common in people with type 2 diabetes treated with insulin as in people with type 1 diabetes. It is associated with considerable NHS resource use that has a significant economic and personal cost.

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Hypoglycemia is a common side-effect of insulin therapy in diabetes, particularly in people with type 1 diabetes. Mild (self-treated) episodes occur frequently (1–2 episodes/week) (1,2), while severe hypoglycemia, defined as any episode requiring external help, affects up to 30% of people with type 1 diabetes annually (1–5), with an incidence ranging from 1.0 to 1.6 episodes per patient per year in unselected northern European populations. Although annual prevalence was similar in the intensively treated group of the Diabetes Control and Complications Trial (DCCT) in North America, the recorded incidence was lower at 0.62 episodes per patient year, but people at high risk of severe hypoglycemia were excluded in this study (6). Lower rates have been recorded in German centers where patients have had intensive education to avoid hypoglycemia, but the definition of severe hypoglycemia was restricted to coma and/or parenteral glucose for resuscitation (7). In contrast, the rate of severe hypoglycemia in people with type 2 diabetes treated with insulin is reported to be low (8,9), but these have been recorded in the context of clinical trials and often in people with a short duration of insulin therapy. In the U.K. Prospective Diabetes Study (UKPDS) (9), where the frequency of severe hypoglycemia was low initially, it was increasing in the latter part of the study. With increasing duration of treatment with insulin in people with type 2 diabetes, the frequency of severe hypoglycemia begins to approach that observed in type 1 diabetes (10).

Most episodes of severe hypoglycemia are treated effectively at home or at work by friends, relatives, or colleagues and do not require the assistance of the emergency medical services (11). Cases treated in the hospital accident and emergency department are recognized to represent the "tip of the iceberg" (12), and the annual frequency of all emergency-treated episodes is uncertain because of incomplete ascertainment. However, this possibly has a significant resource implication from the viewpoint of ambulance use, general practitioner emergency call outs, hospital accident and emergency department attendance, and, for a small number of patients, hospital admission (13).

Our aim was to use the resource of a

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**Abbreviations:** DCCT, Diabetes Control and Complications Trial; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

comprehensive community-based database to identify all episodes of severe hypoglycemia treated by emergency medical services in the entire diabetic population in a 12-month period. We also quantified the approximate cost to the local health service budget associated with this problem.

## RESEARCH DESIGN AND METHODS

The DARTS (Diabetes Audit and Research in Tayside Scotland)/MEMO (Medicines Monitoring Unit) Collaboration collects routine data from the population of Tayside, Scotland, which can be record-linked using a unique patient identifier (14,15). These include a register of all people with type 1 and type 2 diabetes in Tayside, which has been validated and shown to have high sensitivity and specificity for the diagnosis of diabetes (14), a record of all inpatient hospital admissions in Tayside from 1980 with ICD-9 diagnostic codes (16), and regional biochemistry and primary care records of all people with diabetes registered with the 78 general practices in Tayside that have all been inspected by dedicated research nurses. These resources were used for the present study, and in addition, population-based records of all Tayside ambulance activity, and attendance at the three hospital accident and emergency departments in the region and at the seven primary care after-hours facilities were examined. Each of these data sources contains recorded information on individual patient contacts, diagnoses, and treatment administered. Dedicated research nurses abstracted data to create a longitudinal record of emergency care. This was linked to existing records of hospitalization records (Scottish Morbidity Register) for those patients who ultimately had been admitted to hospital.

The study population comprised patients who were alive and resident in Tayside in June 1997 and who were either still alive in Tayside in June 1998 or who had died but had not emigrated from Tayside during the period of study. All episodes of hypoglycemia between June 1997 and May 1998 inclusive that required emergency treatment from primary care, ambulance, and accident and emergency or hospital services were identified. Episodes of severe hypoglycemia were defined as blood glucose <3.5 mmol/l associated with the need for treatment with glucagon or intravenous dextrose to effect recovery or paramedic confirmation of hypoglycemia with rapid recovery following treatment. The date, time, precipitant cause (if known), blood glucose (if recorded), duration, nature of treatment given, and clinical outcome were all recorded. Episodes of severe hypoglycemia that did not receive emergency treatment by health care personnel were excluded.

In the present study, a diabetic group was defined, which included all people who were known to have type 1 and type 2 diabetes before the index date. A diagnosis of type 1 diabetes was made if diagnosed at <35 years of age with a requirement for insulin and/or a diagnosis at any age with evidence of ketonuria and insulin requirement within 28 days. All other subjects were judged to have type 2 diabetes. Patients with type 2 diabetes were categorized as either on insulin, sulfonylurea tablets, or other (on metformin, glitazones, or diet alone). The primary outcome was incidence rates of hypoglycemia for type 1 and type 2 diabetes expressed per 100 patient-years with 95% CIs. Potential predictors of severe hypoglycemia including age, sex, duration of diabetes, Carstairs social deprivation score (17,18), and diabetes control (expressed as most recent $HbA_{1c}$ before episode of hypoglycemia) were evaluated by *t* test for continuous variables and frequence table for categorical variables. The Carstairs score uses U.K. decennial census data to calculate a single score for each postcode area using the *Z*-score technique from information on unemployment, overcrowding, car ownership, and social class. Seven categories are defined ranging from the most affluent (class 1) to the most deprived (class 7) (16,17). The direct cost of hypoglycemia was calculated using the Information Statistics Division (ISD) cost book. Thus, we estimated the average cost per ambulance or accident and emergency encounter or hospitalization costs (per patient day in a specific ward hospitalization) by calculating the length of each period of care and the average daily cost of each specialty (18). The local research and ethical committee and four Caldicott Guardians responsible for secondary use of clinical information approved the study. Following linkage, all data were made anonymous before statistical analysis, which was performed using SAS version 6.12.

**Table 1—*People in Tayside with diabetes and number of hypoglycemic events***

| | Type 1 diabetes | Type 2 diabetes |
|---|---|---|
| *n* | 977 (57% male) | 7,678 (52% male) |
| Mean age (years) | 33.1 | 65.8 |
| Mean diabetes duration (years) | 17.0 | 8.0 |
| Number of episodes | 112 | 132 |
| Number of patients | 69 | 91 |

**RESULTS** — Among 367,051 Tayside residents, there were 977 (0.26%) with type 1 diabetes and 7,678 (2.09%) with type 2 diabetes. From 1 June 1997 to 31 May 1998 there were 39,010 ambulance calls, 77,021 hospital accident and emergency visits, and 39,464 primary care visits at the seven community sites. A total of 244 episodes of severe hypoglycemia were identified in 160 patients with diabetes (Table 1). There was clear evidence of some individuals experiencing recurrent hypoglycemic events, with 69 individuals with type 1 diabetes suffering 112 events and 91 individuals with type 2 diabetes suffering 132 events. Of the 260 episodes, 89 (34%) involved contact with the ambulance service only, 19 (7%) were with accident and emergency/primary care services only, and 134 (52%) were with both. Only 52 cases (28%) resulted in direct or indirect hospital admission, resulting in hospital occupancy of 230 bed days.

The incidence of severe hypoglycemia in patients with type 1 and type 2 diabetes is shown in Table 2. The incidence was highest for people with type 1 diabetes, whereas in people with type 2 diabetes there was a clear "dose-response," with insulin-treated patients having a 13-fold higher incidence of severe hypoglycemia than those treated with oral medication alone.

In total, 7.1% of patients with type 1 diabetes, 7.3% of patients with type 2 di-

**Table 2—*Incidence of severe hypoglycemia requiring NHS resource use***

| Type of diabetes | Treatment modality | Incidence |
|---|---|---|
| Type 1 | Insulin | 11.5 (9.4–13.6) |
| Type 2 | Insulin | 11.8 (9.5–14.1) |
| Type 2 | Sulphonylurea tablets | 0.9 (0.6–1.3) |
| Type 2 | Metformin or diet | 0.05 (0.01–0.2) |

Data are events expressed per 100 patient-years (95% CI).

**Table 4—*Relation between material deprivation (Carstairs score) and severe hypoglycemia requiring NHS resource use***

| | Social class | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| No cases | 9 | 23 | 31 | 23 | 20 | 51 | 0 |
| Percent | 1.56 | 1.60 | 1.53 | 1.42 | 2.09 | 2.99 | 0.00 |
| Total patients | 578 | 1,441 | 2,025 | 1,616 | 955 | 1,704 | 3 |

Data are *n* and %. The Carstairs score uses U.K. decennial census data to calculate a single score for each post-code area using the *Z*-score technique. Seven categories are defined ranging from the most affluent (class 1) to the most deprived (class 7) (16, 17). $P = 0.002$ (Cochran-Mantel-Haenszel test).

abetes treated with insulin, and 0.8% of patients with type 2 diabetes treated with oral hypoglycemic therapy suffered at least one event.

Table 3 shows the predictors of severe hypoglycemia and demonstrates that for all people with diabetes, people who experienced severe hypoglycemia requiring treatment by the health service emergency facilities were older, had a longer duration of diabetes, and a higher $HbA_{1c}$ (all $P < 0.001$). Hypoglycemia was associated with age and duration of diabetes for insulin-treated patients with type 2 diabetes and for people with type 1 diabetes. There was a trend toward more severe hypoglycemia in males with type 1 diabetes, but this did not reach statistical significance. An association was observed between increasing socioeconomic deprivation and severe hypoglycemia (Table 4). This was evident for the group as a whole but was especially associated with type 1 diabetes ($P < 0.001$).

Table 5 shows the estimated total direct costs of treating hypoglycemia in Tayside. The total cost was estimated as ≤92,078, of which hospital care accounted for ≤50,140. Based on the prevalence figures of diabetes in Tayside, we estimate that the annual direct cost of treating severe hypoglycemia could be in excess of ≤13 million in the U.K.

**CONCLUSIONS** — Achieving good glycemic control to minimize the risk of diabetic microvascular complications in type 1 and type 2 diabetes (5,6,9,19) is reputed to be cost effective in that the increased treatment costs are offset by reduced cost of treating complications and improved quality of life (20). Hypoglycemia is the principal problem associated with strict glycemic control (5,6,21). Our study indicates that the frequency of severe hypoglycemia requiring emergency services in patients with type 2 diabetes treated with insulin may be as great as that in patients with type 1 diabetes.

Most previous surveys have addressed the frequency of severe hypogly-

**Table 3—*$HbA_{1c}$, age, duration of diabetes, and percentage male in groups of patients with diabetes who have had hypoglycemic (hypo) events and those who have not had hypoglycemia (no hypo)***

| | Treatment | *n* | $HbA_{1c}$ (%) | Age (years) | Duration of diabetes (years) | BMI ($kg/m^2$) | Sex (% male) |
|---|---|---|---|---|---|---|---|
| Type 1: no hypo | Insulin | 908 | 7.93 (7.76–8.10) | 32.8 (31.8–33.8) | 16.7 (15.8–17.7) | 24.7 (24.4–25.0) | 56.1 |
| Type 1: hypo | Insulin | 69 | 7.77 (7.29–8.25) | 37.7 (34.1–41.3) | 20.7 (17.7–23.7) | 25.0 (24.3–25.7) | 66.7 |
| *P* | | | 0.533 | 0.009 | 0.013 | 0.557 | 0.078 |
| Type 2: no hypo | Insulin | 835 | 8.23 (8.09–8.37) | 63.2 (62.4–64.1) | 11.8 (11.2–12.4) | 30.1 (29.4–30.8) | 47.7 |
| Type 2: hypo | Insulin | 66 | 7.87 (7.47–8.28) | 66.6 (63.5–69.6) | 13.5 (11.3–15.8) | 26.7 (25.7–27.7) | 47.0 |
| *P* | | | 0.097 | 0.038 | 0.137 | <0.001 | 0.914 |
| Type 2: no hypo | Sulphonylurea tablets | 2,800 | 7.16 (7.08–7.23) | 65.4 (65.0–65.9) | 6.3 (6.0–6.5) | 29.6 (29.5–29.7) | 52.2 |
| Type 2: hypo | Sulphonylurea tablets | 23 | 8.00 (7.10–8.91) | 65.0 (59.1–70.9) | 7.2 (4.3–10.0) | 28.1 (26.7–29.5) | 47.8 |
| *P* | | | 0.064 | 0.884 | 0.517 | 0.122 | 0.687 |
| All diabetes: no hypo | All therapies | 8,495 | 7.19 (7.14–7.24) | 62.3 (61.9–62.6) | 8.9 (8.6–9.2) | 29.0 (28.9–29.1) | 52.6 |
| All diabetes: hypo | All therapies | 160 | 7.85 (7.57–8.14) | 53.8 (50.8–56.9) | 15.6 (13.8–17.4) | 26.1 (25.5–26.7) | 55.6 |
| *P* | | | <0.001 | <0.001 | <0.001 | <0.001 | 0.454 |

Data are mean (95% CI). The study groups include patients with type 1 diabetes, those with type 2 diabetes treated with insulin, and those with type 2 diabetes treated with tablets. Additionally patients have been analyzed as an overall combined group.

**Table 5—*Cost analysis of hypoglycemia in Tayside (for comparison costs per case in Scotland for ambulance, Accident and Emergency [A&E] attendance, and ward admission [per day] is £130, £41, and £1593, respectively.)***

| | Ambulance | A&E | Ward |
|---|---|---|---|
| Number of episodes | 223 | 153 | 52 |
| Tayside (case per day) | £127 | £89 | £218 |
| Cost of hypoglycaemia | £28,321 | £13,167 | £50,140 |

cemia in populations of people with type 1 diabetes, mostly attending specialist clinics. The present study has observed that nearly 1 in 14 people with insulin-treated diabetes experiences one or more episodes of severe hypoglycemia annually that requires the urgent therapeutic intervention of health service personnel. An unexpected and clinically important finding was that the prevalence of severe hypoglycemia in insulin-treated patients with type 2 diabetes was much higher than that reported previously (9,22) and in the community setting was equal to that seen in patients with type 1 diabetes outwith the environment of controlled long-term clinical trials like the DCCT. This observation confirms a previous observation in a small group of selected patients with diabetes (23). Insulin treatment rather than type of diabetes seems to be the important feature. Data in the present report include episodes of severe hypoglycemia that did not require admission to the hospital (72%), which may reflect the under-reporting in the UKPDS. The ambulance service does not usually inform general practitioners of emergency call outs that do not result in hospital admission. This is an important finding because people with type 2 diabetes are generally perceived to have a low absolute risk of severe hypoglycemia, even when treated with insulin (24). Insulin resistance may be protective in the first few years after commencing insulin (9); however, a much higher incidence of severe hypoglycemia has been recorded in people with insulin-treated type 2 diabetes who have required insulin for several years (10) and who have developed pancreatic β-cell failure.

In the present study, the rate of hypoglycemia recorded by people with type 1 diabetes was very similar to that observed in the intensively treated group of the DCCT (6,21). An important caveat, however, is that the average glycated hemoglobin of the Tayside diabetes population (8.5%) was significantly higher than that achieved in the intensively treated DCCT group who had strict glycemic control (7.0%). It is likely that the rate of severe hypoglycemia in this unselected and older diabetic population on insulin would be significantly higher if the glycemic targets of the intensive arm of the DCCT were to be achieved in Tayside. However, the DCCT excluded people at greatest risk of severe hypoglycemia, as they did not recruit patients who had a history of previous recurrent severe hypoglycemia (6,21). People with impaired awareness of hypoglycemia were probably excluded, and they have a sixfold higher incidence of severe hypoglycemia than those with normal awareness (25). Direct comparisons with the DCCT are difficult because the participants were younger, were highly motivated, were of above-average intelligence, had a short duration of diabetes, and had access to resources and a level of professional support much greater than can be provided by the average specialist center.

The present study has certain strengths in providing an accurate clinical picture of frequency of hypoglycemia requiring emergency treatment both in primary and secondary care settings. First, it is population-based. Second, it uses information from a validated diabetes information system. Thus, the diagnoses of type 1 and type 2 diabetes, treatment types, and episodes of severe hypoglycemia have all been validated according to standard diagnostic criteria by dedicated research nurses who have inspected the case records and ambulance records of all people with diabetes in Tayside. However, episodes of hypoglycemia treated either at home or in the workplace, by family or friends, were not recorded and may result in an underestimate of all severe hypoglycemia. Despite this limitation, the results reveal a previously unrecognized problem of hypoglycemia in people with insulin-treated type 2 diabetes, which may be a very conservative estimate.

The present survey suggests that the burden of severe hypoglycemia may be much greater in people with type 2 diabetes treated with insulin than has been recognized previously. One in three of all severe hypoglycemia was treated by the ambulance service alone, and only one in four were admitted to hospital. The cost of hypoglycemia may be greater than previously recognized.

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