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# The management of severe hypoglycemia by the emergency system: The HYPOTHESIS study

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**Abstract** *Background and aims:* Severe hypoglycemia is not rare in diabetes and markedly impacts on health resource use. We aimed to describe the characteristics of patients attending emergency departments (EDs) following a severe episode of hypoglycemia, the factors associated with the management of events and the final outcome.
*Methods and results:* We carried out a retrospective analysis of cases attending 46 Italian EDs for hypoglycemia from January 2011 to June 2012. A total of 3753 records were retrieved from the databases of the participating centers, part of a network repeatedly involved in collaborative studies; 3516 episodes occurred in subjects with diabetes (median age, 76 years; range, 1–102). Comorbidities were recorded in 2320 (65.9%) diabetes cases; association with trauma or road accidents in 287 (8.2%) and 47 (1.3%), respectively. Patients were treated with insulin (49.8%), oral agents (31.4%), or combination treatment (15.1%). The event required assistance by the out-of-hospital Emergency services in 1821 cases (51.8%). Following the ED visit, admission to hospital departments was deemed necessary in 1161 cases (33.1%). Diabetes treatment (oral agents: OR, 1.63; 95% confidence interval (CI), 1.37–1.94), increasing age (OR, 1.39; 95% CI, 1.31–1.48) and the number of comorbidities (OR, 1.51; 95% CI, 1.38–1.66) were the main drivers of admission. The in-hospital death rate was 10%, associated with the number of comorbidities (OR, 1.28; 95%CI, 1.01–1.63).
*Conclusion:* Severe hypoglycemia requiring referral to EDs is associated with a significant work-up of the Emergency services and a remarkable in-hospital death rate in frail individuals with diabetes.
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## Introduction

Hypoglycemia represents a major issue in both type 1 (T1DM) and type 2 diabetes mellitus (T2DM) [1]. Severe episodes, defined by the need of external help, may be life-threatening [2], whereas mild iatrogenic events severely impact quality of life [3]. The resulting fear of hypoglycemia limits treatment and metabolic control, favoring complications.

Hypoglycemia occurs at a rate around 1.0 per patient-year in T1DM, and reportedly less frequent in insulin-treated T2DM. This myth has however been challenged, and a recent study showed that the event rates of severe hypoglycemia requiring emergency assistance are similar in T1DM and insulin-treated T2DM with poor metabolic

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control and longstanding and complicated disease [4]. The importance of hypoglycemia in diabetes was highlighted by recent trials of intensive metabolic control in T2DM, where the negative results were partly related to the adverse effects of hypoglycemia [5,6]. The recent availability of new classes of glucose-lowering drugs, less prone to produce hypoglycemia further drew the attention of the scientific community on the topic [7].

The economic cost of hypoglycemia is remarkable and goes beyond the personal burden. The use of health resources (ambulance call, on-site treatment, hospital admission [8]) is probably much higher than estimated by administrative data [9], and particularly relevant in T2DM [10], often characterized by long-term disease and complex comorbid profiles.

Very few data exist on the emergency management of hypoglycemia and its related outcomes [10,11]. A recent combined analysis of different US databases estimated a total of nearly 100,000 emergency department (ED) visit per year, with high rates of hospital admission and poor outcomes in insulin-treated diabetes [12]. We collected data on demographic and clinical characteristics of subjects attending the EDs of Italian general hospitals following a hypoglycemic event requiring emergency treatment. The study was intended to determine the associated factors, the out-of-hospital and in-hospital management, and the final outcome of severe hypoglycemia.

## Methods

### *Data collection*

In 2012, the Study and Research Center of Italian Society of Emergency Medicine (SIMEU) launched a study on all cases attending the EDs for a hypoglycemic event between January 2011 and June 2012 (HYPOTHESIS Study: HYPOglycemia Treatment in the Hospital Emergency System – Italian Study). According to a predefined case report form, 46 EDs covering an area of approximately 12 million inhabitants (scattered throughout Italy, in both rural and metropolitan areas), collected data on all cases with an acceptance diagnosis of hypoglycemia. The terms “hypoglycemia” or “hypoglycemic event” were used to search the ED databases.

The case report form included data on age, gender, previous diagnosis of diabetes or solid tumors, current alcohol abuse and malnutrition. Association with trauma or road accidents, glucose-lowering drug use and blood glucose values at the time of the event, as well as procedures to treat hypoglycemia (initial medication at home, intervention of the out-of-hospital Emergency service), were extracted from history, as recorded by the ED medical personnel.

Comorbidities were recorded according to a predefined form. Cardiovascular morbidity included both arrhythmias (atrial fibrillation, bundle blocks) and any diagnosis of coronary artery disease; chronic kidney disease included any diagnosis of moderate to severe chronic renal failure; liver disease was limited to cirrhosis or hepatocellular carcinoma. ED treatment was available in all cases; disposition (referral to general practitioners [GPs] or Diabetes Units; short-term (<24 h) intensive observation; admission to hospital wards) and post-admission outcomes were available for 40 centers (Fig. 1).

The ethical committee of Bologna University approved the study (175/2012/O/OssN, September 11, 2012).

### *Data analysis*

The population was described as number of cases and percentages (categorical variables) or as means with standard deviation (SD) (continuous variables). We then tabulated data on disposition according to drug use and differences between groups were analyzed by $\chi^2$. Treatment modalities were studied according to the age of patients, using $\chi^2$ to evaluate differences. An analysis of factors associated with disposition following the ED visit and treatment was carried out by logistic regression analysis as crude odds ratios (ORs) and corresponding 95% confidence interval (CI). We repeated the analysis considering in-hospital death as dependent variable. Independent variables were age, sex, blood glucose at the event time, occurrence of trauma or road accidents, previous treatment with either insulin or oral agents and the presence of comorbidities. For each dependent variable, we fitted a multivariate model including age, gender, and the number of comorbidities as covariates. As a sensitivity analysis, we recomputed the regression analyses in subjects with a pre-hospital recorded blood glucose ≤3.9 mmol/L, fulfilling the definition of hypoglycemia as defined by the American Diabetes Association (ADA) [1]. $p$ values <0.05 were considered statistically significant. Analyses were performed using StatView 5.0™ (SAS Institute Inc, Cary, NC, USA).

## Results

### *Hypoglycemic events*

Overall, we identified 3753 hypoglycemic events. Cases without diabetes ($n$ = 237, 6.3%) included a high number of patients with cancer (18.5%; 3.1% with hepatocellular carcinoma), poor nutritional status (22.3%), alcohol abuse (13.1%), hypothyroidism (8.4%), anorexia nervosa (4.1%), liver failure (9.3%). This subpopulation without diabetes is no longer considered in the present report. Information on cases with diabetes are shown in Table 1. A total of 3516 (93.7%) events occurred in subjects with diabetes (repeated events in the same individual, 4.1%). Cases with diabetes had a median age of 76 years (range, <1–102) and 50.5% were males. The duration of disease varied from less than one month to 60 years (median, 100 months). Association with trauma was present in 287 cases (8.1%); with road accidents in 47 (1.3%). Blood glucose at the time of event (mean, 2.33 ± SD 1.22 mmol/L) was recorded in 2314 cases. A value ≤3.9 mmol/L was confirmed in 2122 cases (91.7%); in 1244 (53.7%) it was ≤2.2 mmol/L.

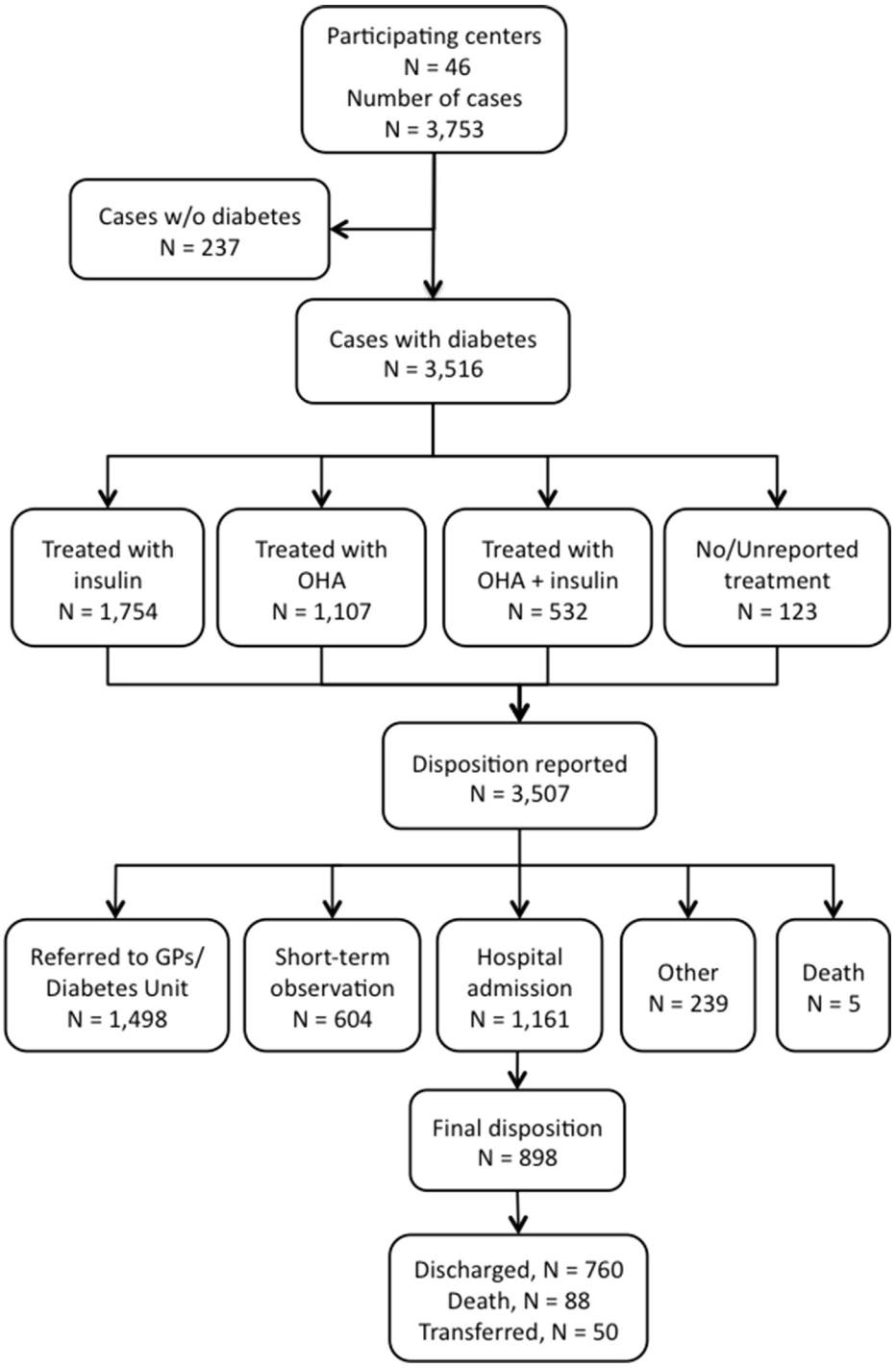


**Figure 1** Flow chart of the study. Abbreviations: OHA, oral hypoglycemic agents; GPs, general practitioners.

Hypoglycemia was initially treated at home (with/without external help); almost half cases ($n$ = 1,821, 51.8%) received additional treatment both at home and in the ambulance from the personnel of the out-of-hospital ED services (i.v. glucose: 1430 cases, i.m. glucagon: 22 cases). In EDs, neurological or sensory defects were recorded in 587 cases (16.7%), heart problems requiring immediate treatment in 122 patients (3.4%), respiratory distress in 135 cases (3.8%). In-hospital blood glucose was on average 4.32 ± SD 2.94 mmol/L (≤3.9 mmol/L in 57.3% of cases and still ≤2.2 mmol/L in 20.8%). Treatment was continued with oral glucose ($n$ = 564, 16.1%), i.m. glucagon ($n$ = 63, 1.7%) or i.v. glucose ($n$ = 2483, 70.6%).

Insulin was the only glucose-lowering treatment in 49.8% of cases (mean age, 65 ± SD 20 years); 31.4% were treated by oral agents (age, 79 ± SD 11 years, $p < 0.0001$

**Table 1** Demographic and clinical characteristics of patients with diabetes requiring ED visits following a hypoglycemic episode.

| Characteristics of patients with diabetes ($n$ = 3516) | $N$ (%) |
|---|---|
| *Demographics* | |
| Female | 1775 (50.5) |
| Age, years[a] | 71.2 [17.5] |
| Duration of diabetes, months[b] | 100 [156] |
| *Associated events* | |
| Trauma | 287 (8.1) |
| Road accidents | 47 (1.3) |
| Ambulance call | 1821 (51.8) |
| *Blood glucose* | |
| At time of event, mmol/L ($n$ = 2314)[a] | 2.33 [1.22] |
| At admission, mmol/L ($n$ = 3368)[a] | 4.32 [2.94] |
| *Associated glucose-lowering drugs* | |
| Insulin | 1754 (49.8) |
| Oral agents | 1107 (31.4) |
| Metformin | 69 (1.9) |
| Sulfonylureas | 300 (8.5) |
| Glinides | 129 (13.1) |
| Metformin + sulfonylureas | 463 (13.1) |
| Metformin + glinides | 79 (2.2) |
| Thiazolidinediones | 22 (0.6) |
| DPP4 inhibitors | 19 (0.5) |
| Alpha-glucosidase inhibitors | 31 (0.8) |
| Insulin + oral agents (combined treatment) | 532 (15.1) |
| Metformin | 350 (9.9) |
| Sulfonylureas | 206 (5.8) |
| Glinides | 110 (3.1) |
| Thiazolidinediones | 2 (0.1) |
| DPP4 inhibitors | 4 (0.1) |
| Alpha-glucosidase inhibitors | 29 (0.8) |
| Undetermined or untreated | 123 (3.4) |
| *Comorbidities* | |
| Malnutrition | 165 (4.6) |
| Alcohol abuse | 119 (3.3) |
| Hypothyroidism | 148 (4.2) |
| Cardiovascular disease | 1884 (53.5) |
| Chronic kidney disease | 411 (11.6) |
| Cancer[c] | 312 (8.8) |
| Pancreatic disease[d] | 65 (1.8) |
| Chronic liver disease[e] | 138 (3.9) |
| Psychiatric disease | 148 (4.2) |
| Cognitive decline | 272 (7.7) |
| Chronic respiratory disease | 312 (8.8) |

Abbreviations: DPP4, dipeptidyl peptidase-4.
[a] Variables described as mean and [standard deviation].
[b] Variable described as median and [interquartile range].
[c] Patients with a diagnosis of pancreatic or hepatocellular carcinoma are included.
[d] Includes 40 patients with pancreatic carcinoma.
[e] Includes 9 patients with hepatocellular carcinoma.

vs. insulin), 15.1% were on combination treatment (insulin + oral agents; age, 75 ± SD 12 years; $p < 0.001$ vs. other groups). In very few cases treatment was unrecorded ($n$ = 60, 1.7%) or subjects were reported as untreated ($n$ = 63, 1.8%). No hypoglycemic events were reported in association with glucagon-like peptide-1 agonists. Insulin was associated with either metformin or insulin-secretagogues in 15% and 14% of insulin-treated cases, respectively, frequently combined. In non-insulin-treated cases, insulin secretagogues (sulfonylureas/repaglinide), either alone or combined with metformin, were reported in 87% of cases (6% in subjects on metformin alone), few cases ($n$ = 23) received DPP-4 inhibitors (DPP4i) and in 6% the glucose-lowering drug was undetermined. Notably, among DPP4i-treated patients, insulin was present in 4, metformin was present in 18, sulfonylureas in 11, repaglinide in 4, thiazolidinediones in 2, variably combined. The type of sulfonylurea was recorded in 872 of 966 cases (90.2%). Glibenclamide was the most frequently used drug (56.2%), followed by glimepiride (25.2%), gliclazide (17%) and a very rare use of gliquidone ($n$ = 9) and glipizide ($n$ = 4).

A total of 2320 (65.9%) cases with diabetes were characterized by one or more comorbidities, including cardiovascular disease, chronic kidney disease, chronic respiratory disease, cancer, cognitive decline, malnutrition, psychiatric disease, hypothyroidism, chronic hepatic failure (0.3% with hepatocellular carcinoma), alcohol abuse, and pancreatic disease (1.1% with pancreatic carcinoma).

### *Disposition*

Disposition was recorded in 3507 cases with diabetes (99.7% of total cases). Following the ED visit, 1498 cases (42.7%) were sent home and referred for outpatient visits to their GPs/Diabetes Units; 604 cases (17.2%) received a short-term intensive observation; 1161 (33.1%) were admitted to different departments according to specific conditions and/or local hospital organization (Internal Medicine, Pediatric, Geriatric Departments, 84.6%; Critical Care Departments, 2.3%; Endocrine/Metabolic Departments, 6.2%; Surgical/Trauma Centers, 1.1%; other Departments, 5.8%). Five patients died (no death occurred in subjects with trauma or involved in road accidents). The remaining 239 cases (6.8%) either refused admission to hospital or were referred to nursing homes (<1%).

Patients' disposition is reported in Table 2. Outpatient referral to GPs/Diabetes Units was much more common in insulin-treated cases and in subjects on combination treatment vs. cases treated by sole oral agents; whereas short-term intensive observation and admission to hospital was more common for events associated with oral glucose-lowering drugs.

Factors associated with either a short-term intensive observation or hospital admission are reported in Table 3. Compared to outpatient referral to GPs/Diabetes Units, both short-term intensive observation and hospital admission were associated with older age. The risk of hospital disposition was reduced by insulin use and increased by treatment with oral agents. Trauma or road accidents at the time of hypoglycemia were also associated with prolonged observation, as were several comorbidities, and the risk increased by 26% for any additional registered comorbidity. The results of the sensitivity analysis performed on patients with a recorded pre-hospital blood glucose ≤3.9 mmol/L were not systematically different from the overall findings.

**Table 2** Disposition of subjects with diabetes attending the EDs according to the reported glucose-lowering treatment.

| | Referred to GPs/diabetes units ($n$ = 1498) | Short-term observation ($n$ = 604) | Admission to hospital ($n$ = 1161) | Refused admission/sent to nursing homes ($n$ = 239) |
|---|---|---|---|---|
| Insulin-treated ($n$ = 1749) | 877 (50.1%) | 280 (16.0%) | 446 (25.5%) | 146 (8.3%) |
| Treated by oral agents ($n$ = 1104)[a] | 330 (29.9%) | 218 (19.7%) | 499 (45.2%) | 55 (5.0%) |
| Combination treatment ($n$ = 532)[a] | 238 (44.7%) | 98 (18.4%) | 161 (30.3%) | 32 (6.0%) |
| No/undefined treatment ($n$ = 122) | 53 (43.4%) | 8 (6.6%) | 55 (45.1%) | 6 (4.9%) |
| $p$ Value | | | | |
| Insulin vs. oral | <0.0001 | 0.012 | <0.0001 | 0.0008 |
| Insulin vs. combination | 0.032 | 0.213 | 0.033 | 0.096 |
| Oral vs. combination | <0.0001 | 0.569 | <0.0001 | 0.450 |

[a] Five patients died in the ED; 2 cases were on oral agents and 3 cases on combination treatment.

### *Hospital admission*

Follow-up data after admission was available in 898 of 1161 cases (77.3%). A total of 760 cases (84.6%) were discharged after a median length of stay of 6 days (range, 1–80), without differences in relation to diabetes treatment. A total of 88 cases (9.8%) died in hospital; 50 (5.7%) were transferred to other institutions/nursing homes. No differences in death rate were observed in relation to the type of glucose-lowering drugs associated with hypoglycemia (insulin, 33/334 = 9.9%; oral agents, 39/396 = 9.8%; combination treatment, 13/144 = 9%). Three patients initially classified with no/undefined treatment also died. After adjusting for covariates, in-hospital death was associated with the number of comorbidities (OR, 1.28; 95% CI, 1.01–1.63) (data not shown).

## Discussion

The study identified a large number of severe hypoglycemic events requiring hospital treatment in the diabetes population. The episodes were associated with a significant work-up of both the out-of-hospital and in-hospital emergency services and were followed by a high number of admissions with a remarkable death rate.

Based upon the evidence collected in our study, in Italy (60 million inhabitants), approximately 12,000 individuals with diabetes are thus expected to attend the EDs for a severe hypoglycemic event each year, which will require the intervention of out-of-hospital Emergency services in nearly 6000 cases. Considering that the large majority of hypoglycemic episodes are corrected at home without the intervention of the out-of-hospital Emergency services, or

**Table 3** Analysis of factors associated with final disposition in subjects with diabetes attending the EDs after a hypoglycemic event (OR and 95% CI). Out-of-hospital referral to GPs/Diabetes Units was considered as reference ($n$ = 1498).

| | ORs and 95% CI | | ORs and 95% CI | |
|---|---|---|---|---|
| | All patients with diabetes | | BG at event ≤3.9 mmol/L | |
| | Short-term observation ($n$ = 604) | Admission to hospital ($n$ = 1161) | Short-term observation ($n$ = 348) | Admission to hospital ($n$ = 708) |
| Age (years/10)[a] | 1.17 (1.10–1.24) | 1.39 (1.31–1.48) | 1.21 (1.12–1.32) | 1.40 (1.30–1.51) |
| Female gender[a] | 1.08 (0.89–1.30) | 0.91 (0.78–1.08) | 1.01 (0.79–1.31) | 0.87 (0.71–1.06) |
| BG at event (mg/dL/10)[a] | 0.97 (0.93–1.02) | 0.92 (0.88–0.96) | 0.96 (0.87–1.05) | 0.87 (0.81–0.95) |
| Insulin use[a] | 0.61 (0.50–0.76) | 0.45 (0.38–0.54) | 0.64 (0.48–0.84) | 0.42 (0.34–0.54) |
| Oral agents[a] | 1.57 (1.28–1.94) | 1.63 (1.37–1.94) | 1.31 (1.01–1.72) | 1.58 (1.27–1.97) |
| Trauma[a] | 1.41 (1.01–1.99) | 1.31 (0.97–1.78) | 1.29 (0.83–2.03) | 1.32 (0.91–1.93) |
| Road accident[a] | 2.75 (1.31–5.76) | 1.58 (0.69–3.62) | 3.75 (1.56–9.05) | 1.92 (0.73–5.04) |
| Number of comorbidities[a] | 0.92 (0.82–1.04) | 1.51 (1.38–1.66) | 0.92 (0.81–1.10) | 1.39 (1.24–1.56) |
| Malnutrition[b] | 1.37 (0.83–2.27) | 2.59 (1.76–3.08) | 1.63 (0.89–2.90) | 2.37 (1.47–3.82) |
| Cardiovascular disease[b] | 0.94 (0.77–1.16) | 1.60 (1.34–1.90) | 0.99 (0.75–1.30) | 1.33 (1.06–1.66) |
| Chronic kidney disease[b] | 0.94 (0.68–1.30) | 1.56 (1.22–1.98) | 0.90 (0.60–1.35) | 1.60 (1.20–2.14) |
| End-stage renal disease[b] | 0.49 (0.14–1.69) | 1.23 (0.57–2.66) | 0.43 (0.10–1.96) | 1.14 (0.48–2.72) |
| Cancer[b] | 0.98 (0.67–1.41) | 1.73 (1.31–2.27) | 1.09 (0.70–1.72) | 1.67 (1.19–2.34) |
| Pancreatic disease[b] | 1.11 (0.54–2.26) | 1.61 (0.91–2.86) | 1.19 (0.52–2.75) | 1.45 (0.74–2.86) |
| Chronic liver disease[b] | 1.09 (0.64–1.87) | 2.13 (1.43–3.17) | 1.32 (0.69–2.54) | 2.06 (1.25–3.38) |
| Psychiatric disease[b] | 0.99 (0.58–1.68) | 1.92 (1.28–2.87) | 0.80 (0.39–1.63) | 1.52 (0.91–2.53) |
| Cognitive decline[b] | 0.86 (0.57–1.30) | 1.45 (1.08–1.95) | 0.82 (0.49–1.37) | 1.30 (0.90–1.87) |
| Chronic respiratory disease[b] | 0.67 (0.45–1.00) | 1.45 (1.11–1.89) | 0.68 (0.42–1.09) | 1.15 (0.83–1.59) |
| Parkinson's disease[b] | 1.10 (0.56–2.19) | 1.79 (1.08–2.97) | 1.37 (0.61–3.07) | 1.76 (0.95–3.29) |

Abbreviations: BG, blood glucose.
[a] Data adjusted for age, gender, and number of comorbidities (except when stratified by the given variable).
[b] Data adjusted for age and gender.

subjects are safely treated at home by Emergency services [13], or admission is refused [12], these events are only the tip of the hypoglycemia iceberg. Our results are in keeping with other reports of the literature [14], although comparison is limited by differences in health services. In a recent study combining two National US databases, approximately 100,000 ED visits for insulin-related hypoglycemia and errors were estimated to occur annually in US [12], with almost one third of events resulting in hospital admission. In the US analysis, 21.1% of insulin-treated patients were on combination therapy with other lowering-glucose medications [12], a percentage similar to our data (23.3%); in UK, 73% of patients with diabetes experiencing a hypoglycemic event during hospital admission were insulin-treated [15], similar to the overall percentage in our setting (65%).

Nearly one in three cases of hypoglycemia occurred in non-insulin treated subjects, and again, in most cases, in subjects using insulin-secretagogues. Similarly, 24% of hypoglycemic events occurring in hospitalized subjects with diabetes were reported in subjects on oral agents alone [15]. The association between insulin-secretagogues and hypoglycemia has been widely described, leads to more intensive work-up and prolongs hospital length of stay because of the risk of prolonged or recurrent hypoglycemia. In Italy, the widespread use of combination pills containing metformin and glibenclamide [16] was responsible for the high risk of secretagogues-associated hypoglycemia, particularly when added to basal insulin. In our setting, very few cases were ascribed to metformin *per se*, or to glitazones, or to the new class of DPP4i. Although DPP4i cover only a limited proportion of subjects with T2DM, the low number of recorded hypoglycemic events is in line with the literature and the monitoring system operated by the Italian Medicines Agency [17].

The hypoglycemic event was associated with trauma or road accidents in several cases, although the retrospective nature of the analysis does not allow us to make any inference on a possible causal relationship. In our survey, trauma was associated with insulin use in 69% of cases and with oral agents in 35%. Similarly, road accidents (mean age of patients, 59 years) were associated with insulin use in 70% of cases and with oral agents in 40%. Johnston et al. [18] reported increased ORs of fall-related fractures in association with hypoglycemia in Medicare-covered patients with T2DM aged 65 or older; Signorovitch et al. [19] reported a 36% increased hazard ratio of accidental falls leading to hospital visits in T2DM individuals with claims of hypoglycemia. People with diabetes are considered at higher risk of being involved in road accidents, but the issue is largely debated. A few studies indicated a 2-fold increased risk in T1DM, but the risk, although rarer, was not limited to insulin-treated subjects [20], and was mostly related to tight glucose control [21].

In addition to glucose-lowering drug, the presence, number and severity of comorbidities dictated the disposition and hospital admission. Furthermore, older age was associated with a high risk of both short-term observation and hospital admission. Hospitalized patients were mostly characterized by a frailty profile, largely explaining the significant in-hospital death rate following the admission (nearly 10%). Mortality has previously been directly linked to documented severe hypoglycemia in both T1DM and T2DM. Severe hypoglycemia may worsen cardiovascular disease (both arrhythmias and coronary artery disease) [22,23], through mechanisms mediated by oxidative stress and atherotrombosis [24], as well as chronic kidney disease (in turn associated with cardiovascular mortality) [25]. The presence of diabetes *per se* was also associated with an increased death risk in cirrhosis, and hypoglycemia was reported in hepatocellular carcinoma [26]. A high death rate was reported in hospitalized patients with diabetes following an in-hospital episode of hypoglycemia [15], as well as in hypoglycemia associated with hospitalization [27], and in community-living diabetes, where severe hypoglycemia more than doubled all-cause 5-year mortality [22]. All these findings support the notion of hypoglycemia as a marker of vulnerability and as the consequence of other acute events associated with mortality, particularly in the elderly with long disease duration [28,29].

The strengths of our study include its setting within a universalistic (Beveridge type) healthcare system, which limits the role of referral bias. All the participating EDs were part of the SIMEU study group, a network repeatedly involved in retrospective data collections, thus reducing the risk of selection bias, however possible. The large number of participating EDs (46 EDs of regional general hospitals, covering a population of more than 12-million people all over Italy) may guarantee good external validity. The study has limitations too. Its retrospective nature may have led to underestimation of events, only based on search terms as a surrogate for actual hypoglycemia, as well as comorbidity rates, recorded from history and not from laboratory values. To minimize this bias, we included in the analysis only data from EDs with a large experience in the collection of retrospective data, where a systematic evaluation of comorbidities, drug use, and final disposition could be retrieved, further confirmed by audits in a few cases. The finding that approximately 92% of events with a recorded pre-hospital blood glucose measure had values below the ADA threshold for the diagnosis of hypoglycemia ($\leq$3.9 mmol/L) [1] supports the accuracy of our event adjudication. Blood glucose at the time of event was available only in 65.8% patients and misdiagnosis of hypoglycemia may thus have occurred. However, the sensitivity analysis restricted to cases fulfilling ADA criteria did not change from the overall results, making this possibility unlikely. Finally, information on the type of diabetes, specific insulin therapy, causes of death as well as other factors playing a role in the pathogenesis of the hypoglycemic event and its final outcome (e.g., infection, etc.) were not investigated.

In conclusion, hypoglycemia, both in association with insulin treatment and with non-insulin glucose-lowering drugs, when severe enough to justify attendance to EDs, represents a remarkable burden for individuals with diabetes, increasing the risk of serious events and adverse

outcomes, especially in elderly and frail patients, and has a considerable impact on resource utilization of National Health Systems. Only recently the clinical standards for metabolic control considered the existing evidence about the risk for hypoglycemia in vulnerable populations [30]. Our report, confirming other very recent data based on community-derived evidence [12], argue that any effort should be made to give emphasis to the risk of hypoglycemic events in diabetes care, by individualizing metabolic targets, by selecting drugs at low risk of hypoglycemia, and by providing adequate education to reduce the impending risk of hypoglycemic events in the large population with diabetes.

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## Conflict of interest

G. Marchesini received honoraria for lectures by Sanofi, MSD, and Novartis; he is a member of Sanofi advisory board and received funding for clinical studies from Boehringer Ingelheim, Sanofi, Lilly, Novo Nordisk. G. Forlani received grants from Boehringer Ingelheim, Sanofi, Lilly, Novo Nordisk, Artsana, MSD. G. Veronese, Giulia Forlani, Laura M. Ricciardi, and A. Fabbri had no conflicts of interest to declare.

## Contribution statement

G. Marchesini, G. Veronese, G. Forlani, and A. Fabbri contributed to conception and design of the study. G. Marchesini and G. Veronese collected and analyzed the data. G. Marchesini, G. Veronese and A. Fabbri reviewed the literature. Giulia Forlani contributed to data collection. Laura M. Ricciardi contributed to study organization. G. Marchesini wrote the initial draft. All authors substantially contributed to conception and design or analysis and interpretation of data and drafting of the article or critical revision for important intellectual content.

## Appendix A. Supplementary material

Supplementary material related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2014.05.012.

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