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Original Research

Severe hypoglycemia in patients with known diabetes requiring emergency department care: A report from an Italian multicenter study

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ABSTRACT

Aims: To describe the characteristics and associated risk factors of patients with established diabetes who required Emergency Department (ED) care for severe hypoglycemia.
Methods: We performed an observational retrospective study to identify all cases of severe hypoglycemia among attendees at the EDs of three Italian University hospitals from January 2010 to December 2014.
Results: Overall, 520 patients with established diabetes were identified. Mean out-of-hospital blood glucose concentrations at the time of the hypoglycemic event were 2.2 ± 1.3 mmol/L. Most of these patients were frail and had multiple comorbidities. They were treated with oral hypoglycemic drugs (43.6%), insulin (42.8%), or both (13.6%). Among the oral hypoglycemic drugs, glibenclamide (54.5%) and repaglinide (25.7%) were the two most frequently used drugs, followed by glimepiride (11.3%) and gliclazide (7.5%). Hospitalization rates and in-hospital deaths occurred in 35.4% and in 2.3% of patients, respectively. Cirrhosis (odds ratio [OR] 6.76, 95% confidence interval [CI] 1.24–36.8, $p < 0.05$), chronic kidney disease (OR 2.42, 95% CI 1.11–8.69, $p < 0.05$) and center (Sapienza University OR 3.70, 95% CI 1.57–8.69, $p < 0.05$) were the strongest predictors of increased rates of hospital admission.
Conclusions: Severe hypoglycemia is a remarkable burden for patients with established diabetes and increases the risk of adverse clinical outcomes (in-hospital death and hospitalization), mainly in elderly and frail patients. This study further reinforces the notion that careful attention should be taken by health care providers when they prescribe drug therapy in elderly patients with serious comorbidities.

Introduction

Severe hypoglycemia is defined as having low blood glucose concentrations that require assistance from another person to treat and has the potential to cause accidents, injuries, coma and death [1]. Severe hypoglycemia is a relatively frequent event in patients with established diabetes that also markedly impacts on health resources [1]. It is estimated that the event rates for severe hypoglycemia range from 115 to 320 per 100 patient/years for patients with type 1 diabetes, and from 35 to 70 per 100 patient/years for those with type 2 diabetes [2,3]. Hypoglycemia may be due to multiple causes, such as the misuse of insulin therapy, the use of oral hypoglycemic drugs with a higher risk of hypoglycemia (*e.g.*, sulfonylureas and repaglinide) or the combination of multiple drugs that may interact with each other, such as antibiotics and sulfonylureas [1–6]. Importantly, Leese et al. reported that the rate of severe hypoglycemia was as common in patients with type 2 diabetes treated with insulin as in patients with type 1 diabetes [7].

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For the clinicians, reaching a tight glycemic control is often an important goal to minimize the development and progression of chronic complications in many patients with type 1 or type 2 diabetes but, as also highlighted by recent clinical trials, many doubts remain regarding the 'optimal' glycemic targets in older patients with type 2 diabetes [8–12]. Several international guidelines suggest that the targets for glucose control should be less stringent in older patients with diabetes, and promote the use of oral hypoglycemic drugs that cause less frequently hypoglycemia in this group of more vulnerable patients [13,14].

Moreover, it is also important to consider that the costs of severe hypoglycemias for public health are very high, especially if we also consider the costs arising from the use of ambulance, on-site treatment, access to emergency department and admission to the hospital [15].

Therefore, it is clinically important to identify and implement new strategies aimed at reducing the risk of severe hypoglycemias in patients with established diabetes. Presently, there is a paucity of available data on the prevalence of severe hypoglycemias in patients with established diabetes attending the emergency department (ED) [4,6].

Thus, the aim of this multicenter study was to describe the main characteristics and the associated risk factors of patients with established diabetes requiring ED care for severe hypoglycemia.

Materials and methods

Patients

We performed a retrospective multicenter study identifying all cases of severe hypoglycemia among patients with established diabetes, who attended the ED of three Italian University Hospitals ('Sapienza' University of Rome, 'Tor Vergata' University of Rome, and University and Azienda Ospedaliera Universitaria Integrata of Verona) over the period between January 2010 and December 2014. Where an individual had had multiple accesses in the ED for severe hypoglycemia during this period, only the first access with complete data was considered for the statistical analysis.

Initially, we electronically searched for the terms "hypoglycemia" or "hypoglycemic event" in the discharge diagnosis from the hospital, or for recorded blood glucose levels less than 3.8 mmol/L (<70 mg/dL) at ED admission, so identifying a total of 879 patients. Patients without previously known diabetes before ED admission (n = 359) were excluded from statistical analysis. We think the relatively high prevalence of hypoglycemic events in this subgroup of patients without previously known diabetes was likely due to the following two factors. Firstly, we used a threshold of 3.8 mmol/L (<70 mg/dL) to identify any hypoglycemic events with a possible overestimation of the events. Secondly, as reported in Supplemental Table S1, there was a high prevalence of cirrhosis and cancer (*i.e.*, two diseases known to cause mild-to-moderate hypoglycemias) among patients attending the ED of Sapienza University, a hospital where many patients, who are in liver transplant list, come to get the cure.

As a result of this selection, 520 (286 men and 234 women) patients with established diabetes were included in final analysis. The diagnosis of the type of diabetes was made according to what reported on the ED's electronic records and then confirmed by the diabetes registers when available (Verona University). A flow chart of the study is summarized in Fig. 1.

The ethics committees of the three University hospitals approved the study protocol. The informed consent requirement for the study was exempted by the ethics committee, because researchers only accessed retrospectively a de-identified database for analysis purposes.

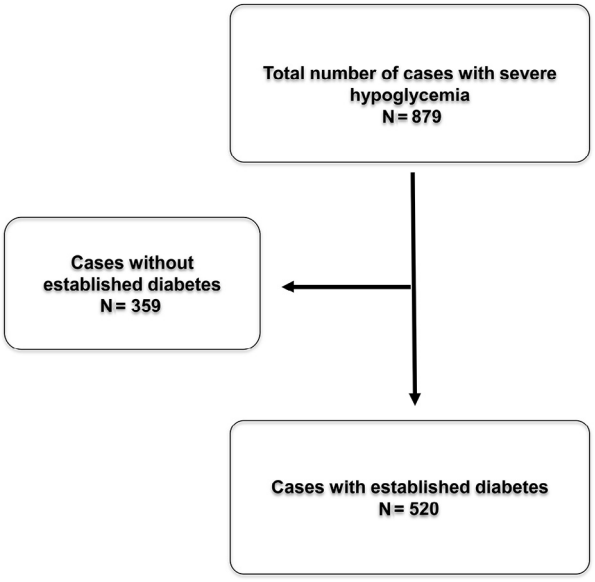

Figure 1. Details of the study design.

Data collection

Information on age, sex, type of diabetes, blood glucose concentrations at the time of the hypoglycemic event (measured at home and/or by the ambulance staff), blood glucose concentrations measured in EDs, use of any medications (including hypoglycemic drugs), alcohol abuse, emergency codes given at the triage, and rates of hospital admission and in-hospital mortality were extracted by the ED's electronic databases. Information on ambulance calls, falls and coma (using the Glasgow Coma Scale) was also extracted by the electronic databases.

Information on main comorbidities was also recorded for all patients. Presence of cardiovascular diseases was defined as a prior diagnosis of ischemic heart disease or ischemic stroke; arrhythmias included a history of any disturbance of cardiac rhythm or use of antiarrhythmic drugs; chronic kidney disease (CKD) included any diagnosis of moderate-to-severe chronic renal failure (defined as an $eGFR_{MDRD}$ <60 or <30 mL/min/1.73 m^2, respectively) and/or dialysis; chronic liver diseases were limited to a prior diagnosis of cirrhosis of any etiology; cancer included both solid and blood malignancies; finally, the presence of a prior history of dementia included any diagnosis of cognitive impairment.

Statistical analysis

Data are presented as means ± standard deviation (SD), medians (interquartile range, IQR) or percentages. Skewed variables (*i.e.*, serum creatinine and alanine aminotransferase levels) were logarithmically transformed to improve normality prior to analysis. The one-way ANOVA test (for continuous variables) and the chi-squared test (for categorical variables) were used to compare the clinical and biochemical characteristics of patients with diabetes stratified either by the type of treatment (secretagogues alone [*i.e.*, glibenclamide, glimepiride, gliclazide, repaglinide], insulin alone, or insulin plus secretagogues) or by the three participating EDs (see Fig. 3 and Supplemental Table S1, respectively). Univariate logistic regression analysis was used to examine the risk factors associated with subsequent hospital admission, which was included as the dependent variable. Subsequently, we performed a multivariate logistic regression analysis that included as covariates all significant

predictors in the univariate analysis (Table 2). We also repeated all these analyses separately in patients with type 1 diabetes and in those with type 2 diabetes (Table 2).

A *p*-value <0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS software, version 22.0 (IBM Corp, Armonk, NY).

Results

Baseline clinical and biochemical characteristics of patients

Of the 520 patients with established diabetes included in the study, 444 (85.4%) patients had type 2 diabetes, 68 (13.1%) had type 1 diabetes and the remaining 8 patients had diabetes due to other secondary causes.

Table 1 shows the main clinical and biochemical characteristics of the study participants. Overall, 332 (55%) were male and their mean age was 72 years. Mean out-of-hospital blood glucose concentrations at the time of the hypoglycemic event (measured at home and/or by the ambulance staff) were 2.2 ± 1.3 mmol/L. Conversely, blood glucose concentrations measured in the ED's laboratories were 4.2 ± 2.8 mmol/L.

Most patients had one or more co-morbidities, such as ischemic heart disease (occurring in 30.1% of cases), cancer (14.4%), cirrhosis (6.8%), dementia (12.3%), arrhythmias (9.0%), chronic obstructive pulmonary disease (15.0%) or end-stage renal disease (4.8%).

Table 1
Main clinical and biochemical characteristics of patients with established diabetes attending the emergency department (ED) for severe hypoglycemia

Characteristics	Overall (n = 520)	Patients with T1DM (n = 68)	Patients with T2DM (n = 444)
Male sex (n, %)	286 (55%)	64%	54%
Age (years)	72 ± 16	43 ± 18	75 ± 13
Type of diabetes (n, %)			
Type 1	68 (13.1%)	68 (100%)	0
Type 2	444 (85.4%)	0	444 (100%)
Others	8 (1.5%)	0	0
Diabetes duration (years)	22 ± 11	25 ± 10	21 ± 8
Out-of-hospital blood glucose (mmol/L)	2.2 ± 1.3	2.1 ± 0.8	2.2 ± 0.9
Blood glucose recorded in ED (mmol/L)	4.2 ± 2.8	5.0 ± 4.1	4.0 ± 2.6
Glucose stick recorded in ED (mmol/L)	4.8 ± 3.0	5.6 ± 3.5	4.7 ± 2.9
Hemoglobin (g/L)	122 ± 19	141 ± 14	120 ± 19
Platelets (× 100,000/mm^3)	243 ± 96	236 ± 89	245 ± 92
Creatinine (umol/L)	97 [70–158]	75 [64–87]	106 [76–158]
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	61 ± 40	93 ± 37	57 ± 39
$eGFR_{MDRD}$ <30 mL/min/1.73 m^2 (n, %)	107 (20.6%)	4.5%	23.4%
$eGFR_{MDRD}$ 30–60 mL/min/1.73 m^2 (n, %)	299 (57.6%)	14.7%	65.1%
ALT (U/L)	19 [13–31]	23 [17–29]	18 [12–31]
Falls at home (n, %)	90 (17.6%)	26.0%	16.4%
Ambulance calls (n, %)	384 (74.1%)	72.0%	75.6%
Medical triage code (n, %)			
White/Green	83 (16.1%)	6.0%	17.8%
Yellow	374 (72.3%)	90.0%	68.7%
Red	60 (11.6%)	4.0%	12.8%
Glasgow coma scale (n, %)			
>7	351 (96.2%)	97.4%	62.4%
≤7	14 (3.8%)	2.6%	2.7%
One oral glucose-lowering agent users (n, %)	99 (19.1%)	0%	22.3%
Two oral glucose-lowering agents users (n, %)	118 (22.8%)	0%	26.5%
Three oral glucose-lowering agents users (n, %)	9 (1.7%)	0%	20.3%
Insulin users (n, %)	223 (42.8%)	100%	34.9%
Combination therapy users (n, %)	71 (13.6%)	0%	15.9%
Statin users (n, %)	164 (33.0%)	19.3%	34.0%
Anti-platelet drug users (n, %)	219 (44.1%)	18.7%	46.3%
Anti-coagulant users (n, %)	63 (12.7%)	10.3%	12.6%
Diuretic users (n, %)	191 (38.4%)	10.0%	41.4%
Beta-blocker users (n, %)	106 (21.3%)	6.6%	22.9%
Calcium channel blocker users (n, %)	105 (21.1%)	12.5%	21.8%
Nitrate users (n, %)	51 (10.3%)	0%	17.9%
ACE-I/ARB users (n, %)	222 (44.7%)	42.4%	43.4%
Cardiac arrhythmias (n, %)	45 (9.0%)	6.6%	9.2%
Ischemic heart disease (n, %)	134 (30%)	9.3%	28.9%
Dialysis (n, %)	21 (4.8%)	2.9%	3.9%
Hypertension (n, %)	346 (73.8%)	56.8%	69.3%
Chronic obstructive pulmonary disease (n, %)	66 (15.0%)	2.3%	14.6%
Cirrhosis (n, %)	29 (6.5%)	6.8%	5.6%
Alcohol abusers (n, %)	12 (5.3%)	0%	2.7%
Dementia (n, %)	54 (12.3%)	4.6%	11.4%
Cancer (n, %)	63 (14.4%)	4.6%	13.5%
Hospital admission rate (n, %)	184 (35.4%)	5.8%	40.5%
Length of hospital stay (days)	14.7 ± 12.2	4.0 ± 1.0	15.1 ± 12.1
Total mortality (n, %)	12 (2.3%)	0%	2.7%

Sample size, N = 520. Data are expressed as means ± SD, medians and interquartile range (IQR) or absolute and relative proportions. Combination therapy was defined as the use of insulin plus oral hypoglycemic agents. ACE-I, ACE-inhibitors; ALT, alanine aminotransferase; ARB, angiotensin II receptor blockers; ED, emergency department; eGFR, estimated glomerular filtration rate; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

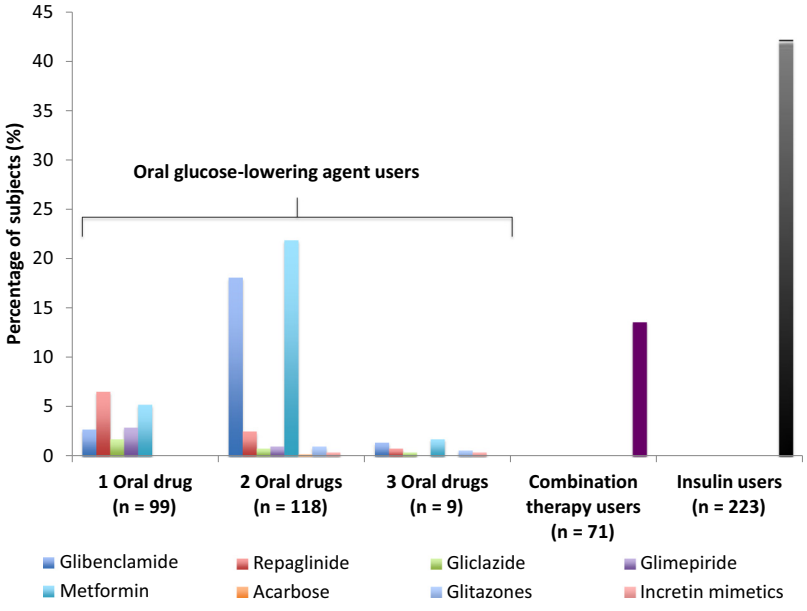

Figure 2. Frequency of various hypoglycemic drugs in patients with established diabetes attending the ED for severe hypoglycemia. N = 520.

Alcohol abuse was present in 5.3% of patients. Overall, severe hypoglycemias requiring extra-familial assistance by the out-of-hospital emergency services occurred in 74.1% of patients and were associated with falls at home in 17.6% of cases. A Glasgow Coma Scale score ≤7 was reported in 3.8% of patients. At the medical triage, the most frequently emergency code assigned was the yellow code (72.3%), which identifies patients with serious health conditions.

The clinical and biochemical characteristics of patients with diabetes stratified by the three participating EDs are shown in Supplemental Table S1. Patients attending the ED of Sapienza University had more severe comorbidities (i.e., cirrhosis, cancer, dementia, ischemic heart disease, chronic obstructive pulmonary disease) than those attending the EDs of the other two University hospitals.

As also shown in Table 1, in the whole sample, hospitalization rates occurred in 35.4% of patients, whereas in-hospital deaths occurred in 2.3% of cases. The average length of hospital stay was 14.7 ± 12.2 days. Interestingly, when patients were stratified by type of diabetes, those with type 2 diabetes were older and had a higher prevalence of main comorbidities (*e.g.*, cardiac arrhythmias, cancer, dementia, ischemic heart disease, chronic obstructive pulmonary disease) than patients with type 1 diabetes. Consequently, the hospital admission rate and the length of hospital stay were lower in patients with type 1 diabetes than in those with type 2 diabetes. No patients with type 1 diabetes died.

Collectively, 43.6% of patients were treated with oral hypoglycemic agents, 42.8% with insulin and 13.6% with combined therapy. Among patients with type 1 diabetes, only a patient was treated with insulin pump therapy, whereas all others were treated with intensive conventional therapy.

When patients with type 2 diabetes were stratified by age, we found that 53% of those aged ≥65 years were treated with oral hypoglycemic drugs alone, 35% with insulin therapy and the remaining 12% with combined therapy (data not shown). Among those treated with oral hypoglycemic drugs, we found that the use of sulfonylureas (*i.e.,* glibenclamide, gliclazide and glimepiride) was similar among patients older than 65 years and those aged <65 years (84.6% *vs.* 72.1%, p = 0.24). Conversely, the use of repaglinide was higher in patients older than ≥65 years compared with those aged <65 years (27.5% *vs.* 1.2%, p = 0.02).

Interestingly, as shown in Fig. 2, among patients treated with a single oral hypoglycemic drug, repaglinide was the most frequently used drug, followed by metformin, glimepiride, glibenclamide and gliclazide. In contrast, glibenclamide and metformin were the two most common used drugs among those treated with two or three oral hypoglycemic drugs. Overall, among the oral hypoglycemic drugs, 73.0% were sulfonylureas, and glibenclamide (54.5%) was the most frequently used sulfonylurea, followed by glimepiride (11.3%) and gliclazide (7.5%). Repaglinide was used in 25.7% of these patients.

Fig. 3 shows the frequency of main comorbidities in patients with type 2 diabetes in relation to the different types of diabetes treatment (*i.e.*, secretagogues alone, insulin, or both). Compared with those treated with either secretagogues or insulin alone, patients with type 2 diabetes treated with combined therapy had a higher prevalence of CKD. Conversely, patients treated with insulin alone had a higher prevalence of cirrhosis.

Predictors of hospital admission

Table 2 shows the independent predictors of hospital admission in patients attending the EDs for severe hypoglycemia. Logistic regression analysis revealed that cirrhosis (OR 6.76, 95% CI 1.24–36.8, p < 0.05), CKD (OR 2.42, 95% CI 1.11–8.69, p < 0.05) and center (Sapienza University, OR 3.70, 95% CI 1.57–8.69, p < 0.05) were the strongest and independent predictors of subsequent admission to the hospital, whereas the type of diabetes treatment was not. We also performed separate analyses in patients with type 2 and type 1 diabetes. Similarly, we found that cirrhosis (OR 3.34, 95% CI 1.12–27.1, p < 0.05), CKD (OR 2.03, 95% CI 1.09–4.20, p < 0.05) and center (Sapienza University, OR 3.57, 95% CI 1.42–9.02, p < 0.05) were the strongest predictors of increased hospitalization rates in patients with type 2 diabetes. Conversely, only cirrhosis (OR 9.14, 95% CI 0.98–85.3, p = 0.05) was a significant predictor of increased hospitalization rates in patients with type 1 diabetes. However, given the small

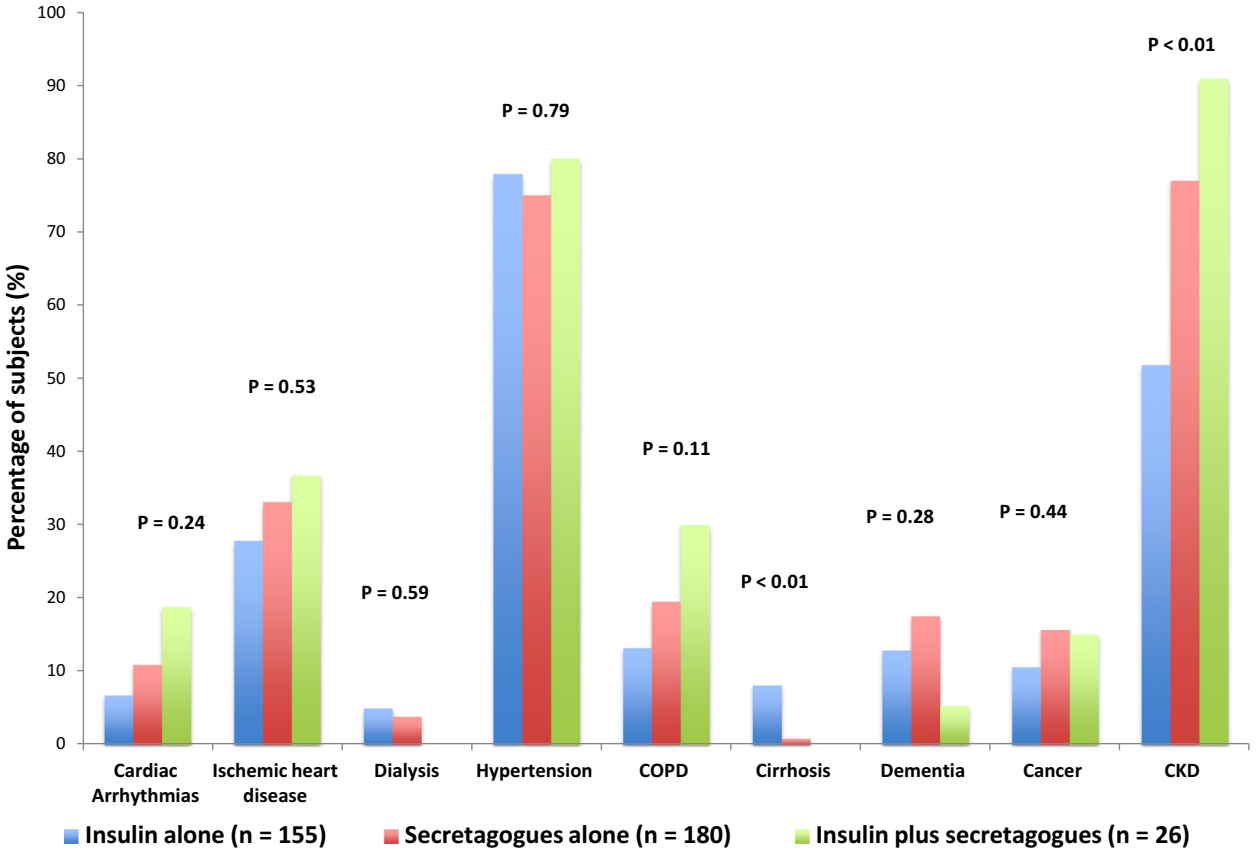

Figure 3. Frequency of comorbidities in patients with type 2 diabetes attending the ED for severe hypoglycemia according to different types of drug treatment for diabetes (i.e., secretagogues alone, insulin, or insulin plus secretagogues). Note: secretagogues include glibenclamide, glimepiride, gliclazide and repaglinide. Chronic kidney disease (CKD) was defined as $eGFR_{MDRD} < 60$ mL/min/1.73 m^2 and/or dialysis. COPD, chronic obstructive pulmonary disease.

number of patients with type 1 diabetes, these results should be interpreted with some caution.

Discussion

It is known that the rates of symptomatic hypoglycemia in patients with established diabetes are relatively high, since nearly 10–15% of patients with type 1 diabetes have severe hypoglycemia with seizure or loss of consciousness per year, and, even though less frequently, these events also occur in patients with type 2 diabetes [1–3,16].

In this multicenter study involving three Italian University hospitals, we identified a relatively high rate of severe hypoglycemias (i.e., a total of 520 cases over a period of 4 years) in patients with established diabetes requiring ED cure. However, since the patients themselves usually treat most of their mild or moderate hypoglycemic events without any assistance from another person, it is important to underline that our results represent only the "tip of the iceberg" of a serious clinical health problem. Therefore, it is plausible to assume that our results may largely underestimate the prevalence of symptomatic hypoglycemias in people with established diabetes.

In this multicenter study, we found that most cases of severe hypoglycemia occurred in older patients with one or more comorbidities. Our findings also confirm the results of another recent Italian multicenter study by Marchesini et al. who showed that older age, diabetes treatment and the number of comorbidities were the main predictors of ED admission for severe hypoglycemia [4]. However, some differences existing between these two studies merit to be discussed. Firstly, we also performed separate analyses in patients with type 1 and type 2 diabetes. Secondly, we examined the association of main comorbidities with diabetes treatment (*i.e.*, secretagogues, insulin, or both) in patients with type 2 diabetes, as we believe that the frequency of comorbidities may vary depending on diabetes treatment. In fact, we found that patients treated with insulin plus secretagogues had a greater prevalence of CKD, whereas those treated with insulin alone had a greater prevalence of cirrhosis. Thirdly, contrarily to our expectations, we did not observe any significant association between different types of diabetes treatment and risk of hospitalization (although there was a borderline significance for the sulfonylurea drug users).

In this study, the treatment of severe hypoglycemia appeared to be timely enough to allow a partial or complete resolution of the acute event, as suggested by the patient's blood glucose levels above the threshold of 3.8 mmol/L that were recorded in the ED's laboratories. However, no complete information was available about the different types of treatment used to correct hypoglycemic events both in EDs and out-of-hospital.

Notably, as shown in Table 1, insulin treatment was the most important drug responsible for severe hypoglycemia, since 56.4% of patients were treated with insulin, either singly (42.8%) or in combination with oral hypoglycemic drugs (13.6%). Accordingly, a recent large study performed in older Americans reported that insulin treatment was one of the most important drugs responsible for hospital admission for any adverse drug events, second only to warfarin use [17]. Similarly, Geller et al. showed that the rates of ED admission and subsequent hospitalization for insulin-induced hypoglycemia(s) were more than twice among patients with 80 years or older than

Table 2
Main predictors of hospital admission in patients with established diabetes requiring ED care for severe hypoglycemia

Multivariate logistic regression models	Odds ratio	95% CI	*P* value
Overall (n = 520)			
Age (years)	1.02	0.99–1.06	0.13
Sex (male *vs.* female)	0.89	0.42–1.87	0.76
Insulin users (yes *vs.* no)	0.61	0.13–2.81	0.53
Sulfonylurea alone users (yes *vs.* no)	1.61	0.32–8.02	0.56
Two or more oral glucose-lowering drug users (yes *vs.* no)	1.63	0.35–7.62	0.53
Ischemic heart disease (yes *vs.* no)	1.34	0.61–2.92	0.46
Cirrhosis (yes *vs.* no)	6.76	1.24–36.8	<0.05
Dementia (yes *vs.* no)	1.94	0.69–5.45	0.20
Chronic kidney disease (yes *vs.* no)	2.42	1.11–8.09	<0.05
Sapienza Hospital (yes *vs.* no)	3.70	1.57–8.69	<0.05
T2DM (n = 444)			
Age (years)	1.03	0.98–1.07	0.26
Sex (male *vs.* female)	1.21	0.53–2.76	0.65
Insulin users (yes *vs.* no)	1.57	0.69–23.2	0.12
Sulfonylurea alone users (yes *vs.* no)	5.53	0.87–35.1	0.07
Two or more oral glucose-lowering drug users (yes *vs.* no)	4.01	0.69–23.2	0.60
Ischemic heart disease (yes *vs.* no)	1.88	0.80–4.42	0.15
Cirrhosis (yes *vs.* no)	3.34	1.12–27.1	<0.05
Dementia (yes *vs.* no)	1.99	0.68–5.80	0.21
Chronic kidney disease (yes *vs.* no)	2.03	1.09–4.20	<0.05
Sapienza Hospital (yes *vs.* no)	3.57	1.42–9.02	<0.05
T1DM (n = 68)			
Age (years)	0.93	0.84–1.05	0.25
Sex (male *vs.* female)	0.52	0.20–1.65	0.09
Ischemic heart disease (yes *vs.* no)	3.78	0.65–7.23	0.52
Cirrhosis (yes *vs.* no)	9.14	0.98–85.3	0.05
Chronic kidney disease (yes *vs.* no)	5.33	0.25–11.7	0.28
Sapienza Hospital (yes *vs.* no)	10.1	0.38–40.9	0.15

Data are expressed as odds ratios (OR) ± 95 % confidence intervals (CI) as assessed by multivariable logistic regression analysis. Hospital admission was the dependent variable in all logistic regression models. Chronic kidney disease was defined as $eGFR_{MDRD}$ <60 mL/min/1.73 m^2 and/or dialysis. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

among those with 45–64 years, and that almost one-third of insulin-induced hypoglycemia resulted in subsequent hospitalization [6].

In our study, glibenclamide and repaglinide were found to be the two oral hypoglycemic agents that were more frequently used by our patients with type 2 diabetes. According to the ARNO observatory database, glibenclamide, singly or in combination with metformin, is widely used in Italy for the treatment of diabetes, whereas repaglinide is frequently prescribed for older type 2 diabetic patients with CKD [18]. However, given the strong ability of both glibenclamide and repaglinide to increase pancreatic insulin secretion, these two oral drugs may confer a higher risk of drug-induced hypoglycemias, especially in older patients with multiple co-morbidities [19]. Conversely, in our study, a very small number of patients were treated with either glitazones or incretin-based therapies. This finding may largely reflect the limited use in Italy of these newer classes of hypoglycemic drugs during the period 2010–2014, when comparing with metformin and secretagogues, while being consistent anyhow with existing data that attribute a (relatively) lower risk of hypoglycemic events to these new hypoglycemic drugs. Notably and surprisingly, only 5% of our patients with type 2 diabetes were treated with metformin alone. It is important to note that these patients were identified using the terms "hypoglycemia" or "hypoglycemic event" in the discharge diagnoses from the EDs. Therefore, we are not able to rule out a misdiagnosis (as it happens quite often in EDs) for those diabetic patients who go to ED for any acute event of faintness, hypotension or loss of consciousness from other causes and get a diagnosis of "hypoglycemia" just because they have diabetes or are treated with any glucose-lowering agents. However, it cannot be also excluded that metformin may cause hypoglycemia especially in older patients with multiple comorbidities [20]. Interestingly, in our study, all patients treated with metformin alone had CKD and other severe comorbidities.

A relatively small number of our patients with severe hypoglycemia (17.6%) also reported an increased risk of falls at home. It is known that insulin treatment is associated with an increased risk of falls, especially in older patients [21]. Unfortunately, given the retrospective design of our multicenter study, we were unable to identify the exact causes or consequences of these falls.

The high prevalence of important comorbidities, such as ischemic heart disease, cancer, cirrhosis, dementia and CKD, we observed in this study, may explain, at least in part, the increased rates of subsequent hospitalization and the long duration of the hospital stay. Indeed, as reported in Table 2, cirrhosis and CKD were the two most important comorbidities that drove the hospital admission in our patients.

Overtreatment or even wrong treatment may be also suggested by the results of our multivariate logistic analyses: advanced liver and kidney diseases are two clinical pathologic conditions in which most of oral hypoglycemic drugs are either not indicated or should be used cautiously. It is well known that serious hypoglycemic events may frequently occur in diabetic patients with decompensated cirrhosis or hepatocellular carcinoma, probably because of an altered drug metabolism by the liver [22]. In our study, the risk of hospital admission associated with cirrhosis was very high (adjusted OR ~7). This finding may be likely due to the fact that, as reported in Supplemental Table S1, patients with established diabetes attending the ED of Sapienza University were quite different from those of the other two University hospitals, especially in terms of prevalence of cirrhosis. In addition, diabetes and CKD are two highly prevalent chronic diseases that frequently coexist in older people. As known, a reduced kidney function results in accumulation of drugs and/or their metabolites with a subsequent increased risk of developing serious side effects. In type 2 diabetic patients treated with sulfonylureas, singly or in combination with insulin, the presence of CKD significantly increases the risk of severe hypoglycemias [23,24]. Therefore, sulfonylureas should be used cautiously in patients with CKD, and dose adjustment or use of other hypoglycemic drugs should always be considered [23,24]. Moreover, in patients with CKD the risk of hypoglycemia may be high even in those treated with insulin, especially if the insulin dose is not properly adjusted or reduced [23,24].

Surprisingly, in our study, we observed that the type of antidiabetic treatment (*e.g.*, insulin *vs.* oral agents) did not independently predict an increased rate of hospital admission (although the use of sulfonylureas alone tended to reach a statistical significance).

In our sample the rate of all-cause mortality was similar to that reported in other recent studies [4]. Of the 12 patients who died, 3 patients died in ED, and 9 patients died during the hospital stay. It is possible to assume that there is a link between severe hypoglycemia and mortality risk in patients with diabetes. For example, severe and/or recurrent hypoglycemias may precipitate or worsen a coexisting cardiovascular disease, especially in terms of increased risk of ventricular arrhythmias [25]. Although a number of other pathophysiological mechanisms may be also implicated in the link between severe hypoglycemia and death, however, the retrospective design of our study does not allow us to draw any firm conclusions on the causes of death in these patients.

Our study has some important limitations that merit to be mentioned. Firstly, the cross-sectional and retrospective design of the study limits our ability to make any causal inferences. Secondly, blood glucose concentrations at the time of the hypoglycemic event and other biochemical parameters (*e.g.*, hemoglobin A1c) were not

available in all patients. Thirdly, the data regarding the specific causes of death and the risk factors playing a role in the pathogenesis of severe hypoglycemia and its consequences were not investigated.

Notwithstanding these limitations, our study has important strengths, including the relatively large sample size, the data analysis stratified by type of diabetes and by diabetes treatment, and the ability to adjust our results for multiple clinical risk factors.

In conclusion, our multicenter study, involving three University hospitals, shows that severe hypoglycemia due to insulin treatment or oral hypoglycemic drugs (mainly sulfonylureas and repaglinide) is a dramatic acute event for patients with established diabetes, increasing the risk of adverse clinical outcomes, mostly in elderly and frail individuals. Our data confirm that insulin treatment is the most important drug responsible for severe hypoglycemic events. From a clinical standpoint, we believe that it is essential to provide adequate education for self-monitoring blood glucose levels, hypoglycemic symptom recognition and its correction as well as for correct management of pharmacological treatment for diabetes [26,27]. Moreover, since glibenclamide and repaglinide were the two most common oral hypoglycemic drugs taken by our patients admitted with severe hypoglycemia, this study further reinforces the concept that careful attention should be taken by health care providers when they prescribe sulfonylureas or repaglinide in elderly patients with serious comorbidities [28,29]. Moreover, overtreatment should be always avoided in these patients [30]. As also suggested by recent guidelines, it is important that health care providers customize glycemic targets and glucose-lowering therapy after taking into consideration age, medical history and comorbidities of their patients with diabetes [13,14]. It is likely that the advent of newer hypoglycemic drugs with a lower risk of drug-induced hypoglycemia should help to reduce the incidence of severe hypoglycemia and its adverse consequences, especially among the more vulnerable patients.

Conflict of interest

The authors have no potential conflicts of interest to disclose.

Appendix. Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcte.2016.08.004.

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