

Incidence and Correlates of Hypoglycemia in Type 2 Diabetes. The Hypos-1 Study

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Abstract

Background: To evaluate the incidence of severe and symptomatic hypoglycemia in type 2 diabetes and identify their correlates.

Materials and methods: HYPOS-1 is an observational retrospective study. Socio-demographic and clinical characteristics, experience of severe hypoglycemia in the past 12 months and experience of symptomatic hypoglycemia in the past 4 weeks were recorded through a patient questionnaire and a clinical record form. Poisson multivariate models were applied.

Results: Overall, 2023 patients were involved by 18 diabetes clinics. Incidence rate (IR) of severe hypoglycemia was of 0.09 events/person-years; IR of symptomatic hypoglycemia was of 9.30 events/person-years. A minority of patients accounted for the vast majority of severe episodes. The risk of severe hypoglycemia was three times higher in patients with previous severe (Incidence Rate Ratio: 3.38; 95%confidence interval: 2.47-4.62) and symptomatic hypoglycemia (IRR 3.05; 95%CI 2.18-4.26); a two-fold risk of severe episodes was associated with basal-bolus insulin regimen (IRR 2.04; 95%CI 1.24-3.35) as compared with oral therapies not including secretagogues. Glucose-lowering therapy (i.e. secretagogues and insulin) and previous severe hypoglycemia represented the strongest predictors of symptomatic hypoglycemia. Female gender was associated with a two-fold risk of severe and a 44% higher risk of symptomatic episodes as compared to male gender. Age, diabetes duration, HbA1c, neuropathy, retinopathy, overall number of drugs, neoplasms, living status and employment status also increased the risk of severe and/or symptomatic episodes.

Discussion: Hypoglycemia still represents a common acute complication for individuals with type 2 diabetes. Identifying patients at higher risk is a key strategy to reduce the burden of hypoglycemia.

Keywords: Type 2 diabetes; Severe hypoglycemia; Symptomatic hypoglycemia; Risk factors

Introduction

The goal of diabetes treatment is the maintenance of an adequate metabolic control to prevent or delay the development of complications [1]. However, therapeutic efforts to keep the values of glycated hemoglobin within the recommended target in many cases lead to an increased risk of hypoglycemia [2]. Hypoglycemic episodes, especially the severe ones, are responsible for a relevant clinical, social and economic impact. From the clinical standpoint, physical morbidity of an episode of hypoglycemia ranges from unpleasant symptoms to seizure and coma; rarely, it causes sudden, presumably cardiac arrhythmic death or, if it is profound and prolonged, brain death [3]. Severe hypoglycemia is associated with a higher risk of cardiovascular disease, as confirmed by a recent meta-analysis [4], and dementia [5,6].

Not only severe hypoglycemia but also mild symptomatic hypoglycemia is associated with an increased risk of cardiovascular events, all-cause hospitalization, and all-cause mortality [7].

From the social point of view, several studies have investigated the impact of hypoglycemia on quality of life, suggesting a negative impact on mental well-being and on the overall self-perception of general health status [8,9]. Hypoglycemia can disrupt many everyday activities such as driving, work performance and recreational pursuits [10]. In addition, fear of hypoglycemia prevails over fear of long-term

complications and is often responsible for poor adherence to therapy or incorrect behaviors of compensation; the latter in turn are responsible for worse metabolic control [11,12].

Hypoglycemia is also an important cause of direct and indirect costs. In the course of a year, up to one third of the subjects with type 1 diabetes of long duration and a fifth of those with type 2 diabetes treated with insulin have at least one episode of severe hypoglycemia, which often requires hospitalization [13,14]. In addition to the direct costs, which have been estimated to exceed 3000 euros per episode in several European countries, indirect costs related to lost productivity and absence from work are also relevant [15,16].

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Improvement of the current care requires an accurate evaluation of the burden of hypoglycemia for the healthcare system and the identification of modifiable factors related to an increased risk of hypoglycemia.

In line with these purposes, the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi - AMD) has promoted the HYPOS-1 initiative, aiming to quantify the incidence of severe and symptomatic hypoglycemia and their determinants in a large cohort of patients with type 2 diabetes.

Materials and Methods

Italian healthcare system

In Italy, all citizens are covered by a government health insurance. Primary care for diabetes is provided by general practitioner (GP) and diabetes outpatient clinics (DOCs). Patients can choose one of the two ways of access to health care system or, more frequently, are referred to DOCs by their GPs.

Study design and data collection

HYPOS-1 is an observational retrospective study involving individuals with type 2 diabetes routinely referred to DOCs.

Eligibility criteria were: male or female gender, age ≥ 18 years, diabetes diagnosis at least 1 year before the recruitment in the study, diabetes treatment based on lifestyle intervention or pharmacologic therapies unchanged since at least 1 year, signed informed consent. Patients were not eligible for the study only if they were judged by the investigator as unable to fill in the questionnaire and understand its content.

On the occasion of a routine visit, a sample of consecutive cases has been asked to fill in the HYPOS-1 patient questionnaire. Sampling was stratified by treatment according to the following proportions, reflecting the distribution of the population with type 2 diabetes attending DOCs [17]:

- 60% treated with oral hypoglycemic agent/GLP-1 receptor agonists (OHA)
- 15% treated with OHA+insulin
- 15% treated with insulin
- 10% treated with lifestyle interventions only

The patient questionnaire investigated the following aspects: socio-demographic and clinical characteristics, including age, gender, school education, employment status, living status, marital status, whether the patient had to care for other people, number of daily medications other than glucose lowering ones, experience of severe hypoglycemia episodes in the past 12 months, and experience of symptomatic hypoglycemia episodes in the past 4 weeks.

Severe hypoglycemia was defined as an episode of hypoglycemia that led to unconsciousness or requiring intervention of a third person; symptomatic hypoglycemia was defined as onset of one or more symptoms including palpitations, tremors, sweating, difficulty concentrating, dizziness, hunger, blurred vision, sense of confusion, difficulty in movement, resolved with the ingestion of sugar, food or sugary drinks. The occurrence of severe hypoglycemic episodes was further confirmed by clinical documentation.

An additional web-based clinical record form (eCRF) was filled in by investigators to collect the following clinical data: weight, height,

year of diabetes diagnosis, last value of HbA1c, last value of serum creatinine, presence of diabetes complications (cardiac/cerebrovascular events, lower limb complications, retinopathy, nephropathy, sensory-motor neuropathy, autonomic neuropathy) and chronic conditions, including neoplasms, glucose lowering therapy, use of self-monitoring blood-glucose (SMBG), antihypertensive treatments, and lipid-lowering treatments.

Glomerular filtration rate (GFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula.

Patients were identified by a unique ID number, also used as a key linkage to merge data from patient questionnaires and eCRFs.

Data were analyzed anonymously. The study was approved by the local ethics committees of all participating centers.

Statistical analyses

Sample size estimation: Assuming an incidence rate of total hypoglycemic events of 0.15 per person-years, a total sample of 2024 patients allows to identify with a statistical power of 80% ($\alpha = 0.05$) the risk factors that have a prevalence of at least 20% and are associated with a higher probability of at least 50% to have the event. The estimate is based on multivariate Poisson model, assuming that among the covariates in the model there is a R^2 of 0.10 [18].

Data analysis: Patients' characteristics according to the presence of severe and symptomatic hypoglycemia are expressed as means and their standard deviations or frequencies. Between-group comparisons are based on the chi-square test for categorical variables and Mann-Whitney U-test for continuous variables. Univariate associations between patient characteristics and risk of severe and symptomatic hypoglycemia were also expressed as relative risks and their 95% confidence intervals.

Incidence rates (IRs) of severe and symptomatic hypoglycemia were evaluated through Poisson regression models and expressed as number of events/person-years. Factors associated with the risk of severe and symptomatic hypoglycemia were evaluated through Poisson multivariate models. Results are expressed as incidence rate ratios (IRRs) and their 95% confidence intervals (95% CI). Covariates included in the models were: age, gender, BMI, duration of diabetes, glucose lowering therapy schemes, HbA1c, GFR, ACE-Inhibitors and beta-blockers treatment (classes of drugs associated with reduced awareness) [19,20], previous severe hypoglycemia (before the past 12 months), retinopathy, autonomic neuropathy, sensory-motor neuropathy, neoplasms, number of drugs other than glucose lowering ones, employment status, level of school education, marital status, living status, taking care of other people. Symptomatic hypoglycemia was tested as a predictor of severe hypoglycemia.

Results

Overall, 18 DOCs enrolled 2023 patients with type 2 diabetes, of whom 202 (10.0%) were treated with lifestyle intervention, 1212 (59.9%) were treated with OHA, 306 (15.1%) with OHA+insulin and 303 (15.0%) with insulin alone. Patients had the following characteristics: 55.3% males, mean age of 66.3 ± 10.2 years, diabetes duration of 11.5 ± 8.9 years, HbA1c $7.1 \pm 1.2\%$. Clinical and socio-demographic characteristics of the study sample according to the occurrence of severe and symptomatic hypoglycemic episodes are shown in Table 1.

Information on severe hypoglycemic episodes was available for

	All	Severe NO	Severe YES	p*	RR** (95%CI)	Symptomatic NO	Symptomatic YES	p*	RR** (95%CI)
N	2023	1791	88			1442	564		
Male (%)	55.3	54.9	50.0	0.36	0.84 (0.56-1.26)	57.4	50.3	0.004	0.81 (0.71-0.93)
Age (years)	66.3 ± 10.2	66.3 ± 10.1	68.8 ± 10.7	0.01	-	66.3 ± 9.9	66.4 ± 10.7	0.40	-
BMI (Kg/m ²)	29.7 ± 5.7	29.7 ± 5.8	30.4 ± 6.0	0.18	-	29.7 ± 5.6	29.9 ± 6.1	0.90	-
Duration of diabetes (years)	11.5 ± 8.9	11.3 ± 8.7	16.1 ± 11.7	0.0001	-	10.6 ± 8.5	13.7 ± 9.4	<0.0001	-
HbA1c (%)	7.1 ± 1.2	7.1 ± 1.2	7.5 ± 1.4	0.002	-	7.1 ± 1.2	7.2 ± 1.1	0.0003	-
GFR < 60 mL/min (%)	25.6	20.5	24.4	0.39	1.24 (0.74-1.98)	18.9	25.7	0.001	1.32 (1.11-1.55)
Diabetes complications (%)									
Cardiac/cerebrovascular	17.8	17.5	19.3	0.67	1.12 (0.64-1.82)	16.4	21.5	0.008	1.25 (1.06-1.47)
Lower limb complications	8.4	8.0	10.2	0.46	1.29 (0.61-2.37)	6.9	12.4	<0.0001	1.54 (1.25-1.85)
Retinopathy	21.0	20.4	40.9	<0.0001	2.54 (1.67-3.82)	16.8	31.6	<0.0001	1.74 (1.51-2.00)
Nephropathy	18.4	17.9	25.0	0.09	1.49 (0.91-2.34)	16.4	24.1	<0.0001	1.40 (1.19-1.63)
Sensory-motor neuropathy	11.9	11.6	25.6	0.0001	2.46 (1.51-3.84)	8.8	19.9	<0.0001	1.84 (1.56-2.14)
Autonomic neuropathy	5.4	5.4	13.8	0.001	2.61 (1.38-4.44)	3.9	9.0	<0.0001	1.75 (1.39-2.14)
Neoplasms (%)	4.5	4.4	9.2	0.04	2.08 (0.95-3.89)	2.0	3.2	0.11	1.23 (0.89-1.61)
Glucose lowering pharmacologic treatments (%)									
Metformin	60.5	61.0	48.9	0.02	0.63 (0.42-0.94)	63.3	53.7	<0.0001	0.75 (0.66-0.87)
Sulphonylureas	21.0	20.9	18.2	0.53	0.85 (0.48-1.40)	21.4	20.0	0.51	0.94 (0.79-1.12)
Glinides	12.0	12.0	13.6	0.63	1.15 (0.61-2.00)	10.8	15.3	0.006	1.31 (1.08-1.57)
Acarbose	4.2	4.0	3.4	0.79	0.86 (0.21-2.22)	4.3	3.9	0.69	0.93 (0.62-1.30)
Glitazones	5.4	5.1	5.7	0.82	1.11 (0.40-2.39)	5.9	4.1	0.11	0.75 (0.50-1.05)
DPP-IV inhibitors	16.7	17.2	9.1	0.05	0.49 (0.22-0.95)	17.6	14.9	0.15	0.87 (0.70-1.05)
GLP-1 receptor agonists	4.8	4.8	8.0	0.17	1.68 (0.72-3.26)	5.3	3.9	0.20	0.79 (0.52-1.11)
Human regular insulin	0.4	0.4	0.0	0.56	0.00 (0.00-0.00)	0.4	0.4	0.98	1.02 (0.19-2.32)
Short-acting insulin analogues	21.6	20.4	52.3	<0.0001	3.90 (2.60-5.86)	14.4	39.9	<0.0001	2.42 (2.12-2.76)
Basal insulin analogues	25.4	24.2	51.1	<0.0001	3.06 (2.04-4.60)	19.3	40.9	<0.0001	2.03 (1.77-2.32)
Premix insulin	4.2	4.3	8.0	0.11	1.85 (0.79-3.58)	3.1	7.1	<0.0001	1.75 (1.35-2.17)
Glucose lowering therapy schemes (%)				<0.0001				<0.0001	
OHA (combination with secretagogues)	33.5	34.1	15.9		1.00	38.4	20.7		1.00
OHA (combination without secretagogues)	26.4	26.4	22.7		1.81 (0.93-3.63)	25.9	28.0		1.70 (1.38-2.11)
Insulin (basal oral)	6.7	6.6	8.0		2.48 (0.96-5.83)	6.6	6.9		1.65 (1.19-2.23)
Insulin (basal bolus)	15.6	14.5	40.9		5.45 (3.06-10.30)	10.5	28.6		2.95 (2.43-3.60)
Insulin (Other schemes)	7.9	8.0	12.5		3.21 (1.45-6.92)	5.8	12.9		2.68 (2.11-3.38)
Diet	10.0	10.5	0		-	12.8	2.8		-
SMBG (%)	86.9	86.3	99.0	<0.001	13.10 (2.94-230.38)	83.8	95.2	<0.0001	2.96 (2.10-4.37)
Number of drugs other than glucose lowering ones	3.3 ± 2.6	3.3 ± 2.6	3.8 ± 2.7	0.03		3.1 ± 2.6	3.7 ± 2.7	<0.0001	-
Antihypertensive treatments (%)	70.7	70.5	70.4	0.99	1.00 (0.65-1.59)	70.6	71.9	0.55	1.05 (0.90-1.23)

ACE-Inhibitors (%)	29.1	29.3	28.4	0.86	0.96 (0.60-1.49)	28.5	31.0	0.26	1.09 (0.94-1.26)
Beta-blockers (%)	24.6	24.1	33.0	0.06	1.51 (0.97-2.31)	23.9	26.8	0.17	1.12 (0.95-1.30)
Lipid-lowering treatments (%)	56.4	56.8	56.8	1.00	1.00 (0.66-1.52)	55.6	59.1	0.16	1.11 (0.96-1.28)
Employment status (%):				0.63				0.94	
Employed	20.9	20.6	18.8		1.00	21.1	20.5		1.00
Unemployed	19.1	19.7	16.5		1.09 (0.54-2.23)	18.9	19.4		0.96 (0.77-1.20)
Retired	60.1	59.7	64.7		1.28 (0.75-2.37)	60.1	60.1		0.98 (0.82-1.18)
Highest level of school education (%):				0.11				0.20	
Primary school	40.3	40.3	52.3		1.00	39.2	43.6		1.00
Middle school	30.6	30.3	28.4		0.73 (0.45-1.17)	31.7	27.5		0.84 (0.70-0.99)
High school	22.8	23.3	14.8		0.50 (0.26-0.89)	22.9	22.1		0.90 (0.75-1.08)
University	6.3	6.1	4.6		0.59 (0.18-1.42)	6.1	6.8		1.00 (0.73-1.30)
Living status (%):				0.89				0.49	
Spouse/sons	77.8	78.0	76.1		1.00	78.6	75.5		1.00
Alone	15.8	15.7	18.2		1.18 (0.67-1.95)	15.4	17.2		1.11 (0.92-1.33)
Other family members	4.3	4.5	3.4		0.79 (0.20-2.07)	4.1	5.1		1.21 (0.86-1.61)
Other	2.1	1.9	2.3		1.20 (0.20-3.62)	2.0	2.1		1.06 (0.61-1.62)
Marital status (%):				0.65				0.08	
Not married	7.4	7.3	4.6		1.00	7.4	7.2		1.00
Married/cohabitant	75.2	75.5	78.4		1.64 (0.69-5.32)	76.5	71.9		0.98 (0.76-1.32)
Separated/divorced	4.3	4.2	5.7		2.12 (0.58-8.35)	3.9	5.4		1.27 (0.85-1.88)
Widower	13.1	13.0	11.4		1.38 (0.47-4.97)	12.1	15.6		1.22 (0.90-1.69)
Taking care of other people (%)	37.3	37.2	29.6	0.15	0.72 (0.45-1.11)	36.1	40.0	0.11	1.12 (0.97-1.30)
Previous experience of severe hypoglycemia (before the last 12 months) (%)	10.0	9.1	36.4	<0.0001	4.93 (3.24-7.37)	6.3	19.3	<0.0001	2.16 (1.85-2.50)

Data are expressed as means and their standard deviations or frequencies.

* chi-square test for categorical variables and Mann-Whitney U-test for continuous variables. **Relative risk and 95%confidence intervals.

Table 1: Clinical and socio-demographic characteristics according to the experience of severe and/or symptomatic hypoglycemic episodes

1879 patients (93.0%), while data on symptomatic hypoglycemic episodes were reported by 2006 patients (99.2%). Patients experiencing at least one severe hypoglycemic episode in the past 12 months were 88, representing 4.7% of the sample, while those experiencing at least one symptomatic hypoglycemic episode in the past four weeks were 564, representing 28.1% of the sample. Among patients with severe hypoglycemia, the number of episodes ranged from 1 to 18, with 57.3% reporting 1 episode, 24.7% reporting 2 episodes, and 18.0% reporting 3 or more episodes.

Among patients with symptomatic hypoglycemia, the number of episodes ranged from 1 to 30 (1-3 episodes for 77.9% of the cases, 4-9 episodes for 18.0% of the cases, and 10 or more episodes for 4.1%).

Among patients with symptomatic hypoglycemia, 89.7% reported diurnal episodes and 23.4% reported nocturnal episodes.

Overall, incidence rate of severe hypoglycemia was of 0.09 events/person-years, while incidence rate of symptomatic hypoglycemia was of 9.30 events/person-years. Incidence rates according to gender,

age, diabetes duration history of cardiac/cerebrovascular disease, and glucose lowering therapy scheme are shown in Table 2. Significantly higher incidence rates of severe and/or symptomatic hypoglycemia were found in female vs. male individuals, in older patients, in patients with a recent diabetes diagnosis (duration≤2 years), and in the presence of cardiac/cerebrovascular complications. Moreover, incidence markedly varied according to the classes of glucose lowering treatments, being more pronounced in patients treated with intensive therapy regimens; in particular, patients treated with secretagogues had a doubled risk of severe episode as compared with those treated with other OHAs, while patients on basal-bolus regimens had an almost 7 fold increased likelihood to report a severe episode and a 3-fold increased likelihood to report a symptomatic episode as compared to patients treated with OHAs schemes not including secretagogues.

Results of the fully adjusted multivariate analyses are shown in Table 3. Table 3a shows correlates of severe hypoglycemia and Table 3b shows correlates of symptomatic hypoglycemia.

	Severe hypoglycemia		Symptomatic hypoglycemia	
	IR (95% CI)	IRR (95% CI)	IR (95% CI)	IRR (95% CI)
Overall	0.09 (0.08-0.11)	-	9.26 (8.81-9.73)	-
By gender				
M	0.06 (0.05-0.08)	0.46 (0.35-0.62)	7.77 (7.22-8.35)	0.70 (0.63-0.77)
F	0.14 (0.12-0.16)	1.00 (RC)	11.08 (10.35-11.86)	1.00 (RC)
By age classes				
<65	0.07 (0.05-0.09)	1.00 (RC)	8.91 (8.24-9.63)	1.00 (RC)
65-74	0.10 (0.08-0.13)	1.50 (1.07-2.11)	9.23 (8.52-10.00)	1.04 (0.93-1.16)
>=75	0.15 (0.12-0.20)	2.30 (1.60-3.31)	9.89 (8.85-11.05)	1.11 (0.97-1.27)
By diabetes duration				
<=2	0.02 (0.01-0.05)	1.00 (RC)	4.63 (3.75-5.72)	1.00 (RC)
2-5	0.08 (0.06-0.12)	3.66 (1.42-9.47)	6.63 (5.76-7.63)	1.43 (1.11-1.85)
5.1-10	0.06 (0.04-0.09)	2.66 (1.03-6.88)	7.38 (6.59-8.27)	1.60 (1.26-2.03)
>10	0.14 (0.12-0.17)	6.30 (2.58-15.38)	11.90 (11.15-12.69)	2.57 (2.06-3.21)
By cardiac/cerebrovascular disease				
NO	0.10 (0.09-0.12)	1.16 (0.79-1.70)	8.7 (8.22-9.21)	0.74 (0.65-0.83)
YES	0.09 (0.06-0.12)	1.00 (RC)	11.83 (10.67-13.13)	1.00 (RC)
By glucose lowering therapy schemes				
OHA (without secretagogues)	0.04 (0.03-0.06)	1.00 (RC)	5.57 (4.98-6.22)	1.00 (RC)
OHA (with secretagogues)	0.08 (0.06-0.11)	2.00 (1.24-3.21)	9.50 (8.64-10.45)	1.71 (1.48-1.98)
Insulin (basal oral)	0.10 (0.06-0.17)	2.49 (1.31-4.73)	10.76 (9.01-12.85)	1.93 (1.57-2.38)
Insulin (basal bolus)	0.29 (0.23-0.35)	6.91 (4.52-10.56)	18.36 (16.79-20.08)	3.30 (2.86-3.80)
Insulin (Other schemes)	0.13 (0.08-0.19)	3.02 (1.70-5.36)	14.55 (12.64-16.75)	2.61 (2.19-3.13)
Diet	0	-	1.60 (1.10-2.34)	0.29 (0.19-0.43)

OHA: Oral Hypoglycemic Agents
 RC: Reference Class
 IR: Incidence Rate
 95% CI: 95% Confidence Interval
 IRR: Incidence Rate Ratio

Table 2: Incidence of severe and symptomatic hypoglycemia in type 2 diabetes

The risk of severe hypoglycemia was about three times higher in patients with previous severe and symptomatic hypoglycemia; furthermore, a doubled risk of severe episodes was associated with female gender, presence of neoplasms and use of a basal-bolus insulin regimen. Additionally, a 73% higher risk was found in the presence of sensory-motor neuropathy. The risk increased by 2% for each unit increase in age and by 2% for each year of diabetes duration increase. The risk was 80% higher in employed patients as compared to unemployed ones.

At multivariate analysis, glucose-lowering therapy (secretagogues and insulin) and previous severe hypoglycemia were the strongest predictors of symptomatic hypoglycemia, followed by relevant clinical characteristics, such as diabetes duration, presence of retinopathy,

and sensory-motor neuropathy. On the other hand, renal function impairment was associated with a lower likelihood of symptomatic episodes. The number of overall drugs taken by the patient was also related to the risk of hypoglycemia, while the use of beta-blockers was associated with a 16% lower likelihood to report episodes. Female gender and taking care of other people were also associated with an increased risk of symptomatic episodes.

Discussion

HYPOS-1 initiative showed for the Italian population with type 2 diabetes followed by DOCs that one in twenty patients experienced at least 1 severe episode and a minority of patients accounted for the vast majority of severe episodes. In terms of disease burden, healthcare

a. Severe hypoglycemia

Variables	IRR (95%CI)
Age	1.02 (1.00-1.04)
Female gender	2.23 (1.61-3.08)
Duration of diabetes	1.02 (1.01-1.04)
HbA1c	1.28 (1.14-1.44)
Previous severe hypoglycemia (before the past 12 months)	3.38 (2.47-4.62)
Symptomatic hypoglycemic episodes in the last 4 weeks	3.05 (2.18-4.26)
Therapeutic schemes	
Insulin (Other schemes)	0.91 (0.48-1.74)
Insulin (basal bolus)	2.04 (1.24-3.35)
Insulin (basal oral)	0.79 (0.38-1.67)
OHA (combination with secretagogues)	1.07 (0.64-1.78)
OHA (combination without secretagogues)	1.00 (RC)
Sensory-motor neuropathy	1.73 (1.24-2.41)
Neoplasms	2.08 (1.23-3.49)
Employment status	
Retired	0.94 (0.62-1.43)
Employed	1.80 (1.08-3.01)
Unemployed	1.00 (RC)

b. Symptomatic hypoglycemia

Variables	IRR (95%CI)
Age	0.98 (0.97-0.99)
Female gender	1.44 (1.29-1.62)
Duration of diabetes	1.02 (1.01-1.02)
HbA1c	0.90 (0.86-0.95)
Previous severe hypoglycemia (before the past 12 months)	1.72 (1.51-1.96)
GFR < 60 mL/min	0.85 (0.74-0.99)
Retinopathy	1.25 (1.10-1.42)
Sensory-motor neuropathy	1.20 (1.04-1.39)
Therapeutic schemes	
Insulin (Other schemes)	2.15 (1.75-2.65)
Insulin (basal bolus)	2.59 (2.18-3.09)
Insulin (basal oral)	1.76 (1.39-2.23)
OHA (combination with secretagogues)	1.63 (1.39-1.91)
OHA (combination without secretagogues)	1.00 (RC)
Beta-blockers treatment	0.84 (0.73-0.96)
Number of drugs other than antidiabetic ones	1.02 (1.00-1.05)
Living status	
Other	1.54 (1.17-2.02)
Other family members	0.70 (0.52-0.95)
Alone	1.32 (1.15-1.53)
Spouse/sons	1.00 (RC)
Taking care of other people	1.45 (1.29-1.62)
Employment status	
Retired	1.39 (1.19-1.63)
Employed	1.08 (0.89-1.30)
Unemployed	1.00 (RC)

RC: Reference Class

Table 3: Factors associated with risk of hypoglycemia. Results of the Poisson multivariate analysis
Table shows only statistically significant rate ratios (95% confidence intervals).

system is expected to manage one severe episode every ten patients seen during a year. Symptomatic hypoglycemia was extremely common, affecting over one in four of the sample.

Incidence of hypoglycemia in our study was higher than incidences

documented in randomized clinical trials [21]. In particular, in the ACCORD, ADVANCE and VADT trials, designed to test whether treatment targeting nearly normal glycemic control reduces the risk of cardiovascular events in type 2 diabetes, showed incidence rates for severe hypoglycemia in intensive insulin group ranging from 0.7 to 12 events/100 person-years. We found an incidence of severe hypoglycemia ranging from 4 (OHA without secretagogues) to 29 (Insulin - basal bolus) events/100 person-years.

Incidence of hypoglycemia in type 2 diabetes, especially self-treated one, has been rarely evaluated outside of clinical trial settings, and studies are almost exclusively focused on insulin-treated patients [22]; in addition, data from the real world are extremely heterogeneous due to the differences in the methods of data collection and population selection [23]. In a consecutive sample identified at Steno Diabetes Center consisting of 401 subjects with type 2 diabetes treated with insulin, an overall incidence of severe hypoglycemia of 0.44 episodes/person year was documented [24]. Data from a Scottish Diabetes register on 173 cases of insulin-treated type 2 diabetes showed a rate of 16.37 non severe events/person-years and a rate of 0.35 severe events/person-years [25]. A large initiative involving 7 European countries (but not Italy) documented an incidence of non severe hypoglycemia of 20-35 events/person-years according to the different insulin regimens [26]. In our study we found incidence rates for patients treated with insulin of 0.25 events/person-years for severe hypoglycemia and 18.8 events/person-years for symptomatic hypoglycemia.

HYPOS-1 adds important information on the global burden of hypoglycemia in Italian patients attending DOCs.

HYPOS-1 documents that some categories of patients are particularly exposed to the risk of hypoglycemia. After adjusting for socio-demographic and clinical characteristics, several independent correlates of severe and symptomatic hypoglycemia were identified. In line with existing literature [24-26], insulin treatment represents the most important risk factor for severe hypoglycemia. In addition, the risk of major hypoglycemia was significantly higher in patients with previous severe episodes [25]; our study shows that also the incidence of symptomatic hypoglycemia is a strong correlate of severe episodes.

In our study, female gender was associated with a two-fold risk of severe episodes. An increased risk of hypoglycemia in women was previously reported in the ACCORD trial [27], but not in observational studies. The reasons for such an increased risk remain to be elucidated.

We also found that the risk of hypoglycemia was significantly higher in the presence of neoplasms, thus underlying the importance of the overall clinical conditions of the patient in determining his risk profile. The importance of the frailty of the patient is further documented by the association with diabetes complications, increasing age and diabetes duration [27,28]. Older age and longer diabetes duration, together with diabetes neuropathy, can also represent proxy indicators for hypoglycemia unawareness, a well known risk factor for severe hypoglycemia [29,30].

In previous studies, being married and low levels of school education were identified as correlates of hypoglycemia [24,27]. We could not confirm an association of socio-economic characteristics with the risk of severe hypoglycemia, with the only exception of a higher risk in employed individuals as compared with unemployed ones. Unfortunately, we have no additional information to evaluate whether specific types of employment confer an excess risk of hypoglycemia.

Risk of severe hypoglycemia increased by 28% for each unit increase

in HbA1c levels. This point deserves consideration. Higher levels of HbA1c in patients experiencing severe hypoglycemia could be the result of compensatory behaviors, less aggressive therapeutic approaches, and/or a proxy of glycaemic variability, previously advocated as having an independent role in determining individual's risk of hypoglycemia [31,32].

Correlates of symptomatic hypoglycemia have been seldom investigated, mainly in dated studies. In a study conducted in 1991 the frequency of hypoglycemia was positively, but only weakly, correlated with insulin therapy, HbA1c and age [33]. In another study conducted in 2001 [34] insulin therapy, lower HbA1c level at follow-up, younger age, and report of hypoglycemia at the baseline visit were independently associated with increased prevalence of hypoglycemia.

Our study confirms an inverse relationship between the risk of symptomatic hypoglycemia and age and HbA1c levels, as well as the excess risk associated with sulphonylureas and insulin therapy. In addition, female gender, increasing diabetes duration, previous severe hypoglycemia, the presence of eye and neuropathic complications and increasing number of drugs other than glucose-lowering ones are associated with a higher likelihood of symptomatic hypoglycemia. On the other hand, a low GFR was associated with a lower risk of hypoglycemia, suggesting that a greater attention is devoted in choosing treatment options in individuals with impaired renal function.

The use of beta-blockers is associated with a 16% lower likelihood of symptomatic hypoglycemia, in line with existing evidence of impaired awareness associated with the use of this class of medications [35].

The significant correlation among different socio-demographic aspects and risk of symptomatic episodes document the importance of daily life and family support in determining an adequate self-management of a chronic disease [36].

Effective approaches identified by a recent ADA consensus to decrease the risk of iatrogenic hypoglycemia include "patient education, dietary and exercise modifications, medication adjustment, careful glucose monitoring by the patient, and conscientious surveillance by the clinician" [37]. Among the current knowledge gaps, it is recognized the difficulty in understanding which patients are most at risk for hypoglycemia.

HYPOS-1 study enlarges the chance to identify patients at increased risk of both severe and symptomatic episodes.

Study results will be used by the AMD scientific society to implement new strategies for promoting a more appropriate use of glucose lowering drugs and for acting on modifiable factors which play a role in the hypoglycemia burden.

The study has strengths and limitations to be discussed. Main strengths are: the evaluation of the impact of both severe and symptomatic hypoglycemia; the inclusion in the analysis of a sample representative of the whole population with type 2 diabetes and not only of those treated with insulin, and the availability of a large number of socio-demographic and clinical variables to be correlated with the risk of hypoglycemia and usually lacking in similar studies. The study also has limitations, including the retrospective design and the self-reported information on symptomatic hypoglycemia, not confirmed by blood glucose self-monitoring values. Furthermore, we used as correlates of hypoglycemia the last available value of HbA1c and serum creatinine. As such, these measures could be posterior to the major hypoglycemic event, and may not strictly reflect the situation of the patients when they experienced the event. Finally, the role of glycaemic variability

as a correlate of the risk of hypoglycemia has been underlined in several studies [38-40]. We could not assess its role due to the lack of information on SMBG.

In conclusion, our study provides an up to date and comprehensive assessment of the incidence and factors associated with the risk of hypoglycemia in everyday clinical practice. Despite the increasing recognition of the risks associated with both severe and symptomatic episodes, hypoglycemia still represents a common acute complication for individuals with type 2 diabetes. Greater attention should be devoted to the choice of individualized targets and treatment schemes, as well as better self-management education, in order to minimize the risk of such a complication, while ensuring adequate metabolic control.

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Contributors

All authors were involved in the concept and design of the initiative. GL and MCR performed data analysis. G.C., A.N. and M.C.R. wrote the manuscript. A.O., S.G., A.C., R.I. and F.B. were involved in critical revision for intellectual content and interpretation of data. All authors were involved in the final approval of the manuscript to be submitted for publication.

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Competing interests

C.B.G. is a member of the advisory board of Novo Nordisk and Bristol-Myers Squibb; he has received speaker fees from Astrazeneca, Boehringer Ingelheim, Bruno Farmaceutici, Novo Nordisk and Bristol-Myers Squibb. S.G. is a member of the advisory board of Sanofi Aventis. A.N. is a member of the advisory board of Novo Nordisk, Novartis, Merk Sharp & Dohme; he has received speaker fees from Novo Nordisk, Novartis, Merk Sharp & Dohme. Other authors declare that they have no conflict of interest.

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