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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Severe hypoglycaemia in elderly patients with type 2 diabetes and coexistence of cardiovascular history

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Abstract

Background: Hypoglycaemia is a condition that occurs when blood glucose levels fall below 3.9 mmol/L (70 mg/dL), while hypoglycaemic coma is usually associated with glycaemia around 1.1 mmol/L (20 mg/dL). Recurrent severe hypoglycaemia may result in permanent neurological disorders and also has a negative impact on the cardiovascular system.

Aim: To evaluate the causes of severe hypoglycaemia in elderly patients with type 2 diabetes and coexistence of cardiovascular history.

Methods: We analysed retrospectively the history of 33 elderly patients with type 2 diabetes and coexistence of cardiovascular history, who were admitted to our clinic due to severe hypoglycaemia with loss of consciousness. The mean age of the patients was 76.0 ± 11.1 years, and the mean duration of diabetes was 12.0 ± 9.8 years. Glycated haemoglobin (HbA1c) was measured and the prevalence of cardiovascular diseases and therapeutic procedures were evaluated.

Results: In the group of patients with severe hypoglycaemia, the mean value of HbA1c was 6.3 ± 1.2% (44 ± 13.1 mmol/mol), which indicates a mean glucose value below 7.8 mmol/L (140 mg/dL). Ischaemic heart disease was diagnosed in 18 patients (eight had a history of myocardial infarction), and 22 patients had arterial hypertension. Severe hypoglycaemia requiring hospitalisation in elderly patients with type 2 diabetes and coexistence of cardiovascular history was related to insulin or sulfonylurea therapy.

Conclusions: A low HbA1c level indicates inappropriate intensification of therapy and was associated with high risk of severe hypoglycaemic episodes in older people. The majority of severe hypoglycaemic episodes were observed in sulphonylurea or insulin-treated type 2 diabetic patients.

Key words: hypoglycaemia, diabetes type 2, elderly

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INTRODUCTION

Hypoglycaemia is a condition of reduced blood glucose levels below the normal range. According to the latest recommendations of the Polish Diabetes Association (PTD), hypoglycaemia is recognised as a decrease in blood glucose below 70 mg/dL (3.9 mmol/L) and poses one of the most common acute complications of diabetes therapy [1]. Drug-induced hypoglycaemia may occur in any type of diabetes as a side effect of treatment, especially with insulin or sulfonylureas. In accordance with the recommendations of the PTD, severe hypoglycaemia is defined as hypoglycaemia requiring the assistance of another person to provide carbohydrates, glucagon, or other procedures. Hypoglycaemic coma may occur at glucose levels in the range of 41–49 mg/dL (2.3–2.7 mmol/L) or lower and constitutes a medical emergency. Recurrent severe hypoglycaemia is defined as two or more cases of severe hypoglycaemia in the previous 12 months [2, 3].

In the UK Prospective Diabetes Study (UKPDS), severe hypoglycaemia occurred in four to six individuals with type 2 diabetes per 1000 patients treated with sulfonylureas

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(glibenclamide or chlorpropamide) during the year and in 23 per 1000 patients treated with insulin [4]. The five-year follow-up as part of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (11 of 140 patients with type 2 diabetes) has been shown to reduce the risk of microangiopathy in patients treated intensively with gliclazide MR. Nevertheless, the incidence of severe hypoglycaemia, defined as the occurrence of transient central nervous system dysfunction requiring the help of others, was higher in the group of patients with intensive treatment compared to the standard treatment group (control group) (2.7% vs. 1.5%). The average frequency of episodes of severe hypoglycaemia in the ADVANCE trial was 0.7 per 100 person-years in the group of intensive glycaemic control and 0.4 per 100 person-years in the control group [5]. Severe hypoglycaemia was often observed in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial involving 10,251 patients with uncontrolled type 2 diabetes (mean glycated haemoglobin [HbA1c] = 8.1%) and high risk of cardiovascular disease (CVD). In the group treated intensively, in which the aim was to reduce the HbA1c level to below 6%, severe hypoglycaemia occurred in 16% of patients. A particularly high risk of severe hypoglycaemia was observed in patients with type 2 diabetes treated intensively (aim — HbA1c < 6%) in the Veterans Affairs Diabetes Trial (VADT). In the six-year follow-up severe hypoglycaemia occurred in 21% of intensively treated patients [6, 7].

Prolonged severe hypoglycaemia may result in permanent neurological disorders. Loss of consciousness can be accompanied by bilateral plantar reflex, muscle tension, and hypothermia. Sometimes in the course of severe hypoglycaemia, unusual symptoms may also appear. Severe hypoglycaemia with generalised seizures may lead to a misdiagnosis of epilepsy. A possible manifestation of hypoglycaemia is pseudobulbar syndrome or pseudotumour syndrome. Recurrent hypoglycaemia may lead to the development of brain degeneration with mood disorders and impaired cognitive functions [3].

Hypoglycaemia also has a negative impact on the cardiovascular system and may exacerbate myocardial ischaemia. This phenomenon is particularly disadvantageous for patients with diabetes. Moderate and severe hypoglycaemia may induce ventricular arrhythmias by QT prolongation, directly or indirectly induce abnormal myocardial repolarisation, ventricular arrhythmias, and myocardial ischaemia probably mediated by adrenergic surges or increased adrenergic tone. Low glucose levels can also lead to falls resulting in fractures or other injuries, and traffic accidents. Severe hypoglycaemia or recurrent hypoglycaemia is a complication that has psychological and social consequences for the patients and their families [3, 8].

The prevalence of hypoglycaemia tends to increase with advancing age. Elderly people are intrinsically prone to hypoglycaemia. Ageing attenuates the glucose counter-regulatory and response to hypoglycaemia, and multiple co-morbidities and polypharmacy correlated with advancing age also increase the hypoglycaemic risk. Because of the heterogeneous health status of the elderly, not all of them benefit from optimal glycaemic control.

The aim of the study was to evaluate the causes of severe hypoglycaemia in patients with type 2 diabetes and coexistence of CVD history, who were hospitalised in the Department of Internal Diseases, Diabetology, and Endocrinology, Warsaw Medical University in Mazowiecki Brodnowski Hospital in the years 2011–2013.

METHODS

In the period from 2011 to 2013, 33 subjects with type 2 diabetes and coexistence of CVD history were hospitalised due to severe hypoglycaemia in the Department of Internal Diseases, Diabetology, and Endocrinology, Medical University of Warsaw, Poland. At admission, all of them experienced a loss of consciousness in the course of hypoglycaemia. All subjects were treated with intravenous infusions of 20% glucose and then repeated capillary blood measurement 10 min later. If glycaemia was still less than 4.0 mmol/L (72 mg/dL), the procedure was repeated. When the capillary blood glucose was greater than 4.0 mmol/L (72 mg/dL) and the patient had recovered, they were given a long-acting carbohydrate of their choice, taking into consideration specific dietary requirements.

We analysed the following parameters in all participants: age, body mass index, duration of diabetes, presence of late diabetic complications, HbA1c level, blood creatinine concentration and glomerular filtration rate (GFR), and type of diabetes treatment. The glucose level was tested in capillary blood with the use of a glucometer and confirmed by the laboratory serum method (enzymatic method using BIOSEN 5040 analyzer, EKF-Diagnostic GmbH, Germany). Only serum glucose measurements were used for statistical analysis. HbA1c was measured with the high-performance liquid chromatography (HPLC) method using the Variant analyser (Bio-Rad Laboratories Inc., Germany. HbA1c values were expressed as a percentage according to the National Glycohaemoglobin Standardisation Program [NGSP]). The GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation.

Statistical analysis

Statistical analyses were performed with the use of the STATISTICA 9.1 data analysis software system (StatSoft, Tulsa, OK, USA). All continuous variables were expressed as the mean ± standard deviation of the mean. Categorised variables were expressed as a number or percentage. They were used for statistical analysis of the Spearman's correlation coefficient and Wilcoxon test. A p value of less than 0.05 was considered statistically significant.

RESULTS

Among the 33 patients with type 2 diabetes who were hospitalised due to severe hypoglycaemia, there were 23 women and 10 men. The mean age was 76.0 ± 11.1 years and the mean duration of diabetes was 12.0 ± 9.8 years. In all patients, low blood glucose values were associated with clinical symptoms (loss of consciousness). All patients had a history of CVDs, like ischaemic heart disease (IHD) (24% of patients were after myocardial infarction [MI]), arterial hypertension had been diagnosed in 67% of patients (45.5% patients with isolated hypertension and 21% patients with coexisting IHD). Characteristic of the study group is presented in Table 1.

The majority of the examined patients were treated with insulin, and the prevalent algorithm of insulin treatment was the twice daily use of premixed insulins (Table 2). Patients were treated with human insulin, and none of the patients received insulin analogues. The mean blood glucose value at the time of the first medical intervention was 2.0 ± 0.6 mmol/L (35.6 ± 11.2 mg/dL). Individuals treated with insulin or insulin and metformin had significantly lower mean glucose concentrations at the onset of hypoglycaemia 1.3 ± 0.5 mmol/L (23.3 ± 9.7 mg/dL) compared with those on sulphonylureas and metformin therapy 2.1 ± 0.6 mmol/L (37.5 ± 0.3 mg/dL; $p < 0.02$). There were no significant differences between the group of patients treated with insulin alone and those applying combined therapy (Table 2). In patients treated with two-dose insulin algorithm we observed slightly lower glucose levels than in patients treated with others algorithms of insulin therapy or than in patients treated with sulphonylurea and/or metformin, but differences between groups were not statistically significant (Table 2). In the whole examined group, relatively low HbA1c was found (6.3 ± 1.2% (44 ± 131 mmol/mol). The slightly lower HbA1c was observed in patients treated with sulphonylurea and with two-dose insulin algorithm, but the differences between these two groups and others were not statistically significant (Table 2). Mean GFR (55.8 ± 22.2 mL/min./1.72 m^2) indicates impaired kidney function (Table 1).

Table 1. Characteristics of study group

Total number of patients	33
Sex (male/female)	10/23
Age [years]	76.0 ±11.1
Body mass index [kg/m^2]	26.0 ± 2.9
Blood glucose [mg/dL]	35.6 ± 11.2
Glycated haemoglobin [%]	6.3 ± 1.2
eGFR [mL/min/1.72 m^2]	55.8 ± 22.2
Creatinine [mg/dL]	1.1 ± 0.95
Concomitant CHD	18 (54.6%)
Concomitant MI	8 (24.2%)
Concomitant AH	22 (66.7%)

Data are presented as number (percentage) or mean ± standard deviation; blood glucose: mg/dL × 0.555 = mmol/L; creatinine: mg/dL × 88.4 = mmol/L; eGFR — estimated glomerular filtration rate; CHD — coronary heart disease; MI — myocardial infarction; AH — arterial hypertension

There was no significant correlation between the glucose level at the time of hypoglycaemia and concomitant coronary heart disease, hypertension, cancer, or diabetic nephropathy. Nor was there any correlation between the values of the glucose and the insulin algorithm ($p < 0.24$), and we did not observe statistically significant correlations between selected biochemical parameters — HbA1c, glucose, creatinine, and estimated GFR (Table 3).

DISCUSSION

The aim of the treatment of patients with type 2 diabetes is to prevent late complications of diabetes. To achieve this goal, it is necessary to obtain good long-term control of diabetes, almost normoglycaemia, and thus HbA1c below 7.0% (53 mmol/mol) [9]. Good metabolic control is almost always associated with a risk of hypoglycaemia. Severe hypoglycaemia is a medical emergency. Analysis of the cases of patients

Table 2. Treatment used before severe hypoglycaemia in the study group (n = 33) and algorithms of insulin therapy

Treatment before hypoglycaemia	N (%)	HbA1c [%]	Glucose [mg/dL]
Patients treated with insulin alone	15 (45.5%)	6.3 ± 1.2	21.4 ± 9.6
Patients treated with insulin and metformin	5 (15.2%)	6.5 ± 1.4	24.3 ± 10.2
Patients treated with sulphonylurea alone	7 (21.2%)	6.1 ± 1.2	37.4 ± 9.8
Patients treated with sulphonylurea and metformin	6 (18.2%)	6.1 ± 1.1	37.8 ± 10.3
Patients treated with insulin	20 (60.6%)	6.3 ± 1.2	22.7 ± 10.3
Algorithm 1 injection of insulin	1 (5.0%)	6.4	25.3
Algorithm 2 injections of insulin	9 (45.0%)	6.1 ± 1.23	21.5 ± 9.9
Algorithm 3 injections of insulin	5 (25.0%)	6.4 ± 1.3	23.5 ± 9.6
Algorithm 4 injections of insulin	5 (25.0%)	6.4 ± 1.4	22.4 ± 10.5

Data are presented as a mean ± standard deviation of the mean or as number (percentage) of examined individuals.

Table 3. Correlations between biochemical parameters

	HbA1c	Glucose	Creatinine	eGFR
HbA1c	–	r = –0.1	r = –0.06	r = –0.005
		p = 0.6	p = 0.7	p = 0.9
Glucose	r = –0.1	–	r = 0.04	r = –0.2
	p = 0.6		p = 0.8	p = 0.4
Creatinine	r = –0.1	r = 0.04	–	r = –0.1
	p = 0.6	p = 0.8		p = 0.6
eGFR	r = –0.005	r = –0.2	r = –0.1	–
	p = 0.9	p = 0.4	p = 0.6	

A p value < 0.05 is considered statistically significant; eGFR — estimated glomerular filtration rate; HbA1c — glycated haemoglobin

with type 2 diabetes who were hospitalised due to severe hypoglycaemia points out that it mostly affects patients over 65 years of age — 87.9% (29 of 33 patients). Those who developed severe hypoglycaemia were also characterised by a low HbA1c level that indicates chronic mean blood glucose levels below 7.8 mmol/L (140 mg/dL). These values were lower than those recommended by the PTD [1]. According to the 2015 recommendations of the PTD, in patients with type 2 diabetes, a generally good metabolic control is characterised by HbA1c level ≤ 7.0% (≤ 53 mmol/mol). In the case of short-term type 2 diabetes, the target value of HbA1c is ≤ 6.5% (≤ 48 mmol/mol). In the observed group, the mean duration of diabetes was 12.0 ± 9.8 years. In the case of patients aged over 70 years with longstanding diabetes (> 20 years) and coexisting significant macrovascular complications (MI and/or stroke), metabolic control is considered satisfactory when the HbA1c level is equal to or below 8.0% (≤ 64 mmol/mol). The mean age of patients in our study group was 76.0 ± 11.1 years. In 54.5% of cases IHD was diagnosed. Moreover, 24.2% of patients suffered MI. The characteristics of this group of patients indicate the need to use less strict criteria for metabolic control. An important observation is that severe hypoglycaemia occurred in 81.3% of those who were using intensive hypoglycaemic therapy and achieved glucose and HbA1c values lower than those recommended by the PTD. In our study, severe hypoglycaemia requiring hospitalisation was related to treatment not only with insulin but also with sulphonylureas (40%). There were no patients with severe hypoglycaemia on monotherapy with metformin, acarbose, gliflozins, gliptins, or glucagon-like peptide 1 receptor (GLP-1) agonists. Our findings are consistent with results obtained in other studies. Thorpe et al. [10] showed that, among tightly controlled older people with type 2 diabetes and coexisting dementia, 75% used sulphonylurea or/and insulin. The risk of hypoglycaemia during the therapy with sulfonylureas may increase the interaction with other drugs, e.g. sulphonamides, acenocoumarol, fluconazole, clarithromycin, ciprofloxacin, or doxycycline [11].

Many investigations performed in recent years have shown new interrelations between the risk of hypoglycaemia and complications. It is important to recognise the factors and consequences of hypoglycaemia. Turchin et al. [12] presented a retrospective analysis of 4368 admissions to a general ward. Among 2582 patients with diabetes, 7.7% of these hospitalisations were due to hypoglycaemia (defined as blood glucose ≤ 2.8 mmol/L (50 mg/dL in that study). Hypoglycaemic episodes were connected not only with an 85.3% increase in the odds ratio of inpatient death but also with a 65.8% increase in post-discharge death during the following year of observation [12]. Another longitudinal analysis of admissions to emergency units and hospitals was presented by Ginde et al. [13]. In the years 1993–2005, 34 cases of hypoglycaemia per 1000 patients with diabetes needed emergency department visits and 25% of them had to be hospitalised. During the analysed period there was no statistical change in frequency of hospitalisations due to hypoglycaemia. Patients aged less than 45 years and over 75 years were at an increased risk of emergency visits due to hypoglycaemia [13].

Antidiabetic treatment has often emphasised strict glycaemic control, but, as mentioned previously, it could be connected with a higher risk of hypoglycaemia. Although precaution in diabetological standards exists, many older people are treated too intensively. The study performed by Thorpe et al. [10] concerning the years 2008–2009 showed that, among veterans aged over 65 years with type 2 diabetes and dementia, tight glycaemic control was achieved in 52%. Among them this effect of therapy was obtained with sulphonylurea or insulin treatment with higher odds in persons over 75 years of age with heart failure, renal failure, and peripheral vascular disease. The authors concluded that these characteristics dispose these patients to be at higher risk of severe hypoglycaemia [14]. Such factors as old age, arterial hypertension, increased creatinine level, and lower cognitive function make persons with diabetes type 2 susceptible to severe hypoglycaemia [15]. In their study, Lipska et al. [16] suggested that a substantial proportion of elderly patients with

type 2 diabetes were over treated. Most of these patients reached tight glycaemic targets regardless of their health status category, and the harm caused by intensive glucose lowering exceeds the benefits for elderly patients with a complex (intermediate) or very complex (poor) health status [16].

Our study population confirms the findings mentioned above concerning patients with type 2 diabetes. The results observed in old persons under our study revealed the greatest risk of severe hypoglycaemia in subjects treated with insulin or sulfonylureas. Although the study group was small, all examined individuals had coexisting CVD: IHD, arterial hypertension, or a history of MI. The coexisting morbidities makes this group vulnerable to the consequences of hypoglycaemia, including death. In our study, one (woman, 81 years old) of 33 analysed patients died during hospitalisation due to MI.

Large analyses of data concerning the complications connected with hypoglycaemia underscore the interconnection between mortality and cardiovascular complications. In a large database in Canada, severe hypoglycaemia in old persons was connected with 2.5-fold increased mortality during the four years of observation following the initial episode. The effect of intensive glucose lowering treatment on cardiovascular death, and microvascular events in type 2 diabetes, was investigated in a meta-analysis of randomised controlled trials performed by Boussageon et al. [17]. Analysis of more than 33,300 patients who received glucose lowering treatment revealed that intensive glucose lowering treatment was associated with a more than 2-fold increase in the risk of severe hypoglycaemia and resulted in a 47% increase in the risk of cardiovascular complication.

This observation points to the development of strict standards preventing episodes of hypoglycaemia, which will decrease the difference between opposite vectors: the benefits of good glycaemic control and the precautions connected with hypoglycaemia. The significant number of cases of hypoglycaemia results from the unnecessary use of drugs associated with an increased risk of hypoglycaemia, especially in old patients with advanced co-morbidities [18]. Moreover, a combination of cognitive dysfunction and hypoglycaemic unawareness, which is clearly noticed more frequently in the elderly, is a critical factor in the treatment of this age group [19].

Modern diabetes therapy could effectively decrease the risk of hypoglycaemia. According to current recommendations of the European Association for the Study of Diabetes (EASD), the American Diabetes Association (ADA), and the PTD, metformin is the first drug of choice in all patients with newly diagnosed type 2 diabetes (after exclusion of contraindications). An important advantage of metformin treatment is low risk of hypoglycaemia, at the level of the placebo [20]. Among other oral antidiabetic agents with a good safety profile, it is worth mentioning acarbose — an inhibitor of intestinal alpha-glucosidase (alone does not cause hypoglycaemia) [21], gliflozins — inhibitors of type 2 sodium-glucose cotransporter (SGLT2) [22], and inhibitors of dipeptidyl peptidase (DPP-4) [23].

In recent years there has been an increase in the use of GLP-1 receptor agonists for the treatment of type 2 diabetes. Significant benefits of such therapy can be obtained in patients over 65 years of age with type 2 diabetes and obesity. The advantage of these drugs is low risk of hypoglycaemia [24]. Unfortunately, the evidence base for glucose lowering therapies in the elderly is poor because about 31% of studies of diabetes treatment exclude patients older than 65 years; almost all exclude patients older than 75 years, and only 0.6% of them target elderly people [25]. In Poland GLP-1 receptor agonists are prescribed relatively rarely because the high costs of this treatment are not acceptable for the majority of patients, especially the elderly.

CONCLUSIONS

In our study we observed that a low HbA1c level indicates inappropriate intensification of therapy and was associated with high risk of severe hypoglycaemic episodes in older people. The majority of severe hypoglycaemic episodes were observed in sulphonylurea or insulin-treated type 2 diabetic patients. The results of our work confirm that severe hypoglycaemia is an important clinical problem, especially in elderly patients, and is usually complicated and prolonged because of coexistence of cardiovascular history. Our study also suggests that among all the algorithms of insulin treatment, probably two-dose insulin therapy with the use of premixed insulins is associated with the highest risk of hypoglycaemia.

One of the reasons for severe hypoglycaemia is overtreatment of diabetes in elderly patients, proven by the alarming values of HbA1c obtained in our study, which are clearly lower than those recommended by the PTD and ADA. We do not know whether the introduction of new antidiabetic drugs will decrease the number of hospitalisations due to severe hypoglycaemia in the elderly in Poland. This issue needs further investigation. We should realise that there is a gap between the recommendations of scientific societies and the treatment algorithms used in general medical practice. The basic principles in the pharmacotherapy of diabetes in elderly people should be: (1) to set an appropriate glycaemic target, (2) to ensure the patients are not over treated, and (3) to not hesitate to discontinue antidiabetic treatment if necessary.

Conflict of interest: *none declared*

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Ciężka hipoglikemia u pacjentów w starszym wieku z cukrzycą typu 2 oraz towarzyszącymi chorobami układu sercowo-naczyniowego

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Streszczenie

Wstęp: Hipoglikemię rozpoznaje się, jeżeli stężenie glukozy w surowicy obniży się poniżej 3,9 mmol/l (70 mg/dl), natomiast śpiączka hipoglikemiczna występuje zwykle przy stężeniach glukozy ok. 1,1 mmol/l (20 mg/dl). Nawracające ostre hipoglikemie mogą być przyczyną zaburzeń neurologicznych i mają negatywny wpływ na układ sercowo-naczyniowy.

Cel: Celem pracy była ocena przyczyn ciężkiej hipoglikemii u pacjentów z cukrzycą typu 2 oraz z towarzyszącymi chorobami układu sercowo-naczyniowego (CVD).

Metody: Przeanalizowano retrospektywnie historie chorób 33 pacjentów z cukrzycą typu 2 oraz z towarzyszącymi CVD, u których rozpoznano ciężką hipoglikemię z utratą świadomości. Średni wiek pacjentów wynosił 76,0 ± 11,1 roku, a czas trwania cukrzycy średnio 12,0 ± 9,8 roku. Oceniano stężenie hemoglobiny glikowanej (HbA_{1c}), częstość występowania CVD oraz sposób postępowania terapeutycznego.

Wyniki: U pacjentów z ciężką hipoglikemią średnie stężenie HbA_{1c} wynosiło 6,3 ± 1,2% (44 ± 13,1 mmol/mol), co odpowiada średniemu stężeniu glukozy poniżej 7,8 mmol/l (140 mg/dl). Chorobę niedokrwienną serca stwierdzono u 18 osób (8 przebyło zawał serca), a u 22 pacjentów — nadciśnienie tętnicze. Ciężka hipoglikemia wymagająca hospitalizacji u pacjentów w starszym wieku z cukrzycą typu 2 oraz towarzyszącymi CVD wiązała się ze stosowaniem insuliny i pochodnych sulfonylomocznika.

Wnioski: Niskie wartości HbA1c wskazują na nieodpowiednią intensyfikację leczenia, prowadzącą do epizodów ciężkiej hipoglikemii u pacjentów w starszym wieku. Większość stanów ciężkiej hipoglikemii występuje u osób z cukrzycą typu 2 leczonych preparatami insulin lub pochodnymi sulfonylomocznika.

Słowa kluczowe: hipoglikemia, cukrzyca typu 2, pacjenci w starszym wieku

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