Research: Treatment

Changes in incidence of severe hypoglycaemia in people with type 2 diabetes from 2006 to 2016: analysis based on health insurance data in Germany considering the antihyperglycaemic medication

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Accepted 3 March 2020

Abstract

Aim To investigate the incidence of severe hypoglycaemia over the past 10 years, taking into account changes in antihyperglycaemic therapy.

Methods This retrospective population-based study used German health insurance data. All adults diagnosed with documented type 2 diabetes (extrapolated to the German population: 6.6 million in 2006; 7.9 million in 2011; 8.86 million in 2016) were screened for severe hypoglycaemia. Anti-hyperglycaemic agents were identified by Anatomical Therapeutic Chemical (ATC) code.

Results The event rate for severe hypoglycaemia was 460 per 100 000 people in 2006, 490 per 100 000 in 2011 and 360 per 100 000 in 2016. The proportion of people with severe hypoglycaemia receiving sulfonylureas, as well as receiving combination therapy of metformin and sulfonylureas decreased from 2006 to 2016 (23.6% vs. 6.2%). Among those with severe hypoglycaemia in 2006, there were no prescriptions for dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists or sodium–glucose co-transporter 2 (SGLT2) agonists. The proportions of people with severe hypoglycaemia receiving DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 agonists in 2011 and 2016 were low. The proportion of people receiving human insulin also decreased (from 11.3% in 2006 to 10.3% in 2011 and 4.3% in 2016); the proportion of people receiving insulin analogues increased from 5.4% in 2006 to 11.5% in 2016. Therapy with mixed insulins was used by 19.7% of people with severe hypoglycaemia in 2006, by 14.0% in 2011 and by 7.3% in 2016. People undergoing therapy with insulin analogues have the highest risk of severe hypoglycaemia adjusted by age, gender, nephropathy diagnosis and year of survey [odds ratio (OR) 14.4, 95% confidence interval (95% CI) 13.5–15.5].

Conclusion The incidence of severe hypoglycaemic events in Germany increased between 2006 and 2011, and decreased in 2016.

Diabet. Med. 37, 1326–1332 (2020)

Introduction

Risk of hypoglycaemia is often the limiting factor for good metabolic control in the management of diabetes [1,2]. Recently, anti-hyperglycaemic medications have been developed with the aim of improving metabolic control while reducing the risk of severe hypoglycaemia. Furthermore, for glucagon-like peptide-1 (GLP1) agonists and some of the new class of sodium–glucose co-transporter 2 (SGLT2) inhibitors, cardiovascular benefit has been demonstrated in endpoint studies [3–5].

An analysis of health insurance data from 2006 and 2011 showed an increase in severe hypoglycaemia, despite a change in prescribing behaviour in favour of anti-hyperglycaemic drugs with a lower risk for hypoglycaemia [6]. In this study, risk factors for severe hypoglycaemia were older age and the presence of nephropathy, irrespective of sex and anti-
hyperglycaemic treatment. Older age and the presence of comorbidities are also risk factors for severe hypoglycaemia in several other studies [7,8]. The ACCORD study, together with numerous other studies and meta-analyses, questioned the benefits of intensive metabolic control in older people (65+). The risk of severe hypoglycaemia was shown to outweigh the benefit of intensive glucose lowering [9–11]. These findings have led to more differentiated treatment targets in the guidelines. For the first time, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommended individualized therapy goals in their 2012 Position Statement, particularly for the majority of older persons with diabetes [2]. German guidelines followed their recommendations in 2013 [12].

Here, we present a follow-up analysis of the 2017 study by Müller et al. [6] on the incidence of severe hypoglycaemia in 2006 and 2011. The current study compares incidences of severe hypoglycaemia for the years 2006, 2011 and 2016 in Germany, and relates the severe hypoglycaemic event to anti-hyperglycaemic drugs provided 3 months previously. The aim of our study was to investigate whether these changed recommendations regarding treatment goals and the availability of new anti-hyperglycaemic therapies led to a decrease in the incidence of severe hypoglycaemia.

Methods

This is a retrospective population-based study of three cohorts based on routine healthcare data collected in 2006, 2011 and 2016 by the largest statutory health insurance company in Germany ‘Allgemeine Ortskrankenkasse’ (AOK), which insured 25.2 million people in 2016, approximately one-third of the German population [13]. For the current analyses, we used three samples of anonymized data for 500 000 AOK-insured people with type 2 diabetes for the years 2006, 2011 and 2016, with at least one day of insurance in the relevant year. The sample was extrapolated to the whole AOK population, and subsequently extrapolated and standardized according to the age and sex distribution of the German population with diabetes mellitus: 6.6 million in 2006, 7.9 million in 2011 and 8.9 million in 2016.

All procedures were carried out in accordance with the ethical standards of the committee on human experimentation of the study institutions and German national standards, as well as with the 1975 Declaration of Helsinki, as revised in 2008 [5].

Identification of people with diabetes and outcome parameters

Identification of people with diabetes was described in detail in the first analysis of the 2006 and 2011 data [6], and is further described in detail in Appendices S1 and S2.

The primary endpoint was the incidence of severe hypoglycaemia for the years 2006, 2011 and 2016. These incidences of severe hypoglycaemia in the respective years were compared with each other. To calculate the incidence for the respective year, all new events of severe hypoglycaemia identified using 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding, hospitalization with that diagnosis, or emergency care for that diagnosis were included in the analysis.

The second endpoint was the prescribing rate for anti-hyperglycaemic agents in persons with and without severe hypoglycaemia. All prescribed anti-hyperglycaemic agents were identified by their Anatomical Therapeutic Chemical (ATC) code [14]. The 11 most common anti-hyperglycaemic agents and 23 most common combinations were evaluated, but only the most prevalent treatments are reported here. The last prescribed anti-hyperglycaemic medication within the 3 months before a severe hypoglycaemic event was considered. Rates of anti-hyperglycaemic agents prescribed most often were compared for 2006 vs. 2011 and vs. 2016.

Statistical methods

For continuous variables (age), mean ± standard deviation (SD) are reported. Rates are reported with 95% confidence intervals (CI). Sex distribution, presence of nephropathy and anti-hyperglycaemic medication were described as relative frequencies. Differences in treatment between people with and without severe hypoglycaemia were tested using Fisher’s exact test. Logistic regression models were applied to determine the relationships of anti-hyperglycaemic treatments and other factors with severe hypoglycaemia, adjusting for age, gender, nephropathy and survey year. Two-tailed P-values ≤ 0.05 were considered statistically significant. All calculations were performed with the statistical software SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

In 2006, there were 30 560 severe hypoglycaemic events in 6.6 million people with type 2 diabetes, the corresponding figures were 38 750 events in 7.9 million in 2011 and 31 895 events in 8.9 million in 2016.

What’s new?

• We were able to follow up the incidence of severe hypoglycaemia in a large cohort of people with type 2 diabetes over a period of 10 years.

• The incidence of severe hypoglycaemia increased from 2006 to 2011 and decreased from 2011 to 2016.

• The highest risk of severe hypoglycaemia is associated with treatment with insulin analogues, after adjustment for age, sex, nephropathy diagnosis and year.
8.9 million in 2016. The numbers of severe hypoglycaemia events were 460 per 100 000 persons in 2006, 490 per 100 000 in 2011 and 360 per 100 000 in 2016.

Compared with people without severe hypoglycaemia, those with severe hypoglycaemia were older in 2006 (72.8 years; P < 0.001) and 2011 (73.4 vs. 69.1 years; P < 0.001), but not in 2016 (73.0 vs. 72.9 years; P = 0.601). Severe hypoglycaemic events occurred more often in women in 2006 (62.0%; P < 0.001) and 2011 (58.0%; P < 0.001), but not in 2016 (55.8% vs. 11.0; P = 0.001). Nephropathy was present more often in people who experienced a hypoglycaemic event in 2006 (42.3% vs. 5.2%; P < 0.001) and 2011 (50.9% vs. 7.2%; P < 0.001) and 2016 (55.8% vs. 11.0; P < 0.001).

Anti-hyperglycaemic treatment before an event of severe hypoglycaemia

The proportion of people with severe hypoglycaemia undergoing treatment with sulfonylureas decreased between 2006 and 2016 (Table 1). In 2006, 10.9% of people with severe hypoglycaemia were treated with sulfonylurea; this was lower in 2011 (7.3%) and in 2016 (1.9%). Similarly, the proportion of people with severe hypoglycaemia receiving combination therapy with metformin and sulfonylureas decreased between 2006 and 2016, from 12.7%, to 9.3% in 2011 and 3.8% in 2016.

DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors were not widely used or available in 2006 (Table 1). In 2006, 10.9% of people with severe hypoglycaemia receiving combination therapy with metformin and sulfonylureas decreased between 2006 and 2011 (7.3%) and in 2016 (1.9%).

In multiple regression analyses, adjusted for age, sex, presence of nephropathy and year of survey, treatment with DPP-4 inhibitors increased from 1.55% in 2011 to 5.2% in 2016, and use of a combination of a DPP-4 inhibitor and metformin also increased, from 2.4% in 2011 to 4.0% in 2016. Few people with severe hypoglycaemia were prescribed a GLP-1 receptor agonist in 2011 (0.17%) or in 2016 (0.4%). SGLT2 inhibitors were also not used in 2011. In 2016, only 0.9% of people with severe hypoglycaemia received SGLT2 inhibitors (Table 1).

Insulin treatment before severe hypoglycaemia

In 2006, the proportion of people with severe hypoglycaemia undergoing therapy with human insulin was 11.3% (Table 1). In 2011, there was a slight decrease to 10.3%. In 2016, the proportion of people with severe hypoglycaemia who were receiving treatment with human insulin decreased significantly to 4.3%. By contrast, the proportion of people with severe hypoglycaemia receiving a combination of short- and long-acting insulin analogues more than doubled from 2006 to 2016 (5.4% in 2006, 8.1% in 2011 and 11.5% in 2016) (Table 1).

In 2006, the majority of people with severe hypoglycaemia were receiving human mixed insulin, but the proportion decreased significantly in 2011 (14.0%) and 2016 (7.3%) (Table 1).

Multiple regression modelling

In multiple regression analyses, adjusted for age, sex, presence of nephropathy and year of survey, treatment with

| Proportion of people with diabetes (%) | 2006 | 2011 | 2016 |
|--------------------------------------|------|------|------|
|                                      | With SH | Without SH | P-value* | With SH | Without SH | P-value* | With SH | Without SH | P-value* |
| n                                     | 30 560 | 6 615 692 | – | 38 750 | 7 865 422 | – | 31 895 | 8 830 026 | – |
| Age, years                            | 72.8 ± 12.4 | 68.7 ± 12.2 | < 0.001 | 73.4 ± 12.3 | 69.1 ± 12.5 | < 0.001 | 73.0 ± 13.2 | 72.9 ± 13.2 | 0.601 |
| % women                               | 62.2 | 56.5 | < 0.001 | 58.4 | 54.8 | < 0.001 | 55.3 | 55.3 | 0.9221 |
| Nephropathy (%)                       | 42.3 | 5.2 | < 0.001 | 50.9 | 7.2 | < 0.001 | 55.8 | 11.0 | < 0.001 |
| Sulfonylureas                         | 10.9 | 9.7 | < 0.001 | 7.3 | 4.7 | < 0.001 | 2.4 | 1.9 | < 0.001 |
| Metformin + sulfonylureas             | 12.7 | 11.7 | < 0.001 | 9.3 | 8.2 | < 0.001 | 3.8 | 3.4 | < 0.001 |
| DPP-4 inhibitors                      | 0.0 | 0.0 | – | 1.55 | 1.27 | < 0.001 | 5.2 | 3.9 | < 0.001 |
| DPP-4 inhibitors + metformin          | 0.0 | 0.0 | – | 2.40 | 0.52 | < 0.001 | 4.0 | 6.3 | < 0.001 |
| GLP-1 analogues                       | 0.0 | 0.0 | – | 0.17 | 0.11 | – | 0.4 | 0.5 | 0.189 |
| SGLT-2 inhibitors                     | 0.0 | 0.0 | – | 0.0 | 0.0 | – | 0.9 | 1.0 | 0.128 |
| Human short- and long-acting insulin  | 11.3 | 3.6 | < 0.001 | 10.3 | 3.3 | < 0.001 | 11.5 | 5.0 | < 0.001 |
| Short- and long-acting insulin analogues | 5.4 | 1.3 | < 0.001 | 8.1 | 2.0 | < 0.001 | 11.5 | 2.5 | < 0.001 |
| Mixed human insulin                  | 19.7 | 5.0 | < 0.001 | 14.0 | 3.0 | < 0.001 | 7.3 | 2.0 | < 0.001 |

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; SGLT-2, sodium–glucose co-transporter 2.

P-values are for the prescription of anti-hyperglycaemic medication in all people with diabetes in 2006 vs. 2011 vs. 2016.

P-values for differences between population with and without severe hypoglycaemia (SH) in 2006, 2011 and 2016.

P-values for differences between population with severe hypoglycaemia in 2006 vs. 2011 vs. 2016 are < 0.001, with the exception of SGLT-2 inhibitors 2006 vs. 2011.
insulin therapy has a 1.3-fold higher risk of severe hypoglycaemia (OR 1.29, CI 1.2–1.4) compared with human insulin therapy. Nephropathy was a consistently important risk factor (adjusted for age, sex, year and treatment type; OR 10.3, CI 10.1–10.7). Older age decreased the risk of severe hypoglycaemia, by 0.5% per decade (adjusted for gender, year, nephropathy and treatment type; OR 0.95, CI 0.94–0.96). Finally, the risk of severe hypoglycaemia overall was 6% higher in 2011 compared with 2006 (OR 1.06, CI 1.04–1.09), but 24% lower in 2016 (OR 0.76, CI 0.74–0.78 adjusted for age, sex, nephropathy and treatment-type) (Table 2).

Focusing on people receiving insulin therapy only, 2011 showed a slightly higher risk for hypoglycaemia than 2006 (OR 1.06, CI 1.0–1.1); the risk was significantly lower in 2016 (OR 0.72, CI 0.7–0.8).

The risk of severe hypoglycaemia under insulin therapy is higher for people with nephropathy than for people without nephropathy. People with nephropathy have a 16 times higher risk of severe hypoglycaemia with human insulin treatment compared with metformin treatment (OR 16.13, CI 14.7–17.4). For people without nephropathy, the risk is only 5.7 times higher (OR 5.72, CI 4.9–6.7). The risk of severe hypoglycaemia with insulin analogues compared with metformin in people with nephropathy is 21 times higher (OR 21.43, CI 19.4–23.6), whereas in people without nephropathy it is 6.8 times higher (OR 6.84, CI 5.9–9.8).

**Discussion**

In the first analysis of the 2006 and 2011 data, we saw an increase in severe hypoglycaemia, whereas in 2016, severe hypoglycaemia occurred less often. Prescribing patterns for anti-hyperglycaemic agents also varied from 2006 to 2016. Prescriptions for sulfonylurea and human insulin decreased, and substances not yet available or not often used in 2006, such as DPP-4 inhibitors, GLP-1 analogues, SGLT-2 inhibitors and especially insulin analogues, increased. Owing to a significant decline in the prescribing of sulfonylurea and human insulin, the event rate for severe hypoglycaemia under this medication also decreased. Similarly, as in the analysis of 2006 and 2011, the highest risk for severe hypoglycaemia is associated with insulin analogues, also adjusted for gender, age, year of survey and nephropathy diagnosis. The substantial increase in the prescribing of insulin analogues in recent years is consistent with results from other studies [15]. This shift took place in spite of meta-analyses of studies comparing insulin analogues with human insulin in type 2 diabetes without results in favour of insulin analogues [16,17]. The event rate of severe hypoglycaemia under analogue insulin can have various causes and it is possible that the indications for therapy with analogue insulin differ from those for therapy with human insulin. Consequently, no therapeutic conclusions can be drawn from this analysis.

The incidence of severe hypoglycaemia decreased significantly from 2011 to 2016 and interestingly, age now is no longer a risk factor for the occurrence of severe hypoglycaemia. In previous analysis of 2006 and 2011, older age increased the risk of severe hypoglycaemia by 6.5% per decade [6]. The more lenient and individualized therapy goals recommended in recent guidelines, especially with regard to older people, could be a possible explanation. Revised national guidelines were published in Germany in 2013. A central therapeutic goal of this revised guideline is the avoidance of hypoglycaemia. The HbA1c target range has been raised from ≤47.5 mmol/mol (6.5%) to 53–63.9 mmol/mol (7–8%) for the elderly, and up to 69.4 mmol/mol (8.5%) in the case of reduced life expectancy [12]. It must also be taken into account that HbA1c has been approved for the diagnosis of diabetes mellitus since 2010. This resulted in a significant increase in diabetes prevalence, especially among people with borderline HbA1c levels who do not require anti-hyperglycaemic therapy [18,19]. The age

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**Table 2** Multiple logistic models of association of selected factors with risk of severe hypoglycaemia

| Factors                                      | Odds ratio | 95% CI   | P-value |
|----------------------------------------------|------------|----------|---------|
| Insulin analogues vs. metformin*             | 14.4       | 13.5–15.5| < 0.001 |
| Mixed insulin vs. metformin*                 | 13.5       | 12.7–14.5| < 0.001 |
| Human insulin vs. metformin*                 | 11.2       | 10.5–12.0| < 0.001 |
| Nephropathy†                                 | 10.3       | 10.1–10.6| < 0.001 |
| Sulfonylureas vs. metformin*                 | 5.7        | 5.3–6.1  | < 0.001 |
| Other anti-hyperglycaemic agents vs. metformin* | 3.6    | 3.4–3.8  | < 0.001 |
| Women > men‡                                 | 1.13       | 1.1–1.2  | < 0.001 |
| Year 2011 > 2006‡                           | 1.06       | 1.04–1.09| < 0.001 |
| Year 2016 > 2006†                           | 0.76       | 0.74–0.78| < 0.001 |
| Greater age (per 10 years)§                  | 0.95       | 0.94–0.96| < 0.001 |

Adjustment factors for each outcome (risk of severe hypoglycaemia) contrast were: *sex, age, year, and diagnosis of nephropathy; †sex, age, year and anti-hyperglycaemic treatment given; ‡age, year, treatment and nephropathy; §age, sex, treatment and nephropathy; and ¶sex, year, treatment and nephropathy.
dependence of the HbA1c value discussed in various publications is not taken into account in the diagnosis [20,21]. This new possibility to diagnose diabetes mellitus led to a marked increase in the number of people without risk of severe hypoglycaemia, which may explain the found decrease in severe hypoglycaemia.

Similar results were also found by Zaccardi et al. in England. The incidence of hypoglycaemia increased from 2005 to 2010, and fell slightly until 2014 [22]. A decrease in hypoglycaemia in elderly adults since 2009 in England was found by Zhong et al. [23] and since 2007 in the USA by Lipska et al. [24]. These authors hypothesize that the decreasing trend may be driven by findings from the ACCORD, ADVANCE and VADT studies, which suggest that elderly adults may not gain macrovascular benefits from intensive glycaemic control, but run an increased risk of hypoglycaemia [9,11,25]. Furthermore, the authors attribute the reduction in the incidence of severe hypoglycaemia to a reduction in the prescription of sulfonylureas. In our data, we also see a significant reduction in prescriptions for sulfonylureas, but this was also the case between 2006 and 2011, during which time the incidence of severe hypoglycaemia increased.

For a long time, the treatment of people with diabetes focused on prevention of hyperglycaemia and its complications. Efforts to intensify glycaemic control were very successful, > 70% of people with type 2 diabetes achieved an HbA1c < 53 mmol/mol (7%) [26]. The proportion of people achieving HbA1c levels < 53 mmol/mol (7%) increased substantially from 2000 to 2014, but this impetus faded in the period from 2007 to 2014 [27]. One side-effect of this intensification may have been an increase in severe hypoglycaemia, as shown in our data to 2011.

The highest risk of hypoglycaemia was still seen in people receiving insulin therapy. For example, a study from Denmark, conducted only on people with insulin-treated diabetes, showed a significantly higher incidence of severe hypoglycaemia compared with our data. However, in this Danish study, hypoglycaemia was recorded using a questionnaire and severe hypoglycaemia was defined as the need for assistance from another person, which is less stringent than the definition used in our study. The most important risk factor for severe hypoglycaemia in the Danish study was hypoglycaemia unawareness [28]. Unfortunately, this variable is not available in health insurance data.

At the start of insulin therapy, the risk of hypoglycaemia increases about six times [29]. Accordingly, in the consensus statement of the ADA and EASD, insulin therapy is delayed in favour of SGLT-2 inhibitors and GLP-1 receptor agonists in particular, which could also provide evidence of benefit in clinical endpoint studies and have an extremely low risk of hypoglycaemia [30]. This deleterious side-effect of insulin therapy can be offset by participation in a treatment and training programme for people receiving insulin therapy, which can help to reduce the risk of hypoglycaemia in this group. This has recently been demonstrated in a study by Kloos et al. [31].

**Strengths and limitations**

The strength of the current study is the large sample size. The anti-hyperglycaemic medication prior to any severe hypoglycaemia was determined using the ATC code. Because we used health insurance billing data, there is no problem with missing responses or lack of data. However, the fact that the data is from one particular health insurance company could cause bias. Compared with other health insurance companies, AOK takes care of a higher proportion of people with diabetes [32]. This may contribute to data bias. Similar to the first analysis [6], the current data were standardized according to the age and sex distribution of the German population, but unrecognized bias such as socio-economic status may have influenced the reported findings. Further limitations of this study include the lack of other potentially important treatment factors, like HbA1c, BMI, hypoglycaemia unawareness and duration of diabetes.

**Conclusions**

We found an increase in the incidence of severe hypoglycaemia between 2006 and 2011, and a decrease from 2011 to 2016. Anti-hyperglycaemic therapy also altered with an overall decrease in the use of sulfonylurea and human insulin, and an increase in DPP-4 inhibitors, SGLT-2 inhibitors and especially insulin analogues. The reduction in the incidence of severe hypoglycaemia is most likely due to more lenient treatment goals and the individualization of therapy.

**Funding sources**

The study was supported by the German Diabetes Foundation and by funds provided by the home institutions of the authors.

**Competing interests**

CG and AK are employees of a statutory healthcare fund. There are no other potential conflicts of interest relevant to this study.

**Acknowledgments**

We thank Catriona Graham, Shrewsbury, UK for language editing.

**Author contributions**

NM researched data and drafted the report; TL researched data and revised the manuscript; AK and researched data,
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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Most common antihyperglycaemic agents.
Appendix S2. Identification of persons with diabetes.