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# Trend of antihyperglycaemic therapy and glycaemic control in 184,864 adults with type 1 or 2 diabetes between 2002 and 2014: Analysis of real-life data from the DPV registry from Germany and Austria<sup>☆</sup>

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## ABSTRACT

**Aims:** To analyse time trends of antihyperglycaemic therapy and glycaemic control in adult subjects with type 1, or type 2 diabetes between 2002 and 2014 in Germany/Austria.

**Methods:** 184,864 adults with diabetes (35,144 type 1 diabetes (T1D), 149,720 type 2 diabetes (T2D)) from the DPV-database documented between 2002 and 2014 were included. Regression models were applied for antihyperglycaemic therapy in T2D (non-pharmacological, OADs only, insulin ± OADs), insulin therapy in T1D (CT, ICT, CSII) and T2D (BOT, SIT, CT,

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ICT, CSII), for the use of insulin analogues, and for glycaemic control (HbA<sub>1c</sub>, severe hypoglycaemia), adjusting for confounders sex, age, and diabetes duration.

**Results:** In T1D, CT (2002:19.7%; 2014:16.0%) and ICT (2002:66.8%; 2014:52.4%) decreased, while CSII increased from 13.5% to 31.5%. In T2D, non-pharmacological treatment became less frequent (2002:36.0%, 2014:21.8%), the use of OADs (2002:19.3%, 2014:28.9%) and insulin ± OADs (2002:44.6%, 2014:49.4%) increased. BOT increased from 7.9% to 18.9%, SIT decreased from 12.0% to 8.3%. ICT slightly increased (2002:44.0%, 2014:45.3%), CT decreased (2002:35.8%, 2014:27.2%). Insulin analogues were used more frequently in T1D (rapid-acting:2002:46.8%, 2014:84.8%; long-acting:2002:26.0%, 2014:54.8%) and in T2D (rapid-acting:2002:26.0%, 2014:43.5%; long-acting:2002:13.7%, 2014:53.6%). Until 2011, HbA<sub>1c</sub> increased in T1D and T2D, but then decreased again. High variability in the rate of hypoglycaemia was observed.

**Conclusions:** This observational study indicates an increased use of insulin pumps in T1D. In T2D, non-pharmacological therapy decreased, and insulin therapy, particular as BOT, rose. An increase in the use of rapid- and long-acting insulin analogues was present in both patient-groups. Time trend was less clear in glycaemic control.

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## 1. Introduction

Since the results of the Diabetes Control and Complication Trial (DCCT) study were published, insulin therapy in subjects with type 1 diabetes was intensified using either intensified conventional therapy (ICT) or continuous subcutaneous insulin infusion (CSII) [1]. Studies suggest a worldwide increase in the use of CSII in type 1 diabetes [2–5]. For example, in the United States, the number of patients on CSII increased from 15,000 in 1993 to >81,000 in the year 2000 [5]. German data indicate an increase in the use of insulin pumps in young adults (>15 to ≤20 years of age) from <3% in 1995 to 22% in 2006 [2].

The development of new insulin preparations as rapid- and long-acting insulin analogues has also led to changes in insulin therapy. Data of the British Health and Social Care Information Centre indicate that in 2005/2006, insulin analogues made up 60.0% of all insulins prescribed in England. In 2012/2013, insulin analogues already made up 84.6% [6]. Other studies also indicate an increase in the use of insulin analogues [7,8]. In Germany, the situation may be different due to several financial restrictions on insulin analogues [9].

In patients with type 2 diabetes, changes in antihyperglycaemic therapy were reported as well. For example, a study from Japan suggested a reduction of non-pharmacological interventions [10]. The use of OADs as well as the combined therapy of OADs and insulin became more frequent, whereas the exclusive use of insulin decreased [10]. A study from the Swedish National Diabetes Register found similar trends for exclusive non-pharmacological treatment and for the sole use of OADs [11]. However, a small reduction in the combined use of OADs and insulins was present. The authors also reported a constant use of insulin therapy [11]. For Germany, such analyses seem to be rare. Only data of a disease management program (DMP) were used to investigate differences between patients enrolled in the DMP in 2003 and patients enrolled in 2013 [12]. Data suggested an increase in non-pharmacological therapy. Furthermore, a decrease in insulin-treated patients was indicated [12].

Overall, time trend analyses in adult subjects with diabetes appear to be scarce. We therefore investigated time trends of antihyperglycaemic therapy and glycaemic control in subjects with type 1 or type 2 diabetes between 2002 and 2014 in Germany and Austria.

## 2. Subjects materials and methods

### 2.1. Data source and subjects

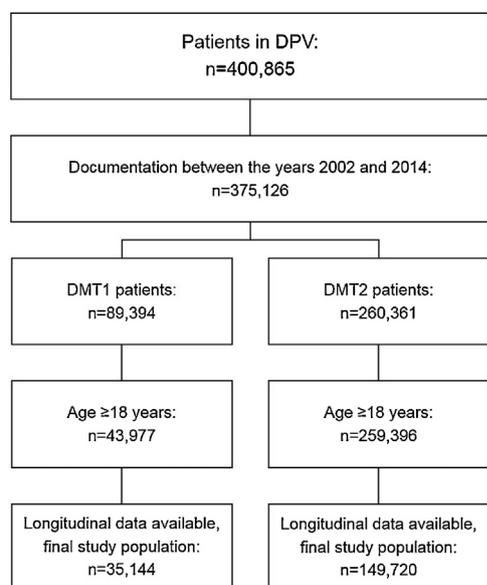
This observational study is based on the Diabetes-Patienten-Verlaufsdokumentation (DPV), a standardized, longitudinal prospective documentation system of diabetes care and outcome which is currently used by 420 centres from Germany and Austria. Twice a year, participating centres transmit their anonymized data to the central administrative unit in Ulm, Germany [13]. Data are then aggregated into a cumulative database for clinical research and quality assurance. In case of implausibility or inconsistency, participating centres are requested to correct data. The DPV initiative was approved by the Ethics Committee of the University of Ulm, Germany and data collection by the local review boards.

Until March 2015, demographic and clinical data of 400,865 patients with any type of diabetes were available in the database. For the present analysis, pediatric patients (<18 years of age) were excluded. Data of patients treated between 2002 and 2014 with longitudinal data (at least ≥2 visits available) were included. The final study population comprised 35,144 subjects with type 1 diabetes and 149,720 subjects with type 2 diabetes (Fig. 1).

### 2.2. Variables

Demographic data included sex, age, age at diabetes manifestation and diabetes duration.

Insulin therapy in patients with type 1 diabetes was categorized as conventional insulin therapy (CT) (1–3 daily injection time points), ICT (>3 daily injection time points), or



**Fig. 1 – Selection of study population.**

as CSII. Antihyperglycaemic therapy in patients with type 2 diabetes was categorized as follows: (i) non-pharmacological treatment/lifestyle only (physical activity, dietary advice), (ii) OADs only, (iii) insulin therapy with/without OADs. Insulin therapy was categorized as basal-supported oral therapy (BOT) (basal insulin only), supplementary insulin therapy (SIT) (prandial insulin only), CT (prandial and basal insulin combined, up to 3 injection time points), ICT (prandial and basal insulin combined, >3 injection time points) and CSII. The use of long and rapid-acting insulin analogues was calculated separately for subjects with type 1 or insulin-treated patients with type 2 diabetes.

Moreover, the frequency of self-monitoring of blood glucose (SMBG), HbA<sub>1C</sub> and the occurrence of hypoglycaemic events were considered. HbA<sub>1C</sub> values were standardized to the DCCT reference range (20–42 mmol/mol; 4.05–6.05%) using the multiple of the mean transformation method [14]. Severe hypoglycaemia was defined as “an event requiring assistance by another person to actively administer carbohydrates, glucagon, or other resuscitative actions” [15], hypoglycaemia with coma was defined when loss of consciousness or seizures occurred. In subjects with type 2 diabetes, the rate of severe hypoglycaemia was considered in insulin-treated patients and in patients only treated with sulfonylureas or glinides, separately.

In case of multiple data sets per patient within one calendar year, quantitative parameters were aggregated as median and count data as cumulative sums. For each patient, the last year of treatment documented within the period 2002–2014 was analysed. Results are presented for the years 2002–2014, separately.

### 2.3. Statistical analysis

For descriptive analysis, median [Q1;Q3] was calculated for continuous variables, percentage for categorical variables and events per 100 patient years (PY) for count data.

In order to correct for demographic differences (sex, age and diabetes duration) between patients in different calendar years (Table S1), regression models were created. In type 1 diabetes, the confounder age was categorized as 18 to <25, ≥ 25 to <40, ≥40 to <55, ≥55 years and diabetes duration as <2, ≥2 to <5, ≥5 years. In type 2 diabetes, age was categorized as ≥18 to <40, ≥40 to <65, ≥65 years and diabetes duration as <5/≥5 years. Logistic regression was applied for categorical variables. Linear regression models were created for continuous variables and negative binomial regression for count data. Results of regression models are presented as adjusted least squares means (LS-means) with regression coefficient  $\beta$  for the year [95% CI]. To analyse changes over time, *p*-value for trend was given. A two-sided *p*-value <0.05 was considered significant. All statistical analyses were implemented with SAS 9.4 (Statistical Analysis Software, SAS Institute, Cary, NC, USA).

## 3. Results

The total study population comprised 184,864 subjects with type 1 (*n* = 35,144) or type 2 diabetes (*n* = 149,720) documented between the years 2002 and 2014.

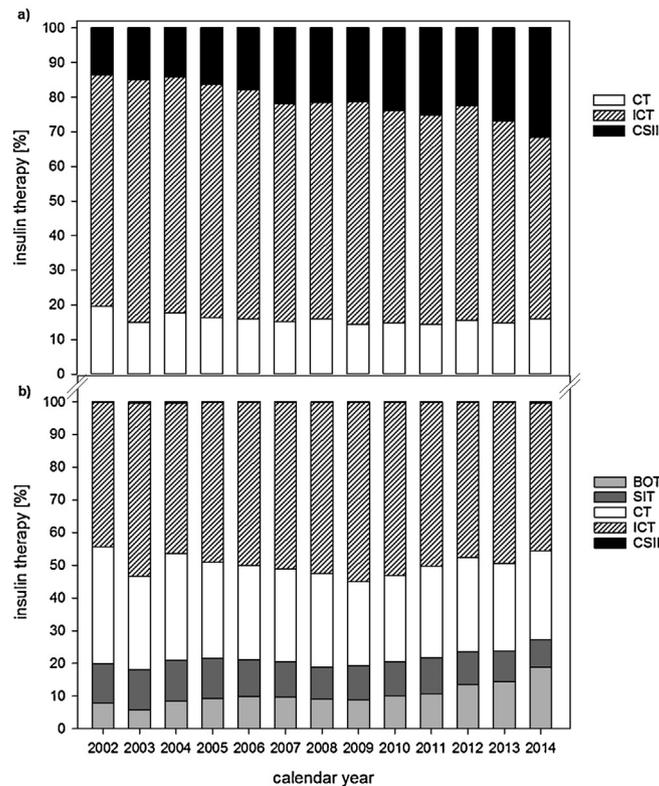
52.9% of the patients with type 1 diabetes were male. Their median age was 34.4 [Q1;Q3: 20.2;53.2] years with a diabetes duration of 12.3 [6.3;22.1] years. Median age at diabetes manifestation was 17.0 [10.5;33.0] years. Sociodemographic data for the years 2002–2014 are presented in Table S1. Median age and median diabetes duration increased from 2002 to 2014.

Patients with type 2 diabetes (male gender: 52.2%) were 69.6 [60.3;77.0] years old with a median diabetes duration of 9.5 [4.1;15.8] years. Median age at diabetes onset was 57.3 [48.0;66.5] years. Stratified by calendar year, subjects with type 2 diabetes became older and diabetes duration steadily increased over the last 13 years (Table S1).

### 3.1. Antihyperglycaemic therapy

In patients with type 1 diabetes, regression analysis revealed a decrease in CT (2002:19.7%, 2014:16.0%;  $\beta_{\text{year}} = -0.016$  [−0.026; −0.006], *p* = 0.0016) and ICT (2002:66.8%, 2014:52.4%;  $\beta_{\text{year}} = -0.055$  [−0.062; −0.048], *p* < 0.0001), while CSII increased from 13.5% to 31.5% ( $\beta_{\text{year}} = 0.083$  [0.075; 0.091], *p* < 0.0001) (Fig. 2a).

In patients with type 2 diabetes, non-pharmacological treatment only became less frequent (2002:36.0%, 2014:21.8%;  $\beta_{\text{year}} = -0.036$  [−0.039; −0.032]). The sole use of OADs (2002:19.3%, 2014:28.9%;  $\beta_{\text{year}} = 0.045$  [0.042; 0.049]) and the use of insulins with or without OADs (2002:44.6%, 2014:49.4%; no linear trend) became more frequent during the last 13 years (all *p* < 0.0001) (Fig. 3). BOT increased from 7.9% to 18.9% ( $\beta_{\text{year}} = 0.093$  [0.086; 0.100]), whereas SIT decreased from 12.0% to 8.3% ( $\beta_{\text{year}} = -0.033$  [−0.039; −0.026]) (both *p* < 0.0001). CT became less frequent (2002:35.8%, 2014:27.2%;  $\beta_{\text{year}} = -0.016$  [−0.021; −0.012], *p* = 0.0089), ICT (2002:44.0%, 2009:54.8%, 2014:45.3%; no linear trend, *p* = 0.8714) slightly increased (*p* < 0.0001, respectively). The number of patients on CSII remained negligible (2002:0.30%, 2014:0.32%,  $\beta_{\text{year}} = -0.020$  [−0.053; 0.012], *p* = 0.2180) (Fig. 2b).



**Fig. 2 – Insulin therapy in subjects with (a) type 1 diabetes, or (b) type 2 diabetes, stratified by calendar year. Data adjusted for age, sex and diabetes duration.**

The use of rapid-acting insulin analogues increased in type 1 diabetes from 46.8% in 2002 to 84.8% in 2014 ( $\beta_{\text{year}} = 0.157$  [0.150;0.165]) and in type 2 diabetes from 26.0% to 43.5% ( $\beta_{\text{year}} = 0.086$  [0.082;0.091]) (both  $p < 0.0001$ ) (Fig. S1). The use of long-acting insulin analogues became also more frequent: type 1 (2002:26.0%, 2014:54.8%;  $\beta_{\text{year}} = 0.087$  [0.080;0.093]) and

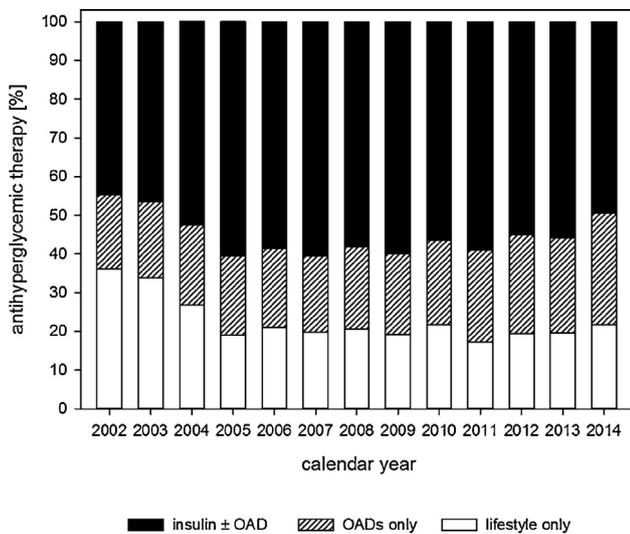
type 2 diabetes (2002:13.7%, 2014:53.6%;  $\beta_{\text{year}} = 0.149$  [0.145;0.154]) ( $p < 0.0001$ , respectively) (Fig. S1).

Similar results were present for the first year of treatment (data not shown).

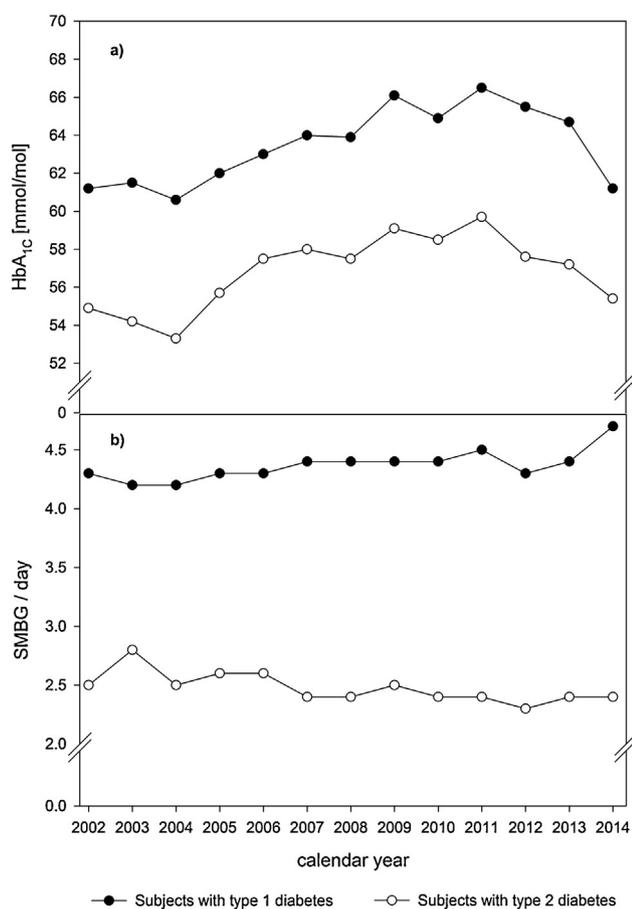
### 3.2. Glycaemic control

HbA<sub>1c</sub> steadily increased in subjects with type 1 diabetes from 7.8% (61 mmol/mol) in 2002 to 8.1% (67 mmol/mol) in 2011, but then decreased again to 7.7% (61 mmol/mol) until 2014 ( $\beta_{\text{year}} = 0.005$  [−0.0004;0.010],  $p = 0.0710$ ) (Fig. 4a). Even in type 2 diabetes, HbA<sub>1c</sub> initially increased from 7.2% (55 mmol/mol) in 2002 to 7.4% (60 mmol/mol) in 2011 and then improved to 7.2% (55 mmol/mol) in 2014 ( $\beta_{\text{year}} = 0.009$  [0.006;0.012],  $p < 0.0001$ ) (Fig. 4a). The number of SMBG per day became more frequent in type 1 diabetes (from 4.3 to 4.7;  $\beta_{\text{year}} = 0.035$  [0.030;0.041]) and slightly less frequent in type 2 diabetes (from 2.5 to 2.4;  $\beta_{\text{year}} = -0.022$  [−0.025; −0.020]) ( $p < 0.0001$ , respectively) (Fig. 4b).

In type 1 diabetes, the rate of severe hypoglycaemia increased from 29.0 events/100PY in 2002 to 42.5 events/100PY in 2006 and then decreased to 18.5 events/100PY in 2014 ( $\beta_{\text{year}} = -0.034$  [−0.046; −0.022],  $p < 0.0001$ ) (Fig. 5a). Compared to 2002, the rate of hypoglycaemic coma decreased (2002: 7.1 events/100PY, 2014: 4.1 events/100PY;  $\beta_{\text{year}} = -0.037$  [−0.055; −0.019],  $p \leq 0.001$ ), but overall, no clear trend was observed. (Fig. 5b). Similar findings were present in patients with type 2 diabetes. Until the year 2008, the rate of severe hypoglycaemia increased in insulin-treated patients (2002:12.0 events/



**Fig. 3 – Antihyperglycaemic therapy in subjects with type 2 diabetes, stratified by calendar year. Data adjusted for age, sex and diabetes duration.**



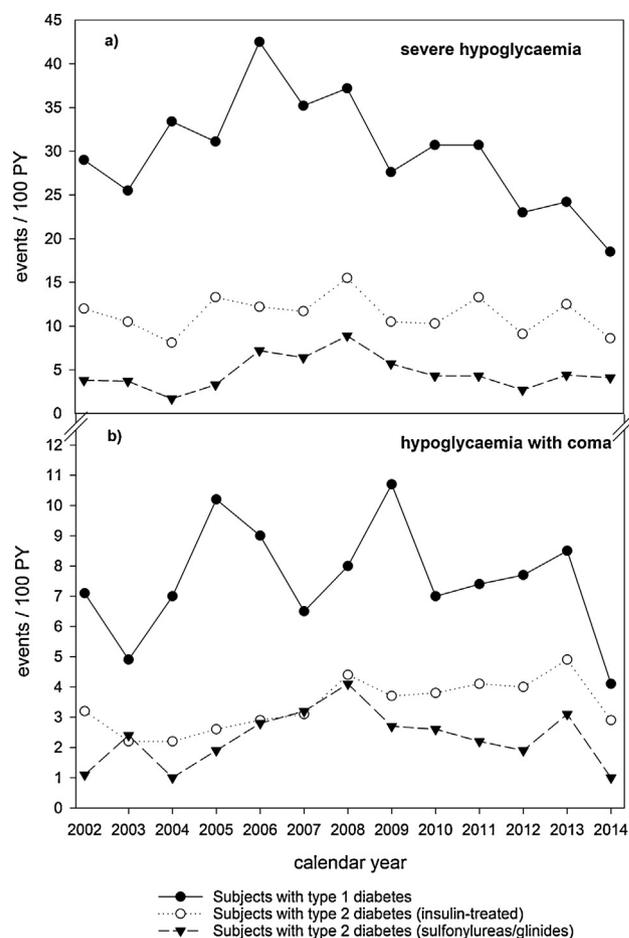
**Fig. 4 – (a) HbA<sub>1c</sub> levels, and (b) frequency of self-monitoring of blood glucose (SMBG) per day in subjects with type 1 or type 2 diabetes, stratified by calendar year. Data adjusted for age, sex and diabetes duration.**

100PY; 2008:15.5 events/100PY) as well as in patients with sulfonylureas or glinides only (2002:3.8 events/100PY; 2008:8.9 events/100PY) but then improved in both patient-groups until 2014 (insulin-treated: 8.6 events/100PY;  $\beta_{\text{year}} = -0.021$  [−0.032; −0.010],  $p = 0.0001$ /sulfonylureas or glinides: 4.1 events/100PY;  $\beta_{\text{year}} = -0.010$  [−0.038;0.018],  $p = 0.4739$ ) (Fig. 5a). Although a direct comparison of the years 2002 and 2014 indicated an improvement in the rate of hypoglycaemia with coma (insulin-treated: 3.2 events/100PY vs. 2.9 events/100PY;  $\beta_{\text{year}} = 0.028$  [0.015;0.041],  $p < 0.0001$ /sulfonylureas or glinides: 1.1 events/100PY vs. 1.0 events/100PY;  $\beta_{\text{year}} = -0.019$  [−0.050; 0.012],  $p = 0.2226$ ), no distinct pattern was present within the last 13 years (Fig. 5b).

Time trends in glycaemic control were comparable in the first year of treatment (data not shown).

## 4. Discussion

Our aim was to analyse trends in antihyperglycaemic therapy and glycaemic control in subjects with type 1 or type 2 diabetes over the last 13 years. We found substantial changes in the treatment of patients with type 1 or type 2 diabetes between the years 2002 and 2014. These changes include an increase in



**Fig. 5 – Rate of (a) severe hypoglycaemia, and (b) hypoglycaemia with coma in patients with type 1 or type 2 diabetes, stratified by calendar year. Data adjusted for age, sex and diabetes duration.**

intensified antihyperglycaemic therapy and a more frequent use of insulin analogues. Analysis of glycaemic control indicated an increase of SMBGs in type 1 and a slight decrease in type 2 diabetes. HbA<sub>1c</sub> increased initially in all subjects but then decreased again. There were also large differences in the rate of severe hypoglycaemia within the last 13 years, but without clear pattern.

### 4.1. Therapy trends in type 1 diabetes

Due to the results of the DCCT study, intensified insulin therapy (ICT or CSII) is recommended for subjects with type 1 diabetes [16,17]. In our study population, patients on CT as well as on ICT became less frequent during the last 13 years, the use of insulin pumps increased. The increase in patients on insulin pumps is consistent with findings from other countries [3–5]. Beside potential benefits on glycaemic control, explanations for the increase in CSII may be a higher flexibility, improvements in pump technologies or physicians/patients preferences. The more frequent use of rapid- and long-acting insulin analogues in our analysis was also reported in other studies [6,7,18]. According to diabetes guidelines from the USA, the use of insulin analogues should be preferred in most patients [16].

Although there are studies indicating small benefits on HbA<sub>1c</sub> and the occurrence of hypoglycaemic events, long-term studies on insulin analogues are still missing [19,20]. Hence, German guidelines do not recommend the use of insulin analogues in patients with type 1 diabetes – except for patients with a high risk of hypoglycaemia [17]. Explanations for the strong increase in our study population may be positive experiences or preferences of physicians or patients, more flexibility in the interval between insulin injection and eating, or marketing by manufacturers.

#### 4.2. Therapy trends in type 2 diabetes

In patients with type 2 diabetes, our observational study showed a significant increase in pharmacological therapy (Fig. 3). This trend was also reported in other countries as Japan, USA, or the United Kingdom [10,21,22]. Results of the German DMP North Rhine are not in line with these findings [12]. However, data of the DMP only compared patients at the time of enrolment in 2003 with 2013. The authors also reported that in contrast to 2003, patients newly enrolled in 2013 were younger and the diabetes diagnosis was more recently. Hence, it is assumed that patients' antihyperglycaemic therapy in 2013 was not yet adjusted properly and this might explain the high percentage of patients without medical treatment [12]. The DMP analysis of all patients in 2013 revealed non-pharmacological treatment in 29.5% of the patients and treatment with insulin (with/without OADs) in 22.4% [12]. Particularly the number of insulin-treated patients differs from our results. In our study population, 49.4% were treated with insulin. Possibly, this could be explained by differences in the patient composition between patients in the DMP and the DPV registry. In DPV, there are mainly specialized private practices with patients having more complex health care needs. In contrast, in DMPs, there are also general practitioners with less complex patients.

We also investigated whether the insulin regimen differed between the years 2002 and 2014. Especially BOT became more frequent, whereas SIT decreased (Fig. 2b). According to guidelines, there is no superior insulin regimen in the treatment of subjects with type 2 diabetes [23,24]. Therefore, treatment decisions should be individualized depending on patients' needs and preferences [23,24].

In subjects with type 2 diabetes, the use of insulin analogues increased substantially during the last 13 years (Fig. S1). This is consistent with findings from other studies [8,21,22]. Analyses investigating benefits of rapid- and long acting insulin analogues compared to human insulins indicated no clinically relevant advantages in subjects with type 2 diabetes [25,26]. Furthermore, there is a lack of studies focusing on insulin analogues and diabetes related long-term complications. However, there are special conditions when insulin analogues could be prescribed preferentially in type 2 diabetes, as e.g. in subjects with a high risk of hypoglycaemia or the request for higher flexibility regarding the interval between insulin injection and eating.

#### 4.3. Trends in glycaemic control

We also found changes in the frequency of SMBG. An increase was present in subjects with type 1 diabetes, whereas the

frequency of SMBG in type 2 diabetes slightly decreased (Fig. 4b). The slight decrease may be related to changes of reimbursement policy of SMBG in Germany. Since 2012 reimbursement has been restricted to insulin-treated patients. We further analysed time trends in HbA<sub>1c</sub> and the occurrence of severe hypoglycaemia. During the last 13 years, HbA<sub>1c</sub> increased initially in subjects with type 1 or type 2 diabetes until 2011 and then decreased again (Fig. 4a). Data of the German DMP North Rhine indicated in patients with type 2 diabetes an increase of up to 0.3% (3 mmol/mol) from 2008 to 2013, depending on initial HbA<sub>1c</sub> [12]. Even in type 1 diabetes, results of the DMP suggest higher HbA<sub>1c</sub> values in 2013 compared to 2008 [12]. The course of this unexpected increase in HbA<sub>1c</sub> is difficult to explain. One hypothesis is that with the implementation of the DMP in Germany, an increasing number of patients with rather poor glycaemic control has been included in DMPs and the DPV registry that formerly have simply been overlooked. This temporary trend towards higher HbA<sub>1c</sub> values does therefore not appear to reflect a deterioration of treatment efforts or treatment quality. A recently published study from the T1D Exchange Clinic Registry (USA) compared HbA<sub>1c</sub> values in 2010 with that in 2013/2014 in patients with type 1 diabetes [27]. Authors reported an increase of the overall average HbA<sub>1c</sub> from 8.2% (66 mmol/mol) in 2010 to 8.4% (68 mmol/mol) in 2013/2014 [27]. In contrast, data of the National Health and Nutrition Examination Survey (NHANES) reported a decrease of mean HbA<sub>1c</sub> in all patients with diabetes from 7.6% (60 mmol/mol) in 1999 to 7.2% (55 mmol/mol) in 2010 [28]. Avoidance of severe hypoglycaemia is one of the main objectives in subjects with diabetes. In our analysis, the rate of severe hypoglycaemia initially increased in patients with type 1 as well as with type 2 diabetes, but then decreased until 2014 (Fig. 5a). No distinct pattern was observed in the rate of hypoglycaemic coma over the last 13 years (Fig. 5b). A recently published study from the USA analysed changes of hypoglycaemia-induced hospital admission in all patients with diabetes between 1999 and 2011 and indicated an increase by 11.7% [29]. A Korean study in patients with type 2 diabetes also reported an increasing trend in severe hypoglycaemia from 2004 to 2009 [30].

#### 4.4. Strengths and limitations

The main strength of the current observational study is its large number of patients. To our best knowledge, this is the first study investigating time trends in antihyperglycaemic therapy and glycaemic control in adult patients with type 1 or type 2 diabetes from Germany and Austria. This study benefits from the same documentation software applied over the last 13 years. However, our analysis does not constitute a complete survey, hence, a selection bias cannot be excluded. Since we only consider patients from the DPV initiative, the generalizability of our results might be limited. One further limitation might be, that HbA<sub>1c</sub> was not measured centrally. However, to reduce variations between laboratories, HbA<sub>1c</sub> levels were mathematically standardized as describe in the method section. Another shortcoming might be an underestimation of hypoglycemic events, because information are based on self-reporting. Additionally, no causality can be deduced with

respect to insulin therapy and outcomes as the HbA<sub>1c</sub> and the occurrence of severe hypoglycemia.

Overall, antihyperglycaemic therapy was intensified in the treatment of type 1 and type 2 diabetes, and the use of insulin analogues rose. Frequency of SMBG increased in type 1 and slightly decreased in type 2 diabetes. Time trends in glycaemic control were less clear.

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## Conflict of interest

None.

## Author contributions

B.B. wrote/edited the manuscript and created figures. W.K., J.S., H.P.K., P.M.J., F.B., M.F., A.K., M.H., J.R., and R.W.H. contributed to the discussion and reviewed/edited the manuscript. R.W.H. conceptualized the study. R.W.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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We thank E. Bollow (Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm) for statistical analysis. Furthermore, we thank all participating centers of the DPV initiative, especially the collaborating centers in this investigation. A detailed list of the collaborating centres can be found in the Supplementary Data.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.diabres.2016.03.008>.

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