Type 2 diabetes in older patients: an analysis of the DPV and DIVE databases

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Abstract

Background: The clinical profile differs between old and young patients with type 2 diabetes mellitus (T2DM). We explored, based on a large real-world database, patient and disease characteristics and actual treatment patterns by age.

Methods: The analysis was based on the DIVE and DPV registries of patients with T2DM. Patients were analyzed by age groups 50–59 (middle-young), 60–69 (young-old), 70–79 (middle-old), 80–89 (old), and 90 years or more (oldest-old).

Results: A total of 396,719 patients were analyzed, of which 17.7% were 50–59 years, 27.7% 60–69 years, 34.3% 70–79 years, 18.3% 80–89 years and 2.0% at least 90 years. We found that (a) T2DM in old and oldest-old patients was characterized much less by the presence of metabolic risk factors such as hypertension, obesity, dyslipidemia and smoking than in younger patients; (b) the HbA1c was much lower in oldest-old than in middle-young patients ($7.2 \pm 1.6\%$ *versus* $8.0 \pm 2.2\%$; $p < 0.001$), but it was associated with higher proportions of patients with severe hypoglycemia (7.0 *versus* 1.6%; $p < 0.001$); (c) this was potentially associated with the higher and increasing rates of insulin use in older patients (from 17.6% to 37.6%, $p < 0.001$) and the particular comorbidity profile of these patients, for example, chronic kidney disease (CKD); (d) patients with late diabetes onset had lower HbA1c values, lower bodyweight and less cardiovascular risk factors; (e) patients with a longer diabetes duration had a considerable increase in macrovascular and even more microvascular complications.

Conclusion: In very old patients there is a need for frequent careful routine assessment and a tailored pharmacotherapy in which patient safety is much more important than blood-glucose-lowering efficacy.

Keywords: age at onset, DIVE, DPV, epidemiology, hypoglycemia, insulin, oldest-old, type-2 diabetes

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Background

The clinical profile differs between old and young patients with type 2 diabetes mellitus (T2DM). In patients with T2DM, the age of the patients as well as the age at the onset of diabetes and diabetes duration is of crucial importance when it comes to treatment goals, therapeutic strategies, and risk of complications.[1] Old patients (>65 years) are usually characterized by multimorbidity and polypharmacy. They show a decreased subjective awareness of hypoglycemia and thus increased hypoglycemia event risk.[2–4] Therefore, the importance of a very low glucose setting may be reduced in this population due to the long-term effects on micro- and macrovascular events. This is considered in the current guidelines with less stringent HbA1c targets, which corresponds to a changed benefit–risk assessment and different treatment strategies compared with younger patients.[4–6]

Based on T2DM patients documented in the large German DIVE/DPV registries, we aimed to investigate patient clinical characteristics, morbidity, and treatment patterns in relation to age, diabetes onset, and diabetes duration.

Materials and methods

Data collection

For this cross-sectional study standardized routine data were obtained from the largest German patient databases on diabetes mellitus DIVE (DIabetes-Versorgungs-Evaluation) and DPV (Diabetes-Patienten-Verlaufsdokumentation). DPV data on patients with all types of diabetes mellitus (regardless of their disease stage and treatment strategy) are collected every 6 months using DPV software and the anonymized data are sent to the University of Ulm. Detailed information on the documentation was published previously.[7] The DPV initiative was approved by the ethics committee of the University of Ulm and data collection was approved by the review boards of the participating centers. The DIVE registry was established in Germany in 2011.[8] Consecutive clinical data on patients with diabetes mellitus are collected and continue to be followed up. They are entered into the online database using DPV software. The research protocol was approved by the ethics committee of the Medical School of Hanover on 25 August 2011 (no. 6003), and all patients provided written informed consent.

Definitions

Hypertension was defined as systolic blood pressure $\geqslant$140 mmHg and/or a diastolic blood pressure of $\geqslant$90 mmHg on more than half of the visits. Dyslipidemia was defined as an low-density lipoprotein (LDL) cholesterol of 100 mg/dL or more without further risk factors and 70 mg/dL or more in patients with cardiovascular disease (CVD) or chronic kidney disease (CKD).[4,9,10] CKD was defined as eGFR $<$ 60 mL/min/1.73 m^2 and/or dialysis and/or renal transplantation and/or microalbuminuria. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[11] The comorbidity profile of each patient was grouped into (patient or physician reported) microvascular and macrovascular diseases. The former included any entered record of retinopathy (including blindness), microalbuminuria, or any form of neuropathy. Neuropathy included autonomous, peripheral, and non-proliferative neuropathy. Macrovascular diseases included transient ischemic attack/prolonged reversible ischemic neurologic deficit, stroke, coronary artery disease (CAD), myocardial infarction (MI), and peripheral arterial disease. HbA1c values were standardized to the Diabetes Control and Complications Trial (DCCT).[12,13] For severe hypoglycemia, the definition of the American Diabetes Association Workgroup on Hypoglycemia was used ("an event requiring assistance by another person to actively administer carbohydrates, glucagon, or other resuscitative actions").[14] Diabetic ketoacidosis (DKA) was defined as pH $<$ 7.3 and/or bicarbonate $<$15 mmol/mol or hospitalization for DKA.

Statistics

Patient data were extracted in May 2019 and included in the current analysis if they had T2DM and were at least 50 years old. Data from the two registries were combined and analyzed as a single data set. If patient data were entered in both databases, DPV and DIVE, only DPV data were included, since documentation in DPV is more extensive. Patient data were aggregated in their respective most recent documented treatment year. To compare younger *versus* older and to focus on oldest-old patients, we categorized patients in age groups (50–59, 60–69, 70–79, 80–89 and $\geqslant$90 years). In the following, 50–59-years-old patients are referred to as "middle-young", 60–69-years-old as "young-old", 70–79-years-old as "middle-old", 80–89-years-old as "old" and those at least 90-years-old as "oldest-old". We additionally compared patients with younger age and diabetes onset and patients older at onset ($</\geqslant$ median value of the cohort), as well as patients with shorter/longer diabetes duration ($</\geqslant$ median value of the cohort). Descriptive analyses were conducted for the overall study population. Categorical variables are presented as percentages and continuous variables are presented as means $\pm$ standard deviation. Comparisons were made between age groups, diabetes duration groups, and age at onset groups, as well as analyses stratified by diabetes therapy (insulin only, oral antidiabetic drug [OAD]/glucagon-like receptor 1 agonist [GLP-1RA], lifestyle only). *p*-values of unadjusted comparisons were calculated using linear and logistic regression. We additionally calculated all regression models with adjustment for sex and diabetes duration in comparison with age groups and age at onset groups,

sex, and age at diabetes onset comparing long and short diabetes duration groups. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.4.

Results

This analysis includes data of 396,719 patients with T2DM aged at least 50 years (Figure 1). More than half of the patients were at least 70 years old including 72,554 patients aged between 80 and 89 years (18.3%) and 8089 patients aged 90 years and over (2.0%).

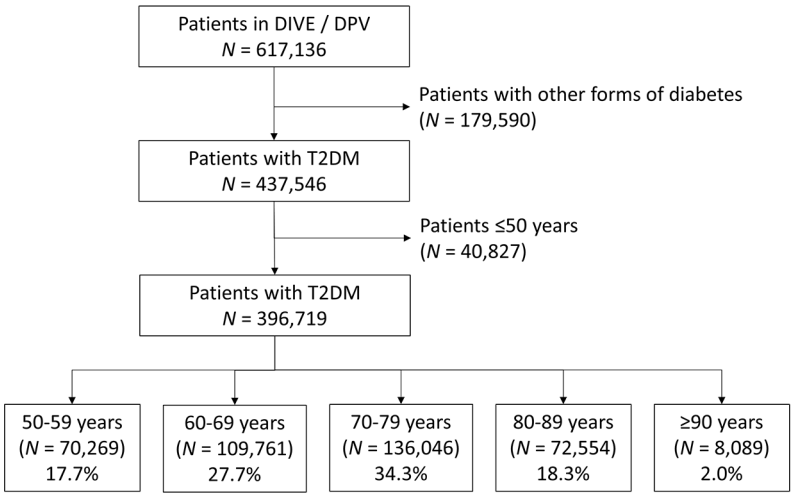

Figure 1. Patient inclusion.
N, patient number; T2DM, type 2 diabetes mellitus.

Patient and disease characteristics by age group

The mean age was 70.8 years, 52.5% of the patients were male, the mean body mass index (BMI) was 30.6 kg/m^2, and the diabetes duration 11.2 years (Table 1). There was an age-related decrease in the proportion of males, mean bodyweight, and BMI (all $p < 0.001$). The most prevalent baseline risk factors among all age groups were hypertension, obesity, and dyslipidemia with decreasing proportions in older age groups. Whereas the proportion of hypertensive patients slightly declined from 41.8% in the youngest group to 37.7% in the oldest, obesity showed a reduction to about one-sixth (61.9–15.7%). The same tendency was true for smoking which was present in one-third (28.6%) of the patients aged 50–59 years compared with 6.6% in the 70–79 years old and 1.1% in those >90 of age (all $p < 0.001$).

The mean age at diabetes onset was 59.7 years. There was a steady rise in the mean age at diabetes diagnosis with increasing age with a mean age of 47.7 years at diagnosis in 50–59-year-old patients and a mean age of 79.1 years in patients aged 90 years and over. As such, oldest-old patients tended to have diabetes for longer but with a very late onset (mean age at onset 79.1 years at a current mean age of 92.5 years) than middle-young patients (50–59 years: mean age at onset 47.7 years at a current mean age of 55.5 years).

Glycemic balance with age

The mean HbA1c of the entire cohort was 7.5 ± 1.8% (62 mmol/mol). It was highest in patients between 50 and 59 years (8.0%) and progressively declined to 7.2% in those 90 years and older (Figure 2). There was an inverse relation of glycemic control with the rate of hypoglycemia/DKA. The overall rate of severe hypoglycemia was 3.3% with a low proportion of 50–59-year-old patients and a high rate in patients ⩾90 years (1.6 *versus* 7.0%). While there was also a slight increase seen in DKA events with age, the overall rate remained 0.5%.

Pharmacotherapy by age group

Among the entire cohort, 48.1% were treated with insulin, with a rising proportion in older patients. The most common (more than 10% use) non-insulin anti-diabetic drugs were metformin (35.0%), GLP-1 analogues (16.9%), DPP4-inhibitors (14.7%), and sulfonylurea (10.6%). Whereas metformin, GLP-1 analogues, and SGLT-2 inhibitors were less frequently used with rising age, the proportion of sulfonylurea and glinide treatment increased (Table 1).

Most patients used long-acting insulins (44.1%), half of those taking neutral protamine Hagedorn (NPH) and half taking long-acting analogues. The use of NPH insulin increased with age, whereas the use of analogues decreased.

Human short-acting insulin was used more frequently in the entire cohort (24.4%) compared with short-acting insulin analogues (18.2%). Human short-acting and premixed insulin use increased progressively with age, while

Table 1. Patient characteristics and pharmacotherapy by age group.

	Total	50–59 years	60–69 years	70–79 years	80–89 years	⩾90 years	Unadjusted *p*-value	Adjusted *p*-value
Age, years	70.8 ± 10.2	55.5 ± 2.9	65.3 ± 2.9	75.0 ± 2.8	83.9 ± 2.7	92.5 ± 2.3		
Male, %	52.5	61.0	58.3	51.8	39.8	26.5	<0.001	<0.001
Bodyweight, kg	87.4 ± 20.1	97.1 ± 22.8	91.7 ± 19.9	84.9 ± 17.4	77.0 ± 15.2	68.8 ± 13.4	<0.001	<0.001
BMI, kg/m^2	30.6 ± 6.4	32.9 ± 7.2	31.7 ± 6.5	30.1 ± 5.8	28.1 ± 5.1	25.9 ± 4.5	<0.001	<0.001
Diabetes duration, years	11.2 ± 9.4	7.7 ± 7.2	10.3 ± 8.5	12.4 ± 9.7	13.3 ± 10.4	13.4 ± 10.7	<0.001	<0.001
Mean age at diabetes onset, years	59.7 ± 12.3	47.7 ± 7.5	55.0 ± 8.8	62.6 ± 10.0	70.5 ± 10.7	79.1 ± 11.0	<0.001	<0.001
Cardiovascular risk factors								
Hypertension, %	41.1	41.8	42.4	40.9	39.2	37.7	<0.001	<0.001
BMI > 30, kg/m^2, %	48.1	61.9	55.7	44.8	31.1	15.7	<0.001	<0.001
Dyslipidemia, %	86.0	85.3	85.6	86.6	86.5	84.3	<0.001	<0.001
Smokers, %	12.2	28.6	15.8	6.6	2.4	1.1	<0.001	<0.001
Antidiabetic drugs								
Insulin, %	48.1	42.9	46.2	50.1	51.9	49.5	<0.001	<0.001
Metformin, %	35.0	48.4	41.5	31.9	20.4	11.9	<0.001	<0.001
GLP-1 analogues, %	16.9	21.1	18.1	15.8	13.7	13.0	<0.001	<0.001
DPP4-inhibitors, %	14.7	15.9	14.9	14.6	13.4	13.0	<0.001	<0.001
Sulfonylurea, %	10.6	8.5	10.1	11.3	11.9	11.6	<0.001	<0.001
Glinides, %	3.1	2.5	2.8	3.3	3.8	3.5	<0.001	<0.001
SGLT-2 inhibitors, %	2.8	5.1	3.9	2.0	0.9	0.2	<0.001	<0.001
Acarbose, %	1.1	1.1	1.1	1.2	1.1	0.9	0.032	0.040
Insulins types								
Long-acting, %	44.1	39.0	42.6	46.2	47.2	44.2	<0.001	<0.001
NPH (= intermediate), %	22.2	16.6	20.1	24.1	26.5	26.9	<0.001	<0.001
Long-acting analogue, %	21.9	22.5	22.5	22.1	20.7	17.4	<0.001	<0.001
Short-acting, %	42.5	37.6	40.9	44.7	45.9	42.1	<0.001	<0.001
Human short-acting, %	24.4	16.7	21.1	27.0	31.1	31.1	<0.001	<0.001
Short-acting analogue, %	18.2	20.9	19.8	17.7	14.8	11.0	<0.001	<0.001
Premixed, %	2.0	0.8	1.4	2.4	3.5	3.5	<0.001	<0.001
Analog *versus* human insulin								
Insulin analogue, %	29.7	31.0	30.6	29.7	27.7	23.5	<0.001	<0.001
Insulin human, %	32.2	24.4	29.1	35.0	38.6	37.9	<0.001	<0.001
Insulin dose, IU								
per day	47.2 ± 41.1	50.9 ± 45.5	51.7 ± 45.1	47.6 ± 40.3	39.3 ± 31.7	30.5 ± 23.4	<0.001	<0.001
per kg and day	0.54 ± 0.48	0.53 ± 0.50	0.57 ± 0.52	0.56 ± 0.47	0.51 ± 0.41	0.44 ± 0.34	<0.001	<0.001

p-values adjusted for sex and diabetes duration.
BMI, body mass index; DPP4, Dipeptidyl peptidase-4; GLP-1, Glucagon-like Peptide 1; HbA1c, hemoglobin A1c; IU, international unit; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug, SGLT-2, sodium/glucose cotransporter 2.

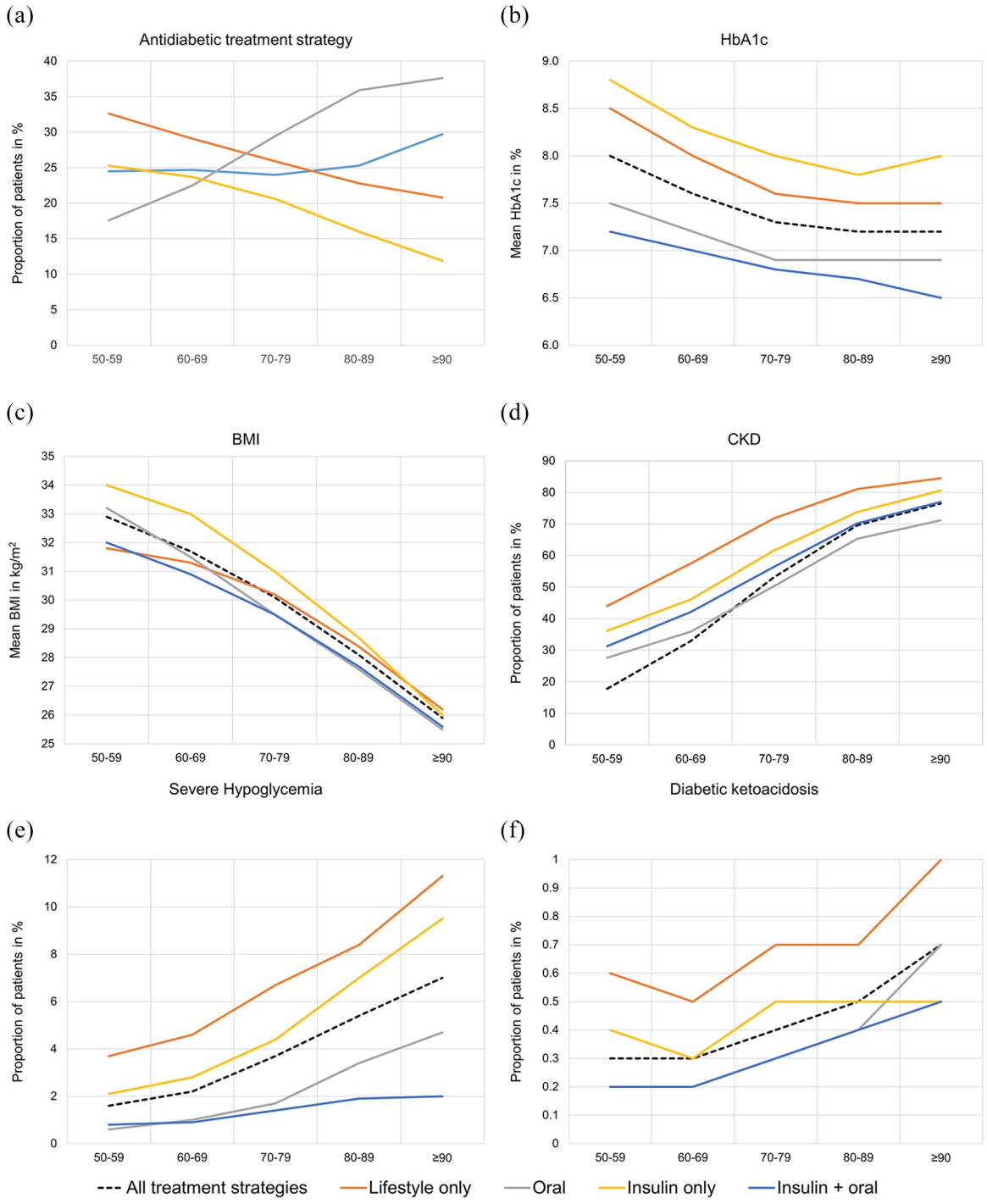

Figure 2. Treatment strategy *versus* clinical variables.
(a) Treatment strategy by age groups; (b) HbA1c and treatment strategy by age groups; (c) BMI and treatment strategy by age groups; (d) CKD and treatment strategy by age groups; (e) Proportion of patients with at least one severe hypoglycemia event during the most actual documented treatment year by treatment strategy and age groups; (f) Proportion of patients with at least one diabetic ketoacidosis event during the most actual documented treatment year by treatment strategy and age groups. Oral, oral antidiabetic treatment or treatment with Glucagon-like Peptide 1. BMI, body mass index; CKD, chronic kidney disease; HbA1c, hemoglobin A1c.

short-acting insulin analogue use decreased. The same pattern with decreasing analogue use was seen when comparing total use of analogue insulin with human insulin. Mean insulin dose per kg bodyweight and day declined from the youngest (0.53 ± 0.50 IU/kg/d) to the oldest group (0.44 ± 0.34 IU/kg/d).

Clinical outcomes and treatment strategies

With age, there was an increase in the rate of treatment strategies that only considered insulin (Figure 2). Rates more than doubled from 17.6% in the youngest group to 37.6% in those 90 years and above ($p < 0.001$). There was also an increase in the rate of patients receiving lifestyle recommendations only. Combination therapy with insulin and OAD/GLP was the most frequently used treatment in 50–59-year-old (32.6% and 25.3%). The use of both treatment strategies declined with age arriving at 20.8% for OAD/GLP combinations ($p < 0.001$) and 11.9% for insulin + OAD/GLP combinations ($p < 0.001$).

Patients were more likely to receive insulin (either alone or in combination) if their HbA1c was on the higher end and if patients had chronic kidney disease. On the other hand, they were more likely to suffer from severe hypoglycemia and DKA than patients not receiving insulin. This pattern was observed across all age groups but with an imbalance between the HbA1c and the rate of severe hypoglycemia in oldest-old patients.

Patients receiving OAD/GLP (without insulin) had a low HbA1c, the prevalence of chronic kidney disease was "only" 44.1% and 1.6% reported severe hypoglycemia. Again, there was a tendency towards lower HbA1c values but higher rates of severe hypoglycemia in older patients (HbA1c 6.9%, severe hypoglycemia 4.7% in patients 90 years and older).

Lifestyle only treatment was obviously only considered in patients with a rather low HbA1c [6.9% (52.0 mmol/mol)] and when CKD was a comorbidity. At least one severe hypoglycemia was observed in 1.3% of the patients. In patients with lifestyle treatment the pattern of clinical variables did not change very much with age but within the same pattern as described before.

Overall, there were only minor differences in the BMI ranging between means of 29.9 kg/m^2 in patients receiving lifestyle advice only and 31.9 kg/m^2 in those receiving insulin in combination with OAD/GLP. Differences were, however, more considerable in the 50–59-year-olds with a general trend for lower BMI with age. The BMI levelled off at around 26 kg/m^2 in patients $\geqslant$90 years.

Morbidity by age group

The prevalence of microvascular complications was 57.1%, of macrovascular complications 34.8%, and of chronic kidney disease was 54.6%. Mental issues such as depression (7.2%) and dementia (4.2%) were much less prevalent (Table 2). On the one hand, microvascular disease was largely similar across age groups with a relative high in the 70–79-year-old patient group (59.8%). Frequent principal diagnoses for microvascular disease were neuropathy (45.2%) and microalbuminuria (31.7%). Depression also had a similar prevalence across age group with an only slightly higher prevalence in the middle-young (8.1%) and oldest-old (8.7%).

On the other hand, there was a considerable increase in the rate of macrovascular disease, chronic kidney disease and dementia with age. Coronary artery disease and peripheral arterial disease were those with the highest prevalence (18.6% and 17.1%, respectively), with an age-dependent increase that levelled off after the age of 89.

Exploration of early versus *late T2DM onset*

To explore whether patients with early onset of T2DM have a different clinical profile compared with patients with late onset diabetes up and beyond the mere difference in age. For this purpose we grouped patients into those with age at diabetes onset below the median of 59.7 years and those above (Table 3).

The majority of early onset patients were male, and they presented more frequently with hypertension, obesity, and smoking than late onset patients. Patients with an early onset also had higher HbA1c values with slightly lower rates of hypoglycemia. From a treatment perspective, patients with early T2DM onset were provided with insulin + OAD/GLP combinations more often than late onset patients. Microvascular

Table 2. Morbidity by age group.

	Total	50–59 years	60–69 years	70–79 years	80–89 years	⩾90 years	Unadjusted *p*-values	Adjusted *p*-values
Morbidities								
Microvascular disease, %	57.1	51.3	57.7	59.8	57.4	50.4	<0.001	<0.001
Retinopathy, %	13.6	11.1	13.7	14.3	14.7	14.1	<0.001	0.040
Diabetic foot, %	10.6	7.7	10.2	11.7	12.1	10.4	<0.001	<0.001
Neuropathy, %	45.2	38.9	46.5	48.1	44.8	36.3	<0.001	<0.001
Microalbuminuria, %	31.7	30.1	31.1	32.7	32.4	30.4	<0.001	<0.001
Macrovascular disease, %	34.8	21.3	31.2	39.5	43.6	42.9	<0.001	<0.001
Myocardial infarction, %	8.6	5.4	8.1	9.8	10.2	8.8	<0.001	<0.001
Stroke, %	8.5	4.0	6.8	10.0	12.2	13.4	<0.001	<0.001
CAD, %	18.6	10.9	16.9	21.5	23.2	20.4	<0.001	<0.001
PAD, %	17.1	10.3	15.1	19.5	21.9	21.7	<0.001	<0.001
Chronic Kidney Disease, %	54.6	33.8	45.0	60.7	73.7	79.1	<0.001	<0.001
Mental status								
Depression, %	7.2	8.1	6.9	6.6	7.8	8.7	<0.001	<0.001
Dementia, %	4.2	0.7	1.6	4.3	9.4	15.0	<0.001	<0.001

Microvascular disease includes retinopathy, diabetic foot, microalbuminuria, or neuropathy. Macrovascular disease includes stroke, coronary artery disease, myocardial infarction, and peripheral arterial disease.
CAD, coronary artery disease; PAD, peripheral artery disease.

consequences of T2DM were seen more often in those with early onset, while macrovascular complications were less prevalent (Figure 3). Noteworthy characteristics of the late onset patients were the lower HbA1c value, the lower bodyweight, and the reduced cardiovascular risk factors. Dementia, however, was a particular issue in these patients with an almost three times increase. Dementia is an independent risk factor for hypoglycemia.[15,16]

Exploration of short versus *long T2DM duration*

Finally, we also aimed to explore the effects of T2DM duration on treatment patterns and outcomes. Patients with a diabetes duration below the median of 9.7 years and those above were comparable with respect to sex, bodyweight, BMI, HbA1c, and the cardiovascular risk profile (Table 3). The proportion of patients with insulin treatment either alone (35.4% *versus* 18.2%; $p < 0.001$) or in combination with OAD/GLP (26.1% *versus* 16.5%; $p < 0.001$) were, however, almost twice as high in those with long T2DM duration while lifestyle changes or OAD/GLP treatment strategies were less prevalent. Micro- and macrovascular complications were generally more frequent in those with a long T2DM duration. This was particularly true for microvascular complications with more than double the retinopathy proportions (20.0 *versus* 6.5%; $p < 0.001$) and diabetic foot syndrome (14.5% *versus* 6.8%; $p < 0.001$). Compared with the increase in diabetic complications, we observed only a modest increase in macrovascular complications such as MI (10.0% *versus* 7.3%; $p < 0.001$) or stroke (Figure 3).

Table 3. Early *versus* late diabetes onset and long *versus* short diabetes duration.

	Early onset < median (59.7 years) *n* = 198,239	Late onset ⩾ median (59.7 years) *n* = 198,480	Unadjusted *p*-value	Adjusted *p*-value	Short T2DM duration < median (9.7 years) *n* = 198,237	Long T2DM duration ⩾ median (9.7 years) *n* = 198,482	Unadjusted *p*-value	Adjusted *p*-value
Age, years	64.7 ± 8.9	76.9 ± 7.5	<0.001		69.1 ± 10.5	72.6 ± 9.7	<0.001	
Male, %	57.0	48.0	<0.001		53.8	51.2	<0.001	
Bodyweight, kg	92.3 ± 21.1	82.3 ± 17.5	<0.001	<0.001	87.5 ± 20.1	87.3 ± 20.0	0.068	<0.001
BMI, kg/m^2	31.9 ± 6.8	29.3 ± 5.7	<0.001	<0.001	30.5 ± 6.3	30.8 ± 6.5	<0.001	<0.001
HbA1c, % (HbA1c, mmol/mol)	7.7 ± 1.8 (61 ± 19.7)	7.3 ± 1.8 (56 ± 19.7)	<0.001	<0.001	7.5 ± 2.0 (58 ± 21.9)	7.5 ± 1.6 (58 ± 17.5)	<0.001	<0.001
Severe hypoglycemia, %	3.1	3.4	<0.001	<0.001	2.0	4.5	<0.001	<0.001
Diabetic ketoacidosis, %	0.3	0.5	<0.001	<0.001	0.4	0.4	0.170	0.497
Risk factors								
Hypertension, %	41.7	40.5	<0.001	<0.001	41.2	41.0	0.354	0.497
BMI > 30, kg/m^2, %	56.5	39.3	<0.001	<0.001	47.0	49.1	<0.001	<0.001
Dyslipidemia, %	85.9	86.1	0.139	0.067	85.4	86.5	<0.001	<0.001
Smokers, %	17.5	6.8	<0.001	<0.001	14.4	10.0	<0.001	<0.001
Drug treatment								
Insulin only, %	27.9	25.7	<0.001	<0.001	18.2	35.4	<0.001	<0.001
OAD/GLP only, %	25.0	29.6	<0.001	0.324	34.7	19.9	<0.001	<0.001
Insulin + OAD/GLP, %	26.2	16.4	<0.001	<0.001	16.5	26.1	<0.001	<0.001
Lifestyle only, %	20.9	28.3	<0.001	<0.001	30.6	18.7	<0.001	<0.001

Data are shown as means ± standard deviation or percent. Severe hypoglycemia and diabetic ketoacidosis show the proportion of patients with at least one event during the most actual documented treatment year.
BMI, body mass index; GLP-1, Glucagon-like Peptide 1; HbA1c, hemoglobin A1c; OAD, oral antidiabetic drug; T2DM, type 2 diabetes mellitus.

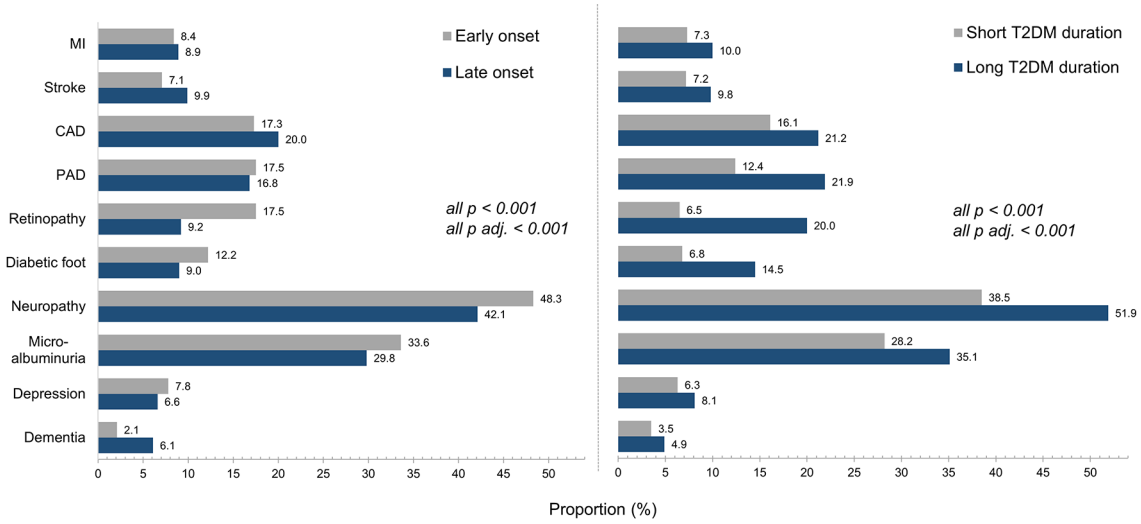

Figure 3. Comorbidities in relation to age at first type 2 diabetes mellitus (T2DM) diagnosis and T2DM duration.
Early onset < median, late onset > median, *p*-values adjusted for sex and diabetes duration; short duration < median, long duration > median; *p*-values adjusted for sex and age at diabetes onset.
CAD, coronary artery disease; HbA1c, hemoglobin A1c; MI, myocardial infarction; PAD, peripheral artery disease.

Discussion

Exploring patient characteristics by age group we found some relevant group differences which may help to overcome barriers in the treatment of patients with T2DM:

(1) Diabetes in elderly patients was characterized much less by the presence of metabolic risk factors such as hypertension, obesity, dyslipidemia and smoking than in younger patients;
(2) The glycemic control was much better in older patients than in middle-young patients, but the proportion of patients with severe hypoglycemic events was higher;
(3) This was potentially associated with the more insulin use in patients (with a preference of human and premixed insulins over analogues) and the particular comorbidity profile of these patients, for example, CKD;
(4) Patients with late T2DM onset had lower HbA1c values, lower bodyweight and reduced prevalence of cardiovascular risk factors;
(5) Patients with long diabetes duration had a considerable increase in macrovascular and even more so microvascular complications.

Metabolic profile of the patients

Obesity is a principal risk factor associated with the development of T2DM. This is particularly true in younger people and the association decreases in elderly patients.[17,18] This also holds true for further risk factors such as dyslipidemia and hypertension and their triangle association.[18–20] Moreover, the metabolic-syndrome-associated risks are reduced in the elderly with a lower impact on mortality.[21] Finally, smoking triggers insulin resistance and is also well known as one of the main risk factors for diabetes.[22] A current study among 8,809 participants showed that smoking leads to significantly higher HbA1c levels than presented by non-smokers in a general population.[23] Against this background, the findings of our current study are within expectations: diabetes in elderly patients was characterized much less by the presence of obesity, dyslipidemia, hypertension, and smoking than in younger patients. As most of the patients are treated in specialist practices and a certain percentage participated in disease management programs, a selection bias might have had an influence on the results. Whether this and the metabolic profile may contribute to the higher age itself (survivorship bias) and the improved glycemic control in the elderly deserves further research. The definition of obesity in our study focuses on BMI. A newer concept that was

not addressed is the risk of frailty and sarcopenic syndrome, both including a progressive loss of muscle and strength with age and therefore leading to weight loss and a reduced functional status.[4,24] Further, recent studies show that obesity and sarcopenia reinforce each other and can lead to an increased risk of morbidity and mortality with increasing age (sarcopenic adipositas).[25] Stratifying old T2DM patients by frailty and/or sarcopenia and incorporating this in database searches might help to get a better insight in treatment decisions.

Glycemic control

In this study, HbA1c values were found to be much lower in old patients. This was associated with a greater percentage of patients with severe hypoglycemia. This finding corresponds well to a subgroup analysis of the ACCORD study, which showed a higher risk for hypoglycemia in older participants compared with younger, independent of the intensity of antiglycemic treatment.[26] Our numbers were, however, higher than in the German DiaRegis registry, where 1.3% of the patients >75 years suffered from severe hypoglycemia (defined as symptomatic with medical assistance and symptomatic with hospitalization).[27] On the other hand, Bahrmann *et al.* showed an incidence of 7.8% per patient and year in care dependent patients.[28]

In our dataset, a mean T2DM duration of about 13 years in patients aged >80 years may have contributed to the frequent insulin use and consequently to a higher number of hypoglycemic events. This is in agreement with a global survey, where insulin treatment and duration of diabetes were the main causes of hypoglycemia.[29] Furthermore, several comorbidities like stroke, the presence of heart failure, depression, and sulfonylurea use in the elderly (>75 years) have been found to be associated with hypoglycemic events.[27] Other analyses showed that a higher rate of dementia and consequently a lower medical adherence also play an important role as well as CKD, causing a higher risk of severe hypoglycemia.[15,30–32] Improved detection of hypoglycemia and, as a result, its reduction has been demonstrated by training programs for older T2DM patients and by continuous glucose monitoring systems.[28,33] Our results show that older adults are at higher risk of hypoglycemia, probably for a variety of these reasons. Therefore, for physicians there may be a genuine challenge in knowing when to adjust insulin doses in oldest-old patients whose physiology may suddenly change. A careful routine assessment of risk factors for an imbalance of glycemic control and hypoglycemia is necessary.[34] As discussed in current guidelines it would also be conceivable to consider an increased use of continuous and flash systems for glucose monitoring.[4]

Pharmacotherapy

Old and very old adults with T2DM may have limited self-management abilities due to multiple morbidities, polypharmacy, renal, hepatic or cognitive impairment, and hormonal dysregulation.[27] Therefore, antidiabetic pharmacotherapy should aim at avoiding complex treatment regimens, polypharmacy, and adverse events such as hypoglycemia. Several drug classes like metformin, sulfonylureas, glibenclamide, and glimepiride are controversial in old and oldest-old patients who are at increased risk of lactic acidosis and/or hypoglycemia due to potential kidney function impairment.[4,35,36] Drug classes with a low risk of hypoglycemia should be preferred.

Long-acting insulin (NPH and analogues) are controversial in this context. Long-acting insulin is generally preferred to short-acting insulin because of the reduced risk of hypoglycemia.[4]

NPH results in a strong reduction of HbA1c but is associated with a certain risk of hypoglycemia. Analogues, on the other hand, have been associated with reduced rates of nocturnal hypoglycemia.[37,38] These were described less often in older patients than in younger patients. Hartmann *et al.* showed in a previous analysis that older patients (>70 years) on metformin were more likely to get an intensification with basal insulin than intensification with oral antidiabetics or GLP-1.[39] One of the potential reasons for the increasing insulin use with age may be a simplification of treatment in the context of polypharmacy.[4,5] While this may not be apparent on an ambulatory basis, care dependency will trigger an increasing use of treatment regimens that can be more easily controlled by the nursing staff.

Late T2DM onset

Mean age at diabetes onset in our study was 59.7 years and was slightly younger than the recently published Swedish national data (61.8 years)[1] Further analysis of this study showed that individuals with late onset of

T2DM were less frequently obese and had lower HbA1c and a slower deterioration in glycemic control compared with those with an early onset.[40] While the results on patient characteristics and clinical profile in studies are largely consistent, the cardiovascular risk of an early onset is not as clear. Sattar *et al.* report that patients with early onset were at a higher risk for cardiovascular outcomes (total mortality, cardiovascular mortality, non-cardiovascular mortality, heart failure, CAD) and the risks decreased progressively with increasing age at the onset of diabetes.[1] In contrast, the UK Prospective Diabetes Study reported an increasing risk of MI with a late onset of T2DM, but no increase in microvascular events.

We found similar results in our study concerning the surrogate and risk factor variables: patients with late diabetes onset had lower HbA1c values, a lower bodyweight, and reduced proportion of patients with cardiovascular risk factors. In our study, microvascular and the major part of macrovascular diseases were more often reported in the early onset group, but the percentages of MI, stoke, and CAD were slightly higher in patients with later onset of diabetes ($p < 0.001$). As there is evidence of a clear association between old age and the risk of MI and stroke in T2DM, this risk might have been overweight in our late onset cohort, in which patients were a mean 12 years older than those in the early onset group.[41,42]

Diabetes duration also correlates with a higher risk of macro-/microvascular events, death, and dementia, and the effects of increasing diabetes duration are greatest in younger patients.[41,43,44] As anticipated we found that patients with a long diabetes duration had a considerable increase in macrovascular and even more so microvascular complications as well as dementia.

Limitations

The data represent the current real-world situation of old patients with diabetes. As such, we are able to report on the more than 8000 patients available in the small group of patients that are 90 years of age and older. As the analysis is designed as a cross-sectional snapshot, no inference on causality can be made. For example, it is rather unlikely that insulin triggers CKD, but the inverse is true, insulin is usually given to patients with diabetes if they have kidney disease. Further, HbA1c values at hypoglycemia level were not excluded, this may contribute to the values in older people which tended to be lower.

Conclusion

T2DM in elderly patients is characterized by a distinct clinical profile with better glycemic control, but increased numbers of hypoglycemia events. Since old patients are more often female, with a lower bodyweight, less metabolic risk factors, but frequent comorbidities such as chronic kidney disease and a physiology which can suddenly change, there is a need for careful routine assessment and tailored pharmacotherapy in which patient safety is probably much more important than blood-glucose-lowering efficacy.

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Author contribution(s)

Gesine van Mark: Conceptualization; Formal analysis; Visualization; Writing-original draft; Writing-review & editing.

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Ivo Buschmann: Investigation; Writing-review & editing.

Jochen Seufert: Conceptualization; Writing-review & editing.

Reinhard W. Holl: Data curation; Methodology; Supervision; Writing-review & editing.

Peter Bramlage: Conceptualization; Project administration; Supervision; Writing-original draft.

Availability of data and material

The datasets generated and analyzed during the current study are not publicly available due to

data privacy but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The DPV initiative, which was established in 1995, was approved by the ethics committee of the University of Ulm, and data collection was approved by local review boards.

The DIVE registry (https://www.dive-register.de) was established in Germany in 2011. The protocol was approved by the ethics committee of the Medical School of Hannover, and all patients included in the DIVE registry provided written informed consent.

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Conflict of interest statement

JS reports grants and personal fees from Abbott, AstraZeneca, and Sanofi, outside the submitted work. PB reports to have received consultancy honoraria from Sanofi and Abbott. The other authors have no competing interests to disclose.

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