Characterisation and clinical outcomes in children and adolescents with diabetes according to newly defined subgroups: a cohort study from the DPV registry

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eClinicalMedicine
2023;64: 102208
Published Online xxx
https://doi.org/10.1016/j.eclinm.2023.102208

Summary

Background Personalised therapy has emerged as a possibly more efficient approach taking disease heterogeneity into account. The aim of this study was to determine whether recently described subgroups of childhood diabetes have prognostic association with diabetes-specific complications and, therefore, might be a basis for personalised therapies.

Methods We applied a previously developed subgroup classification to pediatric patients (diabetes onset <18 years) from the prospective Diabetes Patient Follow-up (DPV) registry with documented data between January 1, 2000 and March 31, 2022, from diabetes centers in Germany, Austria, Switzerland, and Luxembourg. The classification required information on islet autoantibody status, age, haemoglobin A1c (HbA1c), and body-mass index (BMI-SDS) at disease manifestation, as well as follow up data after 2 and after 4 years, which was available in 22,719 patients. Patients without documented data on these parameters were excluded from the analysis. The cumulative risk of severe hypoglycemia, diabetic ketoacidosis (DKA), retinopathy, and nephropathy were analysed by Kaplan–Meier analyses over a median follow-up of 6.8 years (IQR 4.8–9.6).

Findings Patients were classified into 10 subgroups (P1–P7 islet autoantibody-positive, n = 19,811; N1–N3 islet autoantibody-negative, n = 2908). The groups varied markedly with respect to specific acute and chronic complications. Severe hypoglycemia was a characteristic feature in young islet autoantibody-positive subgroups P1, P3, P4 (10-year risk 46, 46 and 47%) and the islet autoantibody-negative groups N1, N2 (43 and 46%). Nephropathy was identified in patient groups P2 and P5 (10-year risk 16%), which had features of moderate disease such as preserved C-peptide, low HbA1c, and very low frequency of DKA at diabetes onset. Group P7, which was defined by a high BMI, was associated with poor metabolic control, DKA, and retinopathy. In contrast, islet autoantibody-negative patients with high BMI (N3) had a low risk for all four complications.

Interpretation Subgrouping of childhood diabetes at diabetes onset provided prognostic value for the development of acute and chronic diabetes-specific complications.

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Funding The DPV initiative is supported by The German Ministry of Education and Research (BMBF) within the German Center for Diabetes Research, the diabetes surveillance of the Robert Koch Institute, the German Diabetes Association (DDG) and INNODIA.

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Keywords: Diabetes; Children; Subgroups; Complications; Personalised medicine

Research in context

Evidence before this study

We searched PubMed for the terms "type 1 diabetes", "endotypes", "subtypes", and "prognosis" up to September 30th, 2022. Several publications describe subtypes of childhood diabetes based on features such as age, body mass index (BMI), insulin sensitivity, immune and genetic parameters. Histologic examinations of human pancreas show that younger children with diabetes have characteristic inflammatory infiltrates that differ from older children. This manuscript builds on our previous study, where we describe subtypes of childhood diabetes at the time of diabetes manifestation. The groups differ substantially in residual β-cell function, inflammatory markers and insulin sensitivity, and show prognostic relevance for long-term metabolic control. No data exist to date on the significance of subgroups for the prognosis of diabetes-specific complications.

Added value of this study

The identification of disease subgroups with prognostic value is important because it can improve and personalise therapies. The simplicity of our subgroup classification, which only requires the measurement of islet autoantibodies along with routine haemoglobin A1c (HbA1c) measurement, age and BMI at disease manifestation, made it applicable to existing cohorts. We applied this subgroup classification to pediatric patients with diabetes from the Diabetes Patient Follow-up registry (DPV) to examine the rate of diabetic complications. The proportions of each subgroup were highly consistent compared to our previous data and the C-peptide concentrations (documented in about 40% of the cohort) at disease onset were also comparable to the previous data suggesting that the subgrouping is robust. The analysis revealed differences between the subgroups in terms of metabolic control, BMI, and insulin use at onset and in the long-term course. Kaplan–Meier analyses identified specific groups at high risk for long-term complications such as hypoglycemia, diabetic ketoacidosis, retinopathy and nephropathy.

Implications of all the available evidence

Children and adolescents with diabetes can be classified into prognostically relevant subgroups at disease onset. This classification, therefore, allows personalised treatment with respect to hypoglycemia training, ketoacidosis prophylaxis, or early monitoring and treatment of retinopathy and nephropathy.

Introduction

Diabetes mellitus in childhood and adolescence is classified according to the generally applicable guidelines into type 1 diabetes (T1D), which is caused by autoimmune or idiopathic destruction of the insulin-producing pancreatic islet β-cells, and the non-autoimmune disease forms type 2 diabetes (T2D) and other specific types such as maturity onset diabetes of the young (MODY), neonatal diabetes, syndromes with diabetes and other forms.[1] The recommended therapy is usually based on this classification. However, clinical practice shows a certain variability in clinical phenotypes, course and prognosis, so that the current classification does not reflect the heterogeneity of diabetes in children and adolescents. Consequently, there have been several efforts to introduce subgroups based on features such as age, body mass index (BMI), immune and metabolic parameters.[2–6] Although these groups are associated with differences in metabolic decompensation at diabetes onset and in therapy, there is little known whether acute and chronic disease complications differ between the subgroups.

We recently performed a multivariable classification and regression tree (CART) analysis using fasting C-peptide concentration as the outcome parameter in over 1000 patients diagnosed prior to age 20 years and described seven subgroups within the islet autoantibody-positive patients and three subgroups within the islet autoantibody-negative patients.[2] The groups differ substantially in several laboratory and clinical parameters, including genetics, inflammatory markers, insulin autoimmunity, insulin treatment, and insulin sensitivity at diabetes onset, and showed prognostic relevance for haemoglobin A1c (HbA1c) at a median follow-up of seven years. The simplicity of this subgroup classification, which only requires the measurement of islet autoantibodies along with routine HbA1c measurement, age and BMI at disease manifestation, makes it applicable to existing cohorts of patients with mid-to long-term follow-up to determine

whether the differences observed at diabetes onset extend to the development of diabetes-related complications.

The Diabetes Patient Follow-up (DPV) cohort includes >80% of pediatric patients with diabetes in Germany and Austria, as well as many patients in Switzerland and Luxembourg, and is one of the largest registries for children and adolescents with diabetes.[7] The registry collects longitudinal follow-up information every six months to monitor therapy and the development of diabetic complications. Here, we apply the CART subgroup classification to patients to the DPV registry and assess whether there are differences between subgroups in the rate of development of diabetes-related complications.

Methods

Study design and participants

This observational study was based on data from the DPV registry, which receives and stores anonymous, standardised, prospective data from routine diabetes care at diabetes centers in Germany, Austria, Switzerland, and Luxembourg twice a year for central validation and analysis. For optimal data validity, inconsistent data are reported back to participating centers, corrected if necessary, and re-entered into the database as previously described.[8] For the current analysis, the March 2022 data set, which included data from 298 centers, was used. Analysis of anonymised data within the DPV initiative was approved by the Ethics Committee of the Medical Faculty of the University of Ulm (no. 314/21), and the institutional review boards at the participating centers. Obtaining informed consent was the responsibility of each participating centre and was not recorded centrally. The reporting of this cohort study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement of guidelines for the presentation of observational studies.

Patients with diabetes onset before 18 years of age and with all documented forms of diabetes except neonatal and gestational diabetes were included. Only patients with data since the year 2000 and documented information on the presence of islet autoantibodies, age, BMI and HbA1c at diabetes onset were included, as these parameters are essential to classify the patient into one of the groups specified by the CART analysis. Additionally, follow-up data at least at two years and four years after diabetes onset were required.

Patient data

HbA1c was used as an indicator of glycemic control. Levels were mathematically standardised to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% with the MOM (multiple of mean) transformation to correct for different laboratory methods used by study centers.[9] The laboratory values were determined in the laboratory affiliated with the respective diabetes center. Anthropometric measurements were performed in the local centers according to in-house protocols and analyzed centrally, using contemporary national reference data for height and weight.[10] The BMI (body mass index: weight in kilograms/(height in meters)^2), is an accepted measure of overweight and obesity in children, adolescents and young adults. BMI-SDS (standard deviation score) values were generated using the LMS method.[11,12] Complications such as severe hypoglycemia, diabetic ketoacidosis (DKA), retinopathy and nephropathy are surveyed at participating centers as part of the DPV initiative. Severe hypoglycemia was defined according to the American Diabetes Association Workgroup on Hypoglycemia as an event requiring assistance by another person to actively administer carbohydrates,[13] glucagon or intravenous glucose and was determined by patient self-report at each clinical visit. DKA was diagnosed according to ISPAD guidelines based on clinical symptoms, and a venous pH <7.3 or serum bicarbonate <15 mmol/l.[14] Severe hypoglycemia and DKA were each summed over the observation period. According to guideline we assume that retinopathy was examined every 1–2 years in patients aged >11 years with a diabetes duration of more than five years, and diagnosed if appropriate ophthalmologic findings were present. Nephropathy was examined annually and diagnosed if there were at least two pathological findings (microalbuminurea) within one year and, in case of more frequent measurements, more pathologic than normal findings within one treatment year. Hypertension was defined as blood pressure values that were systolic or diastolic ≥95th percentile or values >140 mmHg (systolic) or >90 mmHg (diastolic) according to the recommendation of the RKI-KiGGS study on reference percentiles.[10] Migration background was defined as the individual him-/herself or the parents born outside of Germany/Austria/Switzerland/Luxembourg. For the specific categorization of the country of origin of the included children we made a hierarchy of the countries of origin of the children themselves, the mother and the father. If one of the three was born in Syria, Iran, Irak, Jemen, Afghanistan this was considered as the country of origin, following by Turkey, countries in Africa, Eastern Europe and South European countries. Simultaneous use of sensor and pump (SAP) was defined as the simultaneous use of an insulin pump and a continuous glucose monitoring system (CGMS), without mandatory interaction of the two devices.

Statistical analysis

Data were analyzed using SAS 9.4 (TS1M7, SAS Institute, Cary, NC). If data for a specific variable were not available in individual cases, the case was not considered for the analysis of that variable. Descriptive

analyses were conducted for the 10 groups from the CART analysis and presented as median and interquartile ranges (IQR) for continuous variables and numbers (proportions) for binary variables. The risk for developing acute and long-term complications such as DKA, severe hypoglycemia, retinopathy and microalbuminurea during the course of the diabetes disease was analyzed by Kaplan–Meier analysis. The cumulative risk after 10 years of follow-up after diabetes onset was calculated and Cox-Regression was used for calculation of unadjusted and adjusted (for sex) hazard ratios. The four weeks after diabetes onset were excluded from this analysis. For DKA, severe hypoglycemia, and retinopathy, the first documentation of the respective complication was considered the first occurrence. For nephropathy, at least two pathologic findings of microalbuminuria documented within a treatment year and, in case of more frequent measurements, more pathologic than normal findings in a given treatment year were required for the first documentation to be considered the first occurrence. Subgroup P3 was considered as reference group for hazard ratios as it was the largest group. Kaplan–Meier curves are presented for up to 15 years of treatment after diabetes onset, representing diabetes duration to 15 years in these patients. Patients were censored at the time of last contact if the respective complication did not occur.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AE and RWH have directly assessed and verified the underlying data reported in the manuscript. All authors had final responsibility for the decision to submit for publication.

Results

After exclusion of patients diagnosed with neonatal or gestational diabetes, a total of 121,261 patients with diabetes onset before the age of 18 were included in the DPV registry from 01-01-2000 to 03-31-2022. Of these, there were 38,228 with documented information regarding the presence of islet autoantibodies, age, BMI and HbA1c within 4 weeks of diabetes onset who could be classified into one of the subgroups by the original CART analysis (Table 1)[2]; of these 22,719 had at least a 2- and 4- year follow-up and were included in the final analysis (Fig. 1). A comparison between included an excluded patients showed that all parameters (BMI-SDS, sex, migration background, HbA1c and DKA at diabetes onset) revealed a standardised difference of <0.2 indicating a negligible imbalance between the two groups (Supplementary Table S1).

CART subgroup features at diabetes onset

Of the 22,719 included patients, 19,811 had detectable islet autoantibodies and were classified into CART groups P1–P7, and 2908 patients were islet autoantibody-negative and classified into CART groups N1–N3 (Table 2). The proportions of each subgroup were similar to those previously reported,[2] with P3 (37.1%), P4 (20.7%), and P6 (27.6%) representing the largest of the islet autoantibody-positive subgroups and N2 (84.8%) the largest of the islet autoantibody-negative subgroups. C-peptide concentrations were available in 9737 of the 22,719 patients. Consistent with previous data,[2] they were highest in groups P2 (median [IQR], 0.31 [0.20–0.53] nmol/l), P5 (0.47 [0.26–0.76] nmol/l), P7 (0.32 [0.20–0.53] nmol/l), N1 (0.36 [0.20–0.66] nmol/l), and N3 (0.53 [0.28–1.06 nmol/l]), Table 2. Also in agreement with previous data,[2] group P7 had a higher proportion of male patients (63.0%). The frequency of DKA at diabetes onset was relatively low in groups P1 (6.8%), P2 (2.6%), P5 (4.4%), and N1 (3.1%), and HbA1c levels were also relatively low in these groups (Table 2). 20–30% of patients reported migration background. This proportion was highest in the group N3 (46.2%), followed by group P7 (31.4%; Table 2). Group N3 included a larger proportion of patients from Turkey and Africa, other countries or whose origin was not documented, but less from Eastern Europe while the distribution was relatively similar over the other 9 groups (Supplementary Table S2).

Switzerland/Luxembourg, as the register mainly includes patients from these countries. The proportion of patients with elevated blood pressure at diabetes onset was >20% in all groups and was highest in subgroups P7 (34.5%) and N3 (49.1%). No patient had documented antihypertensive medication at this time point.

CART subgroups and diabetes-relevant parameters at follow-up

HbA1c, information on treatment, and BMI were available at 2 and 4 years after diagnosis in all 22,719

CART subgroup	P1	P2	P3	P4	P5	P6	P7	N1	N2	N3
Islet autoantibodies	pos	pos	pos	pos	pos	pos	pos	neg	neg	neg
HbA1c (%)	≤7.9	≤7.9	>7.9	>7.9	≤8.3	>8.3	>8.3	≤7.8	>7.8	n.a.
Age (years)	≤7.2	>7.2 ≤ 10.7	≤8.0	>8.0 ≤ 10.7	>10.7	>10.7	>10.7	n.a.	n.a.	n.a.
BMI-SDS	n.a.	n.a.	n.a.	n.a.	n.a.	≤0.8	>0.8	≤1.6	≤1.6	>1.6

Table 1: **Criteria and thresholds for classification of CART subgroups, as previously described.[2]**

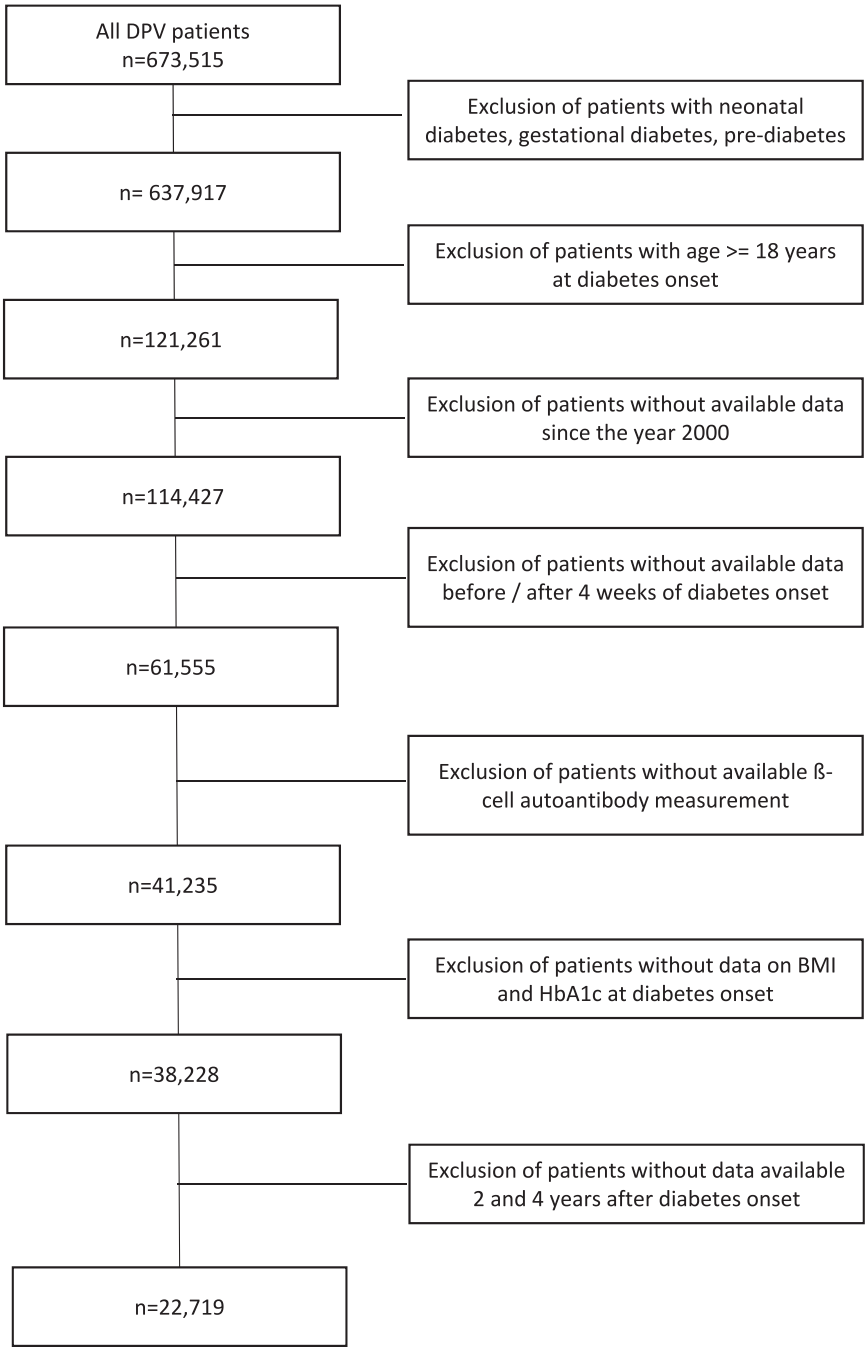

Fig. 1: Selection of patients for the final analysis. DPV: Diabetes Patient Follow-up registry; T1D: type 1 diabetes; BMI: body mass index; HbA1c; haemoglobin A1c.

patients (Table 2, Fig. 2). Median HbA1c values at diagnosis were <8% in groups P1, P2, P5, and N1, and >10% in all remaining groups. Convergence of HbA1c between groups was observed at 2 years- and 4- years follow-up with a marked reduction in HbA1c in those groups which had highly elevated values at diagnosis (Fig. 2A and E). Median HbA1c values for each subgroup varied between 6.7% and 7.7% after 2 years (overall $p < 0.0001$) and between 6.9% and 8.1% after 4 years of follow-up (overall $p < 0.0001$). The median HbA1c was highest in group P7 at both follow-up time points (overall $p < 0.0001$).

	P1	P2	P3	P4	P5	P6	P7	N1	N2	N3	Overall p-value
Patients, n (%)	794 (3.5)	421 (1.9)	7347 (32.3)	4098 (18.0)	658 (2.9)	5475 (24.1)	1018 (4.5)	261 (1.1)	2466 (10.9)	181 (0.8)	
At onset											
Age, years (IQR)	4.2 (2.7–5.6)	9.1 (8.1–9.7)	5.0 (3.1–6.6)	9.4 (8.7–10.0)	13.0 (11.9–14.1)	12.7 (11.7–13.9)	12.6 (11.7–13.7)	8.4 (5.2–12.1)	9.0 (5.5–12.0)	10.9 (7.4–13.1)	<0.0001
Sex, % male (95% CI)	53.1 (49.7–56.6)	52.7 (47.9–57.5)	51.1 (49.9–52.2)	47.4 (45.9–48.9)	55.0 (51.2–58.8)	57.9 (56.6–59.2)	63.0 (60.0–65.9)	57.1 (51.0–63.1)	55.1 (53.1–57.1)	49.2 (41.8–56.5)	<0.0001
Migration background, % [n]	23.4 [701]	22.1 [358]	27.5 [6549]	26.8 [3544]	25.4 [544]	22.2 [4552]	31.4 [841]	26.5 [211]	23.8 [2008]	46.2 [145]	<0.0001
HbA1c, % (IQR)	7.2 (6.6–7.6)	7.2 (6.6–7.6)	10.5 (9.3–11.7)	11.2 (9.9–12.8)	7.4 (6.6–7.9)	11.8 (10.4–13.4)	11.0 (9.8–12.5)	6.8 (6.2–7.4)	11.1 (9.8–12.9)	10.1 (8.1–11.4)	<0.0001
BMI-SDS (IQR)	−0.04 (−0.8 to 0.72)	0.04 (−0.75 to 0.91)	−0.12 (−0.89 to 0.62)	−0.15 (−0.89 to 0.57)	0.13 (−0.65 to 0.97)	−0.53 (−1.17 to 0.04)	1.27 (1.0–1.63)	0.01 (−0.78 to 0.45)	−0.29 (−1.03 to 0.39)	1.92 (1.73–2.21)	<0.0001
Insulin therapy, % (95% CI)	94.0 (92.3–95.6)	89.1 (86.1–92.1)	98.8 (98.6–99.1)	99.0 (98.7–99.3)	86.8 (84.2–89.4)	98.9 (98.6–99.2)	97.2 (96.2–98.3)	78.5 (73.5–83.6)	98.7 (98.2–99.1)	79.0 (73.0–85.0)	<0.0001
Insulin dosage, IU/kg/d (IQR); [n]	0.43 (0.25–0.63) [710]	0.36 (0.22–0.52) [365]	0.64 (0.45–0.88) [7226]	0.68 (0.50–0.92) [4048]	0.41 (0.26–0.61) [555]	0.78 (0.58–1.04) [5401]	0.66 (0.48–0.89) [986]	0.36 (0.21–0.54) [191]	0.67 (0.46–0.91) [2423]	0.49 (0.32–0.72) [138]	<0.0001
DKA, % (95% CI)	6.8 (5.0–8.6)	2.6 (1.1–4.1)	25.7 (24.7–26.7)	23.5 (22.2–24.7)	4.4 (2.8–6.0)	25.9 (24.7–27.1)	25.3 (22.7–28.0)	3.1 (1.0–5.2)	21.5 (19.9–23.1)	10.5 (6.0–15.0)	<0.0001
Elevated blood pressure, % [n]	26.3 [669]	28.5 [383]	31.5 [6354]	31.5 [3748]	26.2 [603]	23.2 [5074]	34.5 [948]	26.6 [214]	28.5 [2193]	49.1 [161]	<0.0001
C-peptide, nmol/l (IQR); [n]	0.20 (0.13–0.40) [330]	0.31 (0.20–0.53) [179]	0.13 (0.07–0.20) [3173]	0.17 (0.10–0.23) [1749]	0.47 (0.26–0.76) [290]	0.16 (0.10–0.26) [2449]	0.32 (0.20–0.53) [467]	0.36 (0.20–0.66) [89]	0.17 (0.10–0.26) [925]	0.53 (0.28–1.06) [86]	0.066
At 2-year-follow-up											
HbA1c, % (IQR)	7.0 (6.5–7.5)	7.2 (6.6–7.8)	7.3 (6.7–7.8)	7.4 (6.8–8.1)	7.2 (6.5–8.2)	7.4 (6.7–8.3)	7.7 (6.9–8.9)	6.7 (6.2–7.3)	7.3 (6.6–7.9)	7.4 (6.5–8.6)	<0.0001
BMI-SDS (IQR)	0.46 (−0.07 to 1.04)	0.14 (−0.51 to 0.74)	0.47 (−0.08 to 1.04)	0.21 (−0.36 to 0.80)	0.22 (−0.41 to 0.93)	0.07 (−0.46 to 0.56)	1.37 (0.97–1.77)	0.21 (−0.44 to 0.75)	0.26 (−0.32 to 0.81)	1.89 (1.58–2.21)	<0.0001
Insulin therapy, % (95% CI)	98.4 (97.5–99.2)	96.9 (95.3–98.6)	99.9 (99.8–99.9)	99.8 (99.7–100)	93.8 (91.9–95.6)	99.8 (99.7–99.9)	97.8 (96.9–98.7)	76.6 (71.5–81.8)	99.6 (99.3–99.8)	72.4 (65.8–79.0)	<0.0001
Insulin dosage, IU/kg/d, (IQR); [n]	0.69 (0.57–0.84) [781]	0.79 (0.64–0.97) [407]	0.72 (0.59–0.85) [7330]	0.82 (0.66–1.00) [4089]	0.78 (0.59–0.99) [615]	0.84 (0.67–1.05) [5458]	0.78 (0.57–0.99) [993]	0.71 (0.52–0.89) [198]	0.74 (0.59–0.92) [2453]	0.69 (0.46–0.88) [130]	<0.0001
Multiple daily injections,%; [n]	40.6 [781]	61.8 [408]	45.1 [7336]	62.8 [4091]	75.4 [617]	72.6 [5465]	77.0 [996]	69.5 [200]	68.5 [2455]	74.0 [131]	<0.0001
Insulin pump therapy, %; [n]	59.4 [781]	38.0 [408]	54.9 [7330]	37.1 [4091]	24.3 [617]	27.3 [5465]	22.9 [996]	30.5 [200]	31.5 [2455]	25.2 [131]	<0.0001
Use of CGMS,%; [n]	31.0 [794]	24.2 [421]	30.9 [7347]	29.4 [4098]	23.3 [658]	28.0 [5475]	27.4 [1018]	16.1 [261]	16.9 [2466]	12.7 [181]	<0.0001
Use of SAP,%; [n]	26.1 [781]	14.7 [408]	23.6 [7336]	15.8 [4091]	9.7 [617]	11.0 [5465]	9.0 [996]	12.0 [200]	8.7 [2455]	8.4 [131]	<0.0001
At 4-year-follow-up											
HbA1c, % (IQR)	7.1 (6.6–7.7)	7.5 (6.9–8.3)	7.4 (6.9–8.0)	7.7 (7.1–8.5)	7.6 (6.8–8.6)	7.7 (7.0–8.6)	8.1 (7.3–9.3)	6.9 (6.2–7.6)	7.5 (6.9–8.3)	7.7 (6.6–9.1)	<0.0001
BMI-SDS (IQR)	0.42 (−0.16 to 0.87)	0.16 (−0.35 to 0.87)	0.36 (−0.2 to 0.92)	0.36 (−0.25 to 0.96)	0.33 (−0.3 to 1.01)	0.21 (−0.35 to 0.73)	1.47 (0.96–1.89)	0.16 (−0.48 to 0.71)	0.25 (−0.32 to 0.82)	1.83 (1.44–2.18)	<0.0001
Insulin therapy, % (95% CI)	98.6 (97.8–99.4)	97.6 (96.2–99.1)	99.9 (99.9–100)	99.8 (99.7–99.9)	93.6 (91.7–95.5)	99.8 (99.7–99.9)	97.5 (96.6–98.5)	77.0 (71.9–82.1)	99.7 (99.5–99.9)	79.0 (73.0–85.0)	<0.0001
Multiple daily injections, %; [n]	30.4 [783]	47.2 [411]	35.6 [7342]	49.4 [4090]	65.4 [616]	65.2 [5463]	69.3 [993]	57.2 [201]	58.2 [2458]	68.5 [143]	<0.0001
Insulin pump therapy, %; [n]	69.2 [783]	52.6 [411]	64.4 [7342]	50.6 [4090]	34.3 [616]	34.8 [5463]	30.5 [993]	41.3 [201]	41.7 [2458]	28.0 [143]	<0.0001
Use of CGMS, %; [n]	44.6 [794]	39.0 [421]	47.2 [7347]	43.6 [4098]	36.5 [658]	41.6 [5475]	40.4 [1018]	24.9 [261]	27.2 [2466]	21.0 [181]	<0.0001
Use of SAP,%; [n]	38.4 [783]	27.7 [411]	37.4 [7342]	26.9 [4090]	17.2 [616]	19.1 [5463]	16.1 [993]	18.4 [201]	15.9 [2458]	13.3 [143]	<0.0001

Data are presented as median and interquartile ranges (IQR) or percentages of cases and 95% confidence interval (CI). CGMS: continuous glucose monitoring; SAP: simultaneous use of sensor and pump.

Table 2: **Characteristics of CART subgroups-islet autoantibody-positive (subgroups P1–P7) and islet-autoantibody-negative (subgroups N1–N3) patients at diabetes onset and after 2 and 4 years.**

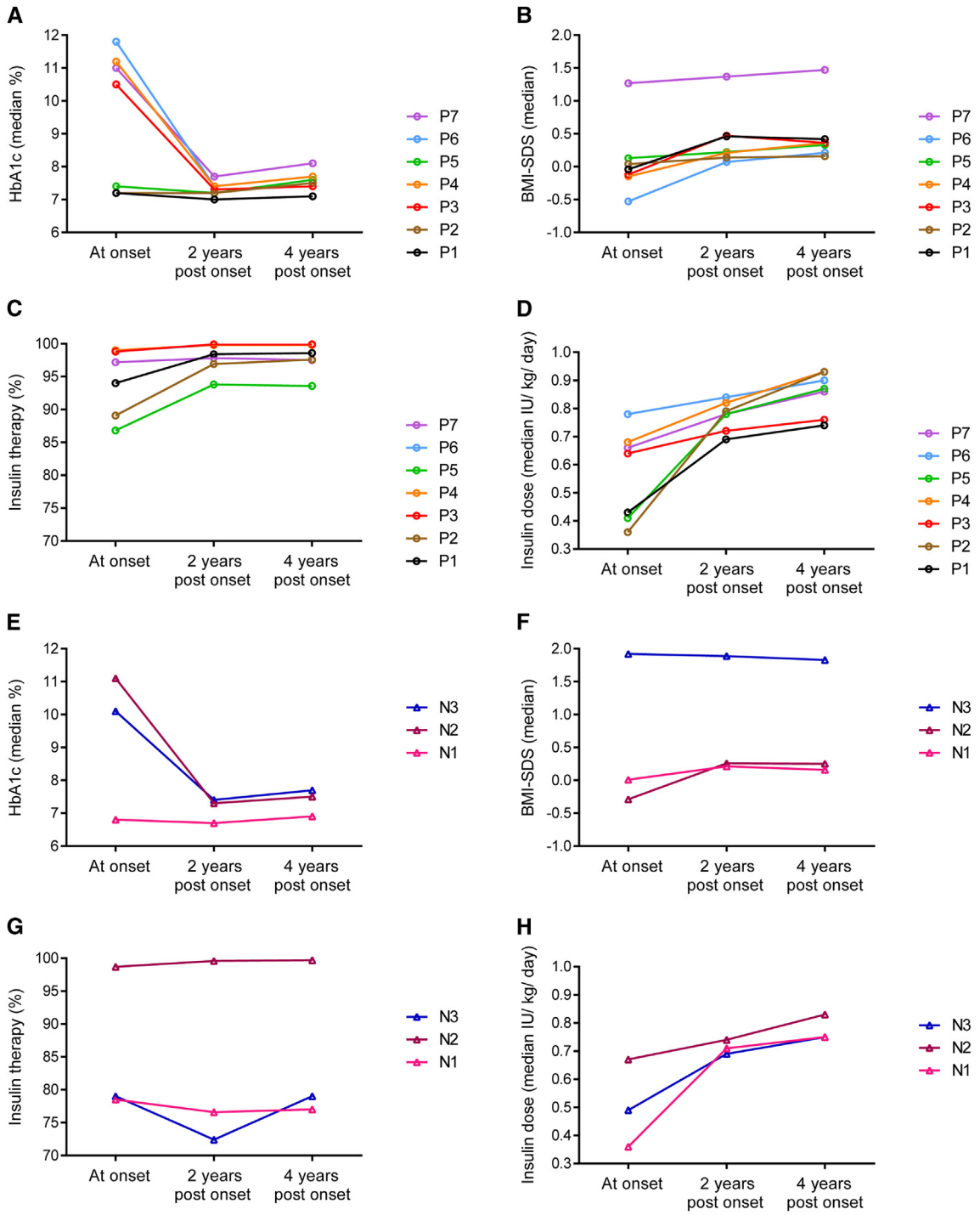

Fig. 2: HbA1c (A and E), BMI-SDS (B and F), proportion of patients with insulin therapy (C and G), and daily insulin dose (D and H) in islet autoantibody-positive (subgroups P1–P7; A–D) and islet-autoantibody-negative (subgroups N1–N3, E–H) patients at diabetes onset and after 2 and 4 years.

BMI at follow-up remained similar to values at onset in each of the groups (Fig. 2B and F). Patients in the P7 and N3 subgroups consistently had significantly higher median BMI-SDS values compared to all other subgroups ($p < 0.0001$). The percentage of patients with elevated blood pressure remained highest in the subgroups P7 and N3 (35.1% and 52.5% at 4 years of follow-up) and was similar or lower compared to the percentages at diabetes onset in the remaining groups. No antihypertensive medication was documented in any of the patients in the study group.

Insulin therapy was administered to 99.4% of the islet autoantibody-positive patients, and to 99.7% in group N2 of the islet autoantibody-negative patients at 4 years follow-up. It was markedly less frequent at diagnosis and after 4 years in the islet autoantibody-negative groups N1 (78.5% and 77.0%), and N3 (79.0% and 79.0%) (Fig. 2C and G). Among the insulin-treated patients, the daily insulin dose increased compared to diagnosis in all 10 groups with the greatest increase in groups with lower insulin demand at disease onset (Fig. 2D and H). The percentage of patients using an insulin pump, sensor or sensor-assisted pump therapy was highest in groups P1 and P3 (younger children autoantibody-positive children), Table 2.

CART subgroups and complications on follow-up

The median (IQR) follow-up time for acute and chronic complications in the analysis cohort was 6.8 (4.8–9.6) years. Information on hypoglycemia and ketoacidosis was available for all 22,719 patients. Information on retinopathy was documented in 20,673 patients (91.0%) and nephropathy in 21,571 (94.9%) of patients. There were marked differences in the risks for each of the assessed complications between subgroups (Table 3; Figs. 3 and 4).

Severe hypoglycemia was prevalent in groups P1, P3, P4, N1, and N2. The groups with the lowest risk for hypoglycemia were those with the highest BMI, P7 (10-year risk 32%) and N3 (25%) and/or the highest C-peptide at diabetes onset, P2 (34%), P5 (34%), and N3 (25%; 95% CI, 17–35). Hazard ratios in relation to group P3 were reduced for these groups (P2: HR, 0.75; $p = 0.0049$; P5: HR, 0.75; $p = 0.0011$; P7: HR, 0.71; $p < 0.0001$; N3: HR, 0.54; $p = 0.0007$; Table 3; Fig. 3A and E).

The 10-year risk for a DKA event ranged from 10.1% in group N1 to 22.2% in group P7 (Table 3; Fig. 3B and F). Compared with group P3, the risk of DKA was increased in groups P4 (HR, 1.28; $p < 0.0001$) and P7 (HR, 1.6; $p < 0.0001$; Table 3).

Retinopathy and nephropathy (persistent microalbuminuria) were assessed as chronic complications (Table 3; Fig. 3C, D, G, and H). Among islet-autoantibody positive patients, groups with the highest residual C-peptide at diabetes onset, P5 and P7, had the highest risk of retinopathy (10-year risk P5 2.06%; HR, 3.78 vs P3; $p = 0.0027$; 10-year risk P7 1.92%; HR, 3.51 vs P3; $p = 0.0008$). Among islet-autoantibody negative patients, group N2, characterised by low C-peptide at diabetes onset, had the highest risk of retinopathy (10-year risk 1.11%; HR, 2.04 vs P3; $p = 0.0036$).

The 10-year risk for nephropathy was highest in group P2 (15.6%, HR, 2.18 vs P3; $p < 0.0001$) and group P5 (16.1% HR, 2.26 vs P3; $p < 0.0001$; Table 3; Fig. 3D and H). Adjustment for sex did not affect these findings. All pairwise comparisons of HR's for the four complications between the 10 subgroups are shown in Supplementary Table S3.

Complication features of the CART subgroups

Radar plots were used to visualise groups with similar complication risk profiles (Fig. 4). Groups P1, P3, P4, N1, and N2 had similar profiles with a high risk for severe hypoglycemia and a low to moderate risk of DKA, retinopathy and nephropathy. All except group N1 had low C-peptide values at diabetes onset. The risk for retinopathy was higher for groups P4 and N2, which had a higher age at diagnosis among these groups. Group P6 had a moderate risk for all complications. Patients in the islet autoantibody-positive groups P2 and P5 had a high risk for chronic complications, with increased risk for nephropathy in both groups and also for retinopathy in group P5 (Fig. 4). Surprisingly, both groups had features of preserved C-peptide, low HbA1c, and very low frequency of DKA at diabetes diagnosis (Table 2). High BMI was a characteristic feature in islet autoantibody-positive patients from group P7 and in islet autoantibody-negative patients from group N3. Patients in group N3 did not have an elevated risk for any of the complications, while children in group P7 had a high risk for poor metabolic control, DKA, and retinopathy.

Discussion

We applied recently described subgrouping of new onset childhood diabetes to the German DPV cohort of pediatric patients with diabetes, and found differences in the risk of long-term complications between the subgroups.[2] With 22,719 patients and a median follow-up time of almost 7 years, this is, to our knowledge, the largest study to investigate diabetes subgroups in children and adolescents for the risk of diabetes-specific complications.

The classification is user-friendly and can be performed easily by a clinician based on routine parameters. The classification has been established using C-peptide as the predicted parameter in a previous cohort using a CART classification model. Validating this approach, both the size of the subgroups and the C-peptide levels at manifestation matched our previous analyses and predictions.[2] Relevant to the interpretation of the risks for complications, we have previously shown

that the islet autoantibody-negative group N1 is enriched in monogenic diabetes, and N3 is typical for type 2 diabetes. Among the islet autoantibody-positive subgroups we previously demonstrated heterogeneity at diabetes manifestation with notable increases in inflammatory markers in groups P1, and P3, and features of type 2 diabetes in P5 (type 2 diabetes family history, vitamin D deficiency), P6 (insulin insensitivity), and P7 (high BMI, insulin insensitivity, hyperlipidemia, vitamin D deficiency).[2] The group N2, the largest group among islet autoantibody-negative patients, has characteristic features of type 1 diabetes, including low C-peptide, high insulin demand, and susceptible type 1 diabetes associated HLA genotypes.

Here, the value of the subgroup classification was shown by the identification of subgroups at increased risk for specific diabetes-associated complications. In agreement with previous reports, the groups with the highest C-peptide at diabetes manifestation (P2, P5, P7, N3) had a lower risk of hypoglycemia.[15,16] An exception was group N1, which had residual C-peptide but a marked risk of serious hypoglycemia, a risk that may be attributed to the treatment of monogenic diabetes or to a poorer counter-regulation caused by monogenic diabetes itself.[17] Also consistent with previous reports, the type 1 diabetes subgroup with high BMI and blood pressure (P7) had elevated risks for complications such as retinopathy, and DKA.[18–21] This group also had the highest HbA1c levels on follow-up. We were unable to confirm recent findings from the USA and India showing that young patients with type 2 diabetes have a higher risk for complications than patients with type 1 diabetes.[22,23] Group N3, which has typical features of type 2 diabetes, had similar or lower risks for complications than all other groups with the exception of a relatively high percentage of patients with elevated blood pressure. In this context, it was interesting that no antihypertensive medication was documented in any of the patients, despite a relatively high proportion of patients with elevated blood pressure values. It is possible that treatment providers are still very reluctant to give medication to very young people. Of interest, the groups previously identified as inflammatory (P1, P3 and N2), which included almost 50% of patients, had remarkably similar follow-up profiles with a marked risk for severe hypoglycemia, but among the lowest risks for other complications. This suggests that patients within these groups may have an acute diabetes onset that could be ameliorated by early anti-inflammatory treatment. Finally, it was noteworthy that groups P2 and P5, representing around 5% of patients, had distinctly higher risks for nephropathy than all other groups, and P5 was the only group with highly elevated risk for both chronic complications, retinopathy and nephropathy. Surprisingly, both groups had a relatively mild diabetes onset characterised by residual C-peptide, low HbA1c and very

	P1	P2	P3	P4	P5	P6	P7	N1	N2	N3
Patients, n (%)	794 (3.5)	421 (1.9)	7347 (32.3)	4098 (18.0)	658 (2.9)	5475 (24.1)	1018 (4.5)	261 (1.25)	2466 (10.9)	181 (0.8)
Follow-up time, median (IQR)	9.4 (5.9–12.4)	7.9 (6.0–9.3)	9.0 (5.9–11.7)	7.6 (5.6–9.1)	5.1 (4.0–6.4)	5.2 (4.1–6.6)	5.1 (4.1–6.5)	7.3 (4.6–10.8)	7.5 (5.2–10.8)	5.5 (4.2–8.1)
Severe hypoglycemia										
10-year-risk, % (95% CI)	46 (41–52)	34 (28–42)	46 (44–48)	47 (44–49)	34 (29–40)	40 (37–42)	32 (28–37)	43 (34–54)	46 (43–50)	25 (17–35)
Unadjusted HR (95% CI)	1.01 (0.89–1.14)	0.75 (0.62–0.92)	Reference group	1.02 (0.95–1.09)	0.75 (0.63–0.89)	0.87 (0.81–0.93)	0.71 (0.61–0.82)	0.95 (0.75–1.19)	1.01 (0.93–1.01)	0.54 (0.38–0.77)
p for unadjusted HR compared to reference	0.90	0.0049		0.56	0.0011	<0.0001	<0.0001	0.63	0.7635	0.0007
Diabetic ketoacidosis										
10-year-risk, % (95% CI)	13.7 (11.2–16.8)	13.7 (10.1–18.6)	13.9 (12.9–14.9)	17.8 (16.2–19.5)	11.8 (8.7–16.0)	14.2 (12.8–15.7)	22.2 (18.4–26.7)	10.1 (6.5–15.7)	13.4 (11.9–15.2)	12.9 (7.8–21.5)
Unadjusted HR (95% CI)	0.99 (0.80–1.22)	0.99 (0.72–1.35)	Reference group	1.28 (1.15–1.43)	0.85 (0.62–1.16)	1.02 (0.91–1.15)	1.60 (1.31–1.94)	0.73 (0.47–1.14)	0.97 (0.84–1.11)	0.93 (0.56–1.55)
p for unadjusted HR compared to reference	0.91	0.94		<0.0001	0.31	0.74	<0.0001	0.16	0.64	0.78
Retinopathy										
10-year-risk, % (95% CI)	0.41 (0.15–1.11)	0.67 (0.17–2.71)	0.55 (0.39–0.77)	1.16 (0.81–1.66)	2.06 (0.91–4.69)	1.40 (0.97–2.04)	1.92 (0.97–3.77)	0.40 (0.06–2.84)	1.11 (0.74–1.68)	n.a.
Unadjusted HR (95% CI)	0.75 (0.27–2.09)	1.23 (0.30–5.11)	Reference group	2.11 (1.33–3.37)	3.78 (1.59–9.01)	2.57 (1.60–4.12)	3.51 (1.69–7.30)	0.73 (0.10–5.28)	2.04 (1.26–3.30)	n.a.
p for unadjusted HR compared to reference	0.58	0.77		0.0016	0.0027	<0.0001	0.0008	0.75	0.0036	n.a.
Nephropathy										
10-year-risk, % (95% CI)	5.5 (4.0–7.5)	15.6 (11.8–20.6)	7.1 (6.5–7.8)	10.4 (9.3–11.6)	16.1 (12.5–20.9)	12.0 (10.7–13.3)	9.7 (7.5–12.7)	10.5 (6.8–16.1)	8.4 (7.2–9.8)	9.2 (5.1–16.6)
Unadjusted HR (95% CI)	0.77 (0.55–1.06)	2.18 (1.63–2.93)	Reference group	1.46 (1.26–1.69)	2.26 (1.72–2.98)	1.68 (1.46–1.93)	1.37 (1.04–1.80)	1.47 (0.95–2.28)	1.18 (0.99–1.40)	1.29 (0.71–2.38)
p for unadjusted HR compared to reference	0.11	<0.0001		<0.0001	<0.0001	<0.0001	0.03	0.085	0.069	0.41

HR: hazard ratio; CI: confidence interval. 10-year-risk, proportion with severe hypoglycaemia/diabetic ketoacidosis/retinopathy/nephropathy after 10 years calculated by Kaplan-Meyer analysis. The hazard ratios for N3 could not be calculated as none of the individuals in this group developed a documented retinopathy within the observed time span.

Table 3: **Complications: 10-year risk and unadjusted hazard ratio for islet autoantibody-positive (subgroups P1–P7) and autoantibody-negative patients (subgroups N1–N3) compared to reference subgroup P3.**

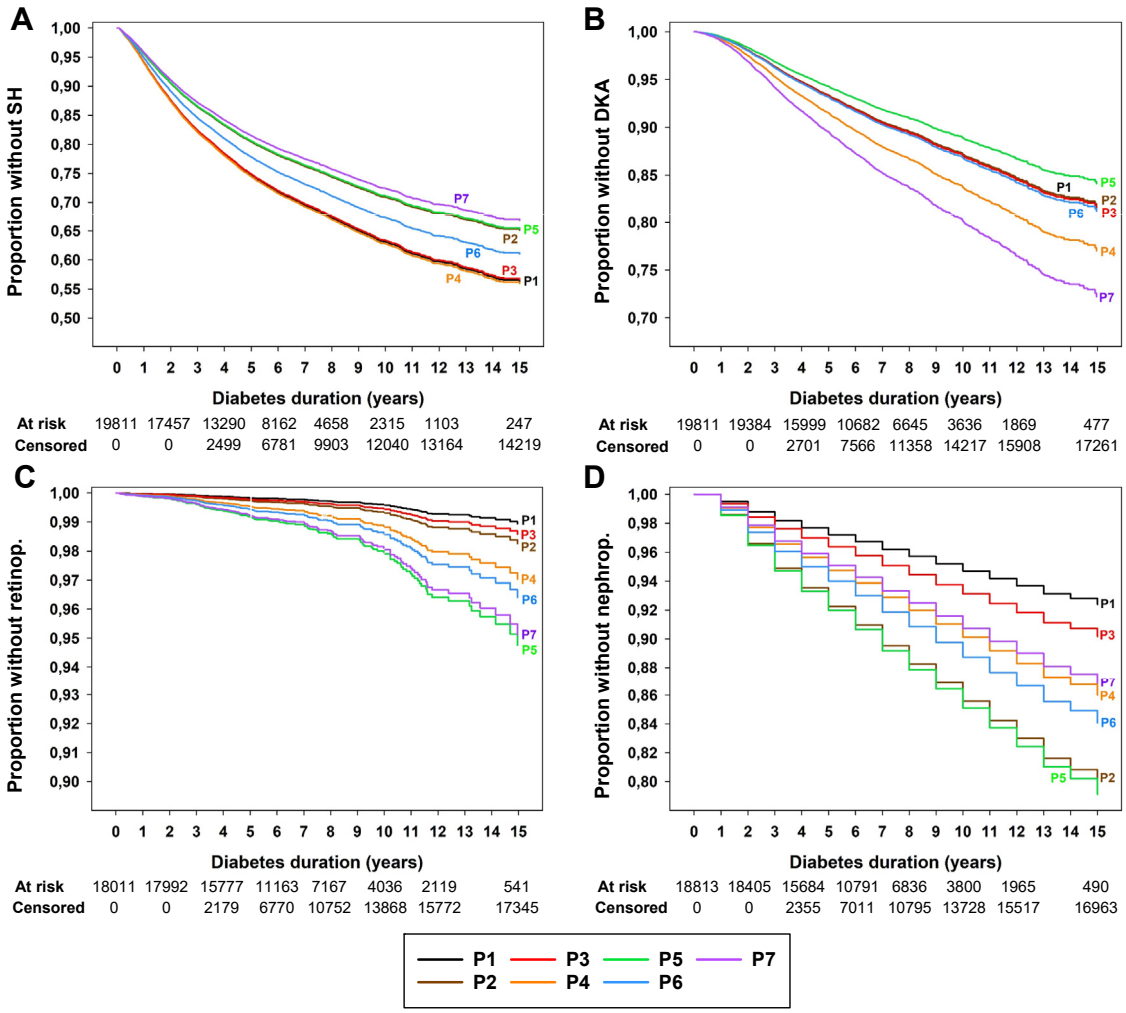

Fig. 3: The risk for developing severe hypoglycemia (SH) (A and E), diabetic ketoacidosis (DKA) (B and F), retinopathy (retinop.) (C and G) or nephropathy (nephrop.) (D and H) in the different subgroups analysed by Kaplan–Meier analysis in islet autoantibody-positive patients (subgroups P1–P7; A–D) and autoantibody-negative patients (subgroups N1–N3; E–H).

low frequency of DKA and both had a diabetes onset in late childhood or adolescence.

A strength of the DPV registry cohort is its inclusion of around 80–90% of pediatric patients with diabetes in Germany and Austria, with the coverage for children with diabetes assumed to be even higher.[7] This allowed us to apply the subgroup classification to a large number of patients with a relatively long follow-up time. The DPV registry has a standardised data collection for clinical parameters related to diabetes diagnosis, management and outcomes, so that it can be assumed that the data quality is high. Limitations of the work included that islet autoantibody status at diabetes onset was available in only 41% of the DPV population, so that the majority could not be classified. Since C-peptide measurement is not always performed as part of routine care, these data were missing from the majority of patients analysed. C-Peptide was not centrally assessed, but was determined by individual centres, and there was no specification at which time point and how often it was determined, nor whether it was measured while the patient was fasting. Regarding the measurement of microalbuminuria, we assume that the participating sites followed the guidelines, but this could not be verified. Missing data on antibody status might have biased our cohort because there might be some diabetes types in which antibodies are more often measured (type 1 diabetes) and therefore other diabetes types might be underrepresented. However, the distribution of subtypes in our final cohort was close to the distribution reported in the paper of Achenbach et al. where the CART analysis was first implemented.[2] This paper was based on the "Di Melli Cohort", a cohort in which diabetes-related autoantibodies were measured in all

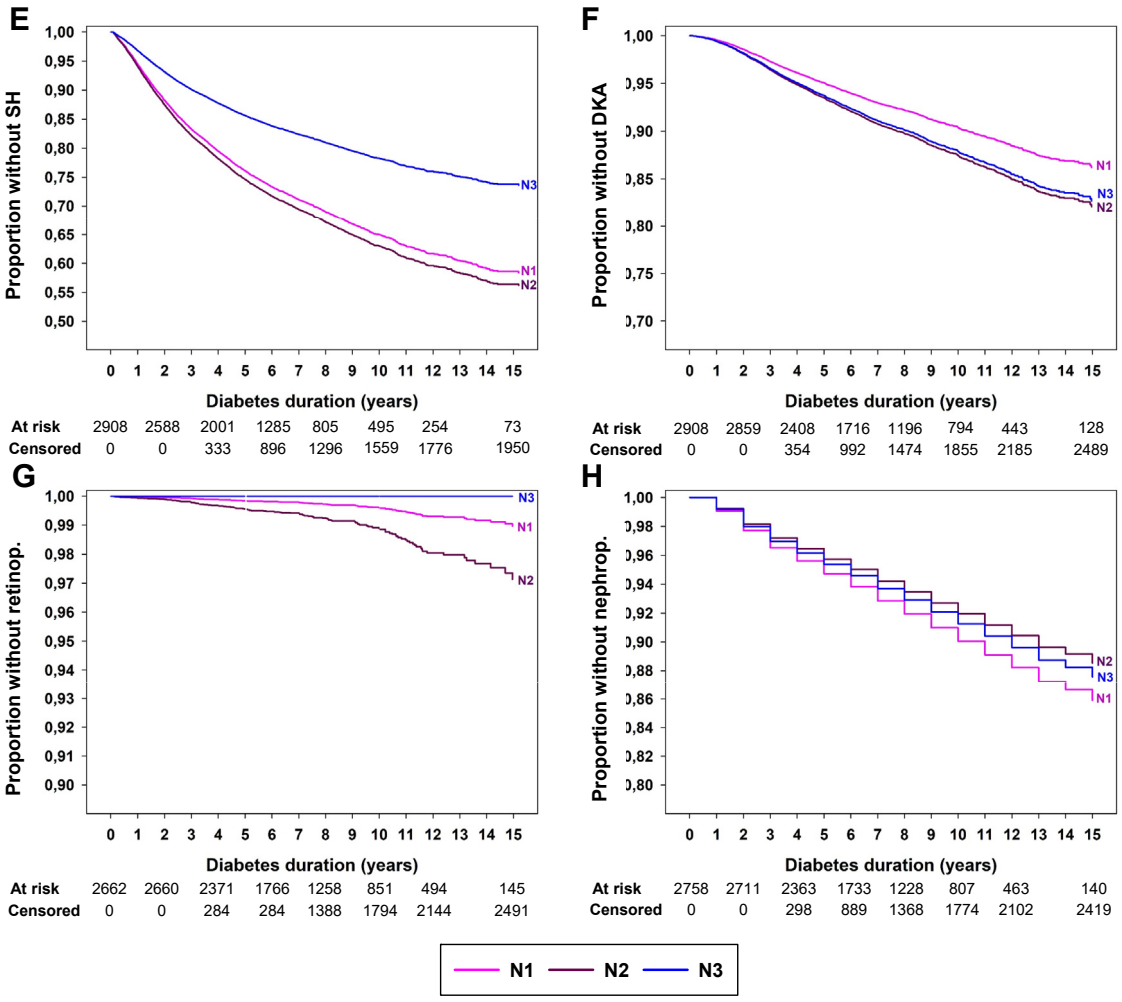

Fig. 3: (continued)

individuals. Therefore, we are confident, that this possible bias is acceptable. In addition, we cannot exclude a bias caused by missing data at the 2- and 4-year follow-up and the drop-out rate, which may be distributed differently across the groups. Another limitation of our study is that laboratory samples were not analysed centrally, but in the respective laboratory with which the clinical center cooperates. However, the laboratories are of course subject to standardised quality controls. An important limitation is that nephropathy and, in particular, retinopathy occur many years after onset and more frequently when patients have reached adulthood.[24,25] Therefore, a longer follow-up period, in particular for retinopathy, is needed to fully determine the heterogeneity of risk among the subgroups. Nevertheless, even within the short observation period, we see patients who already have these complications. Another important point is that the proportion of patients in the groups from different countries of origin cannot be considered representative, as DPV is a registry developed for the medical documentation of individuals with diabetes and there are huge differences between the centers regarding the documentation of ethnicity as this a sensitive topic within the four Middle-European countries participating in the DPV registry. For reasons of practicability we needed to group countries of origin and include a hierarchy between the country of origin of the child itself and its mother and father. We are aware that this problematic and did this without any ulterior motives.

In conclusion, subgrouping of youth-onset diabetes using a previously defined algorithm based on CART analysis can distinguish groups of patients with increased risks for post-onset complications such as severe hypoglycemia, DKA, nephropathy and retinopathy. Subgroups with increased risks may benefit from individualised monitoring, education and interventions to prevent complications.

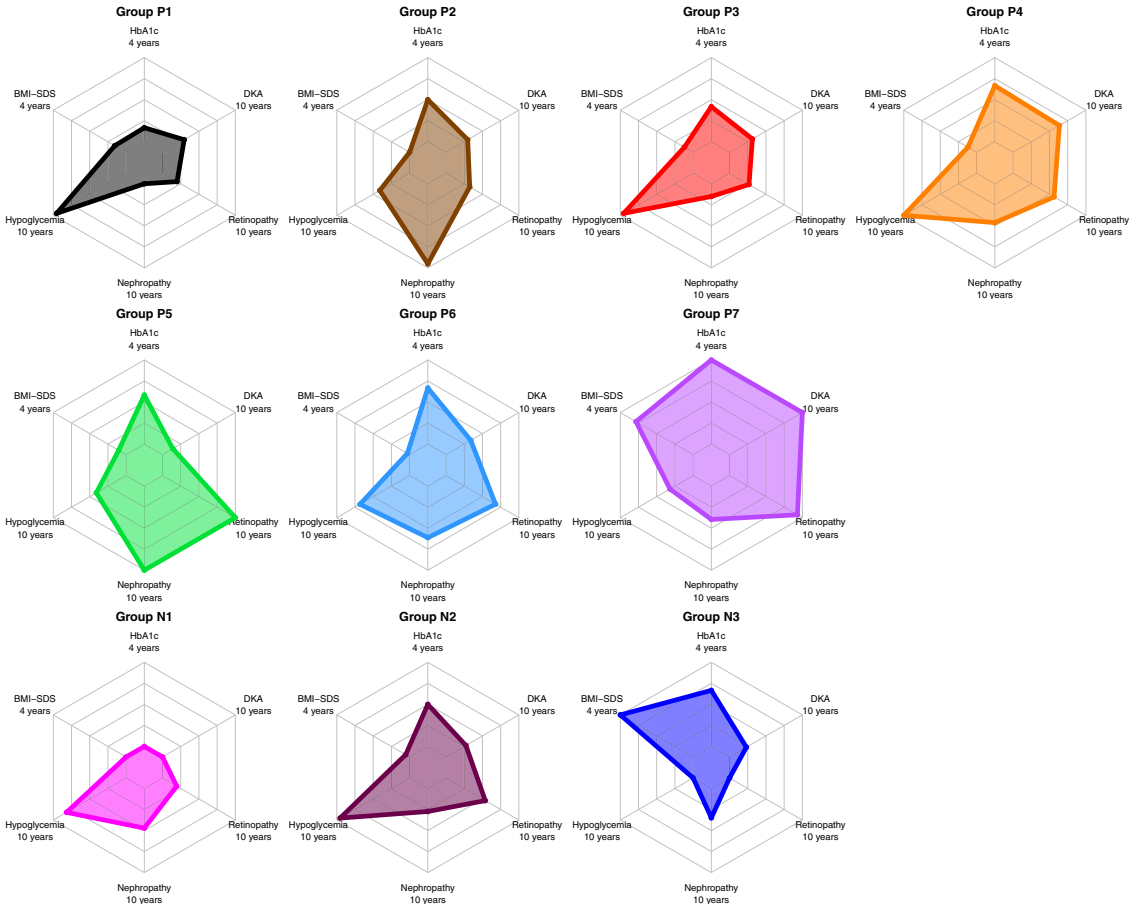

Fig. 4: Characteristics and diabetes-associated complications in islet autoantibody-positive (subgroups P1–P7) and autoantibody-negative patients (subgroups N1–N3). DKA: diabetic ketoacidosis; HbA1c: haemoglobin A1c.

Contributors

RWH and AGZ conceived and designed this project. AE carried out data analysis. PA, EB and AGZ have developed the classification into the groups P1–P7 and N1–N3 used here and have contributed significantly to the analysis and interpretation of the data. KW, OK, TM, UE and WB contributed and acquised data used in the analysis. KW, EB, AGZ and AE drafted the article. AE and RWH have directly assessed and verified the underlying data reported in the manuscript. All authors reviewed the article critically for important intellectual content, had full access to all the data in the study, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement

Aggregated data can be made available upon reasonable request via email to the senior author reinhard.holl@uni-ulm.de after publication for the next 10 years. Remote data analysis (SAS software) or joint research projects are possible. The DPV board will decide on the scientific validity of the research proposal. To ensure patient privacy and to comply with patient consent forms, original patient-level data cannot be shared. In the case of contract analyses, costs have to be covered, and the project partners cannot use the data for other purposes without prior written consent.

Declaration of interests

All authors declare no competing interests.

Acknowledgements

The DPV initiative is supported by The German Ministry of Education and Research (BMBF) within the German Center for Diabetes Research (DZD, grant number: 82DZD14E03), the diabetes surveillance of the Robert Koch Institute, the German Diabetes Association (DDG) and INNODIA. This manuscript is part of a project (www.imisophia.eu) that has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 875534. This Joint Undertaking support from the European Union's Horizon 2020 research and innovation programme and "EFPIA" and "T1D Exchange", "JDRF", and "Obesity Action Coalition". Special thanks to Andreas Hungele and Ramona Ranz for support and the development of the DPV documentation software. We thank Jose Marie Zapardiel Gonzalo for the Radar plots. A list of centers participating in DPV and contributing data to the this analysis is available as a Supplemental File.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102208.

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