Differential associations of glutamic acid decarboxylase antibodies (GADA) and C-peptide with insulin initiation, glycemic responses and severe hypoglycemia in patients diagnosed with type 2 diabetes

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Supplementary methods

Statistical analyses

We examined the independent associations of CP and GADA and their interactions with 1) insulin initiation, 2) glycemic responses and 3) severe hypoglycemia adjusted for covariables based on prior knowledge. Among insulin-naïve patients, we performed Cox regression for insulin initiation without adjustment (model 1) followed by addition of age, sex, diabetes duration, year of assessment (model 2), HbA1c, BMI, Ln(TG:HDL-C) ratio, eGFR and baseline treatment of OGLDs (model 3). In a subset of new insulin users with HbA1c measured at month 0, 6 and 12, we compared HbA1c reduction adjusted for baseline HbA1c (model 1), followed by addition of age, sex, diabetes duration, year of assessment (model 2). For severe hypolgycemia, we performed Cox regression without adjustment (model 1) followed by addition of age, sex, diabetes duration, year of assessment (model 2), HbA1c, BMI, Ln (TG:HDL-C) ratio (model 3), eGFR, CVD history, treatment of OGLDs and insulin at baseline (model 4).

Figure S1. Flow chart of participants selection

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┌─────────────────────────────────────────────────────────────────────┐
│                      HKDR (1995-2019)                                 │
│          Subjects enrolled between 1996 and 2012: n=9816              │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│        Samples with CP/GADA measured between 1996 and 2012: n=5354    │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│  Time difference between sample collection and screening date within  │
│                         ± 35 days: n=5348                             │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  │        ┌──────────────────────────────┐
                                  │───────▶│ Exclude:                     │
                                  │        │ Unknown ethnicity: n=2       │
                                  │        │ Type 1 diabetes: n=110       │
                                  │        │ Unknown types of diabetes:   │
                                  │        │ n=6                          │
                                  │        └──────────────────────────────┘
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│               Subjects included in this study: n=5230                 │
└─────────────────────────────────────────────────────────────────────┘
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Exclude:
Insulin users at or before baseline:
n=1485

Exclude:
History of hospitalization of
severe hypoglycemia:

Subjects included in analysis of association
with incident insulin treatment: n=3745

Subjects included in analysis of association
with severe hypoglycemia: n=5018

Subjects with available HbA1c for glycemic
response: n=1275

Figure S2. Distribution of GADA positivity and C-peptide levels (<200 pmol/L as insulin insufficient) stratified by age of diagnosis of diabetes (<40 years defined as young-onset diabetes, YOD)

A.
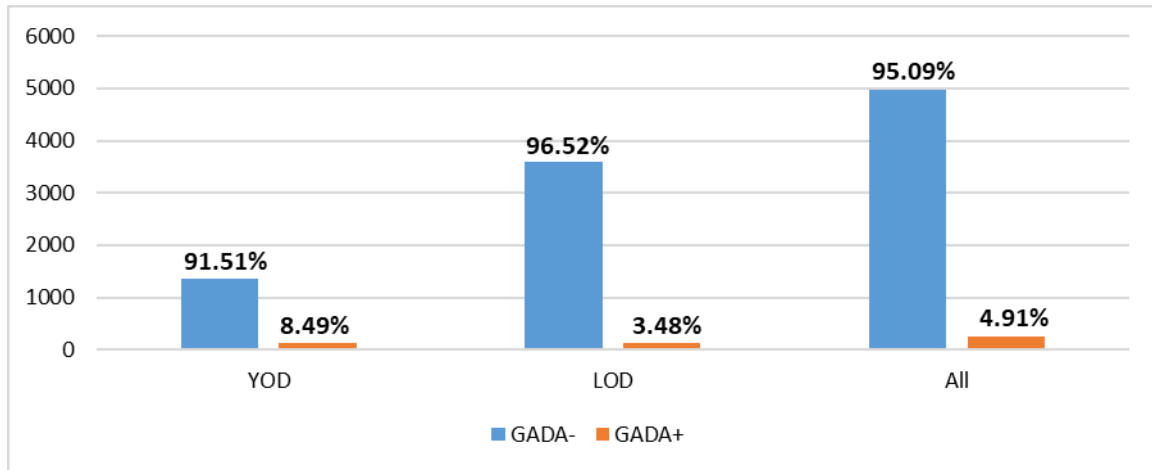
B.
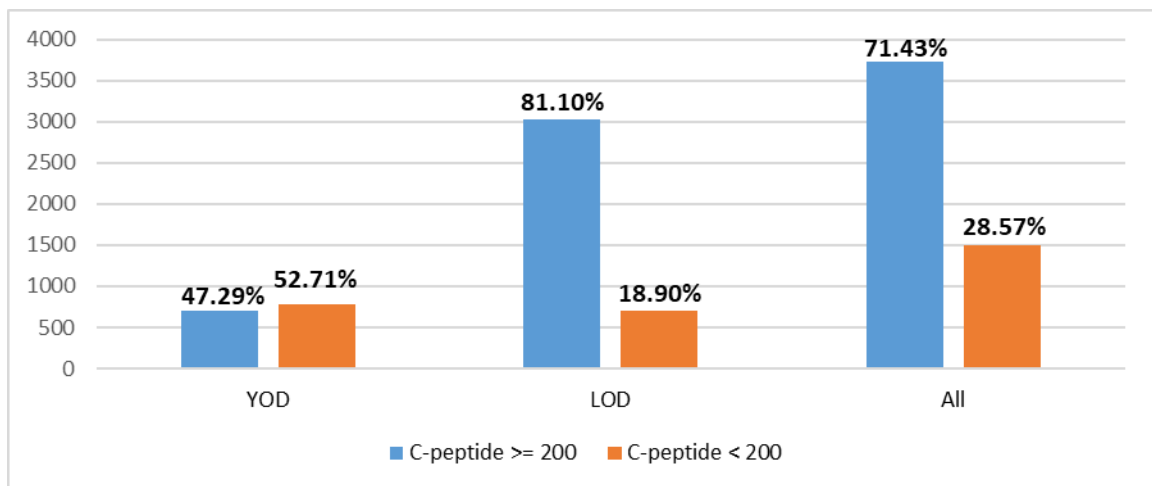
Notes: (1) Abbreviations: YOD, young-onset diabetes; LOD, late-onset diabetes.

Figure S3. Correlation plot of C-peptide and diabetes duration

Correlation plot of C-peptide and diabetes duration

$R = -0.17$, $p < 2.2e-16$

C-peptide (pmol/L)

Diabetes duration
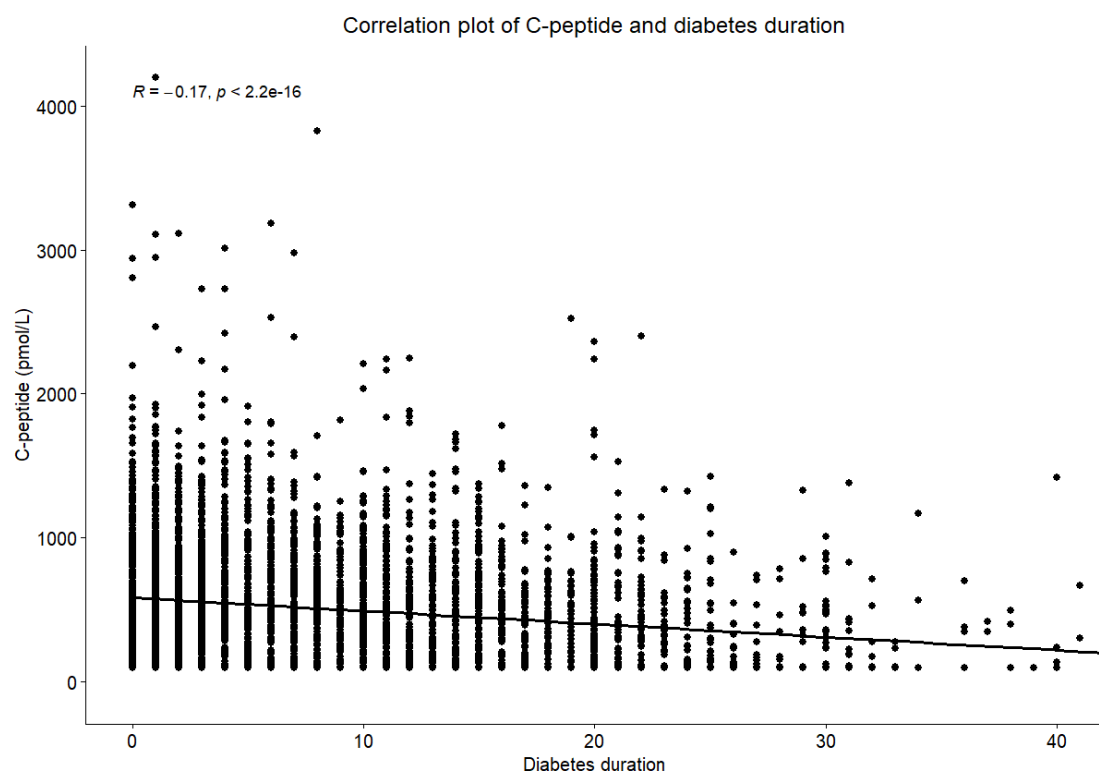
Figure S4. Subgroup analysis of the associations between GADA positivity and incident insulin therapy

Variables	No. (event/total)		HR (95%CI)	P	P(interaction)
C-peptide (pmol/L)					
< 200	502/892		1.23 (0.79-1.91)	0.356	0.892
≥ 200	1515/2853		1.61 (1.18-2.18)	0.003	
Current age (year)					
< 55	1024/1806		1.28 (0.94-1.75)	0.114	0.495
≥ 55	993/1939		1.82 (1.19-2.76)	0.005	
Sex					
Female	1016/1933		1.34 (1.00-1.81)	0.053	0.358
Male	1001/1812		1.64 (1.06-2.53)	0.027	
Age of diagnosis					
YOD	633/1020		1.28 (0.89-1.85)	0.183	0.274
LOD	1384/2725		1.70 (1.21-2.39)	0.002	
Diabetes duration (year)					
< 6	1027/2161		1.47 (1.08-2.00)	0.014	0.57
≥ 6	990/1584		1.65 (1.15-2.38)	0.007	
Obesity					
Yes	1071/1923		1.17 (0.81-1.69)	0.399	0.044
No	938/1800		1.70 (1.26-2.31)	<0.001	
TG to HDLC ratio					
< median	886/1825		1.89 (1.37-2.61)	<0.001	0.035
≥ median	1123/1906		1.00 (0.66-1.51)	0.998	
Metabolic syndrome					
Yes	1380/2449		1.15 (0.82-1.62)	0.413	0.062
No	611/1243		1.74 (1.21-2.52)	0.003	

Hazard Ratio (95% CI): 0.50　1.0　2.0　3.0　5.0

Notes: (1) The reference group in subgroup analysis is patients with GADA-. The HRs of GADA+ for incident insulin therapy were adjusted for age, sex, diabetes duration, year of assessment, HbA1c, BMI, TG to HDLc ratio, eGFR, and baseline treatment of oral glucose lowering drugs.

Figure S5. Subgroup analysis of the associations between C-peptide levels stratified by 200 pmol/L and incident insulin therapy

Subgroups	No. (event/total)		HR (95%CI)	P	P(interaction)
GADA					
Positive	94/139		1.40 (0.43-4.56)	0.575	0.892
Negative	1923/3606		0.86 (0.76-0.99)	0.032	
Current age (year)					
< 55	1024/1806		0.84 (0.70-1.00)	0.048	0.926
≥ 55	993/1939		0.86 (0.68-1.08)	0.195	
Sex					
Female	1016/1933		0.93 (0.77-1.13)	0.47	0.159
Male	1001/1812		0.81 (0.67-0.98)	0.033	
Age of diagnosis					
YOD	633/1020		0.85 (0.68-1.06)	0.15	0.734
LOD	1384/2725		0.89 (0.74-1.07)	0.221	
Diabetes duration (year)					
< 6	1027/2161		0.92 (0.77-1.09)	0.323	0.277
≥ 6	990/1584		0.88 (0.73-1.06)	0.179	
Obesity					
Yes	1071/1923		0.82 (0.69-0.99)	0.035	0.199
No	938/1800		0.93 (0.77-1.11)	0.403	
TG to HDLC ratio					
< median	886/1825		0.84 (0.69-1.04)	0.107	0.968
≥ median	1123/1906		0.85 (0.71-1.02)	0.079	
Metabolic syndrome					
Yes	1380/2449		0.85 (0.72-1.01)	0.062	0.665
No	611/1243		0.89 (0.70-1.12)	0.315	

Hazard Ratio (95% CI): 0.50 1.0 2.0 3.0

Notes: (1) The reference group in subgroup analysis is patients with high CP (CP ≥ 200 pmol/L). The HRs of low CP (CP < 200 pmol/L) for incident insulin therapy were adjusted for age, sex, diabetes duration, year of assessment, HbA1c, BMI, TG to HDLc ratio, eGFR, and baseline treatment of oral glucose lowering drugs.

Figure S6. Subgroup analysis of the associations between GADA positivity and severe hypoglycemia

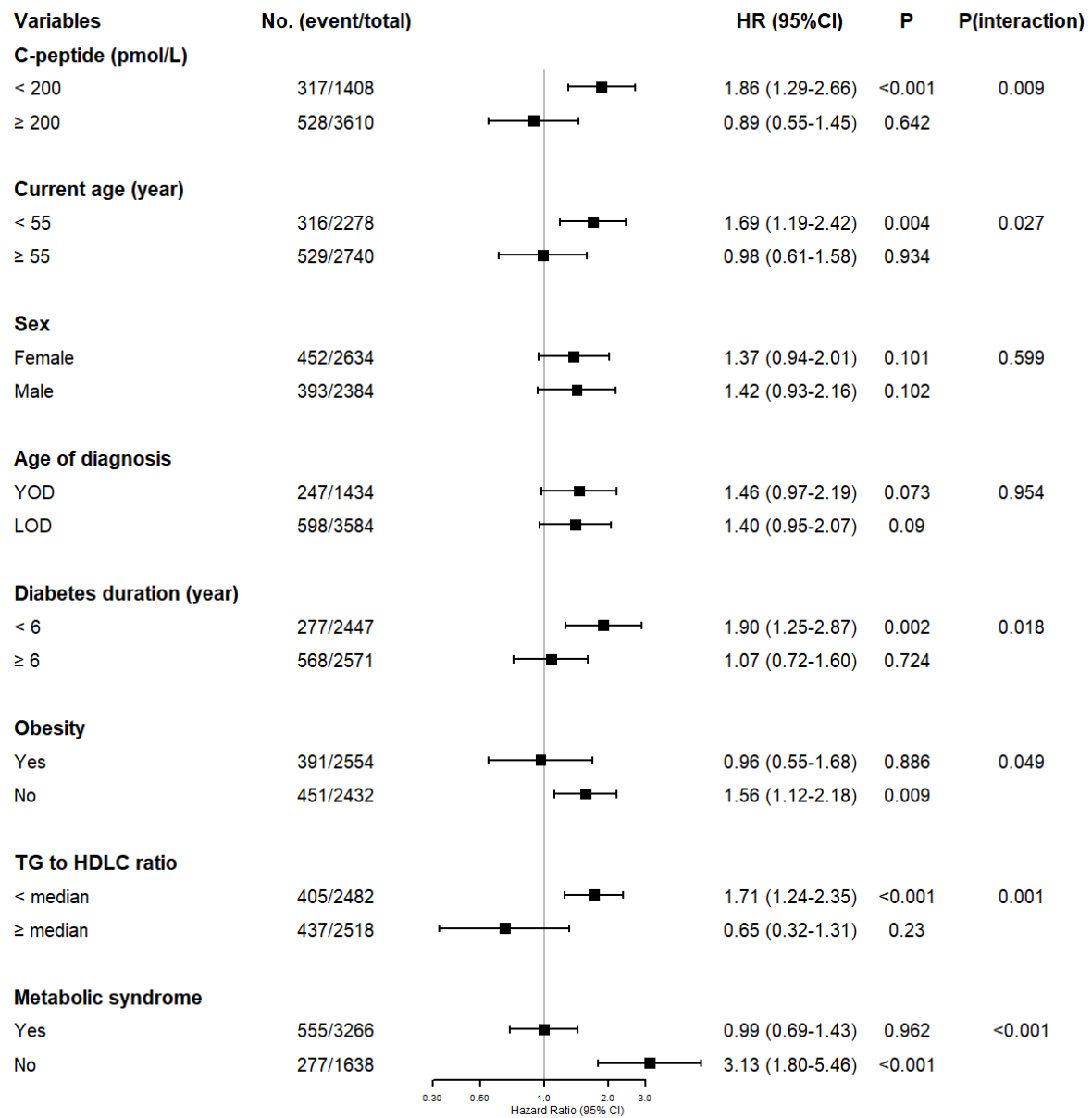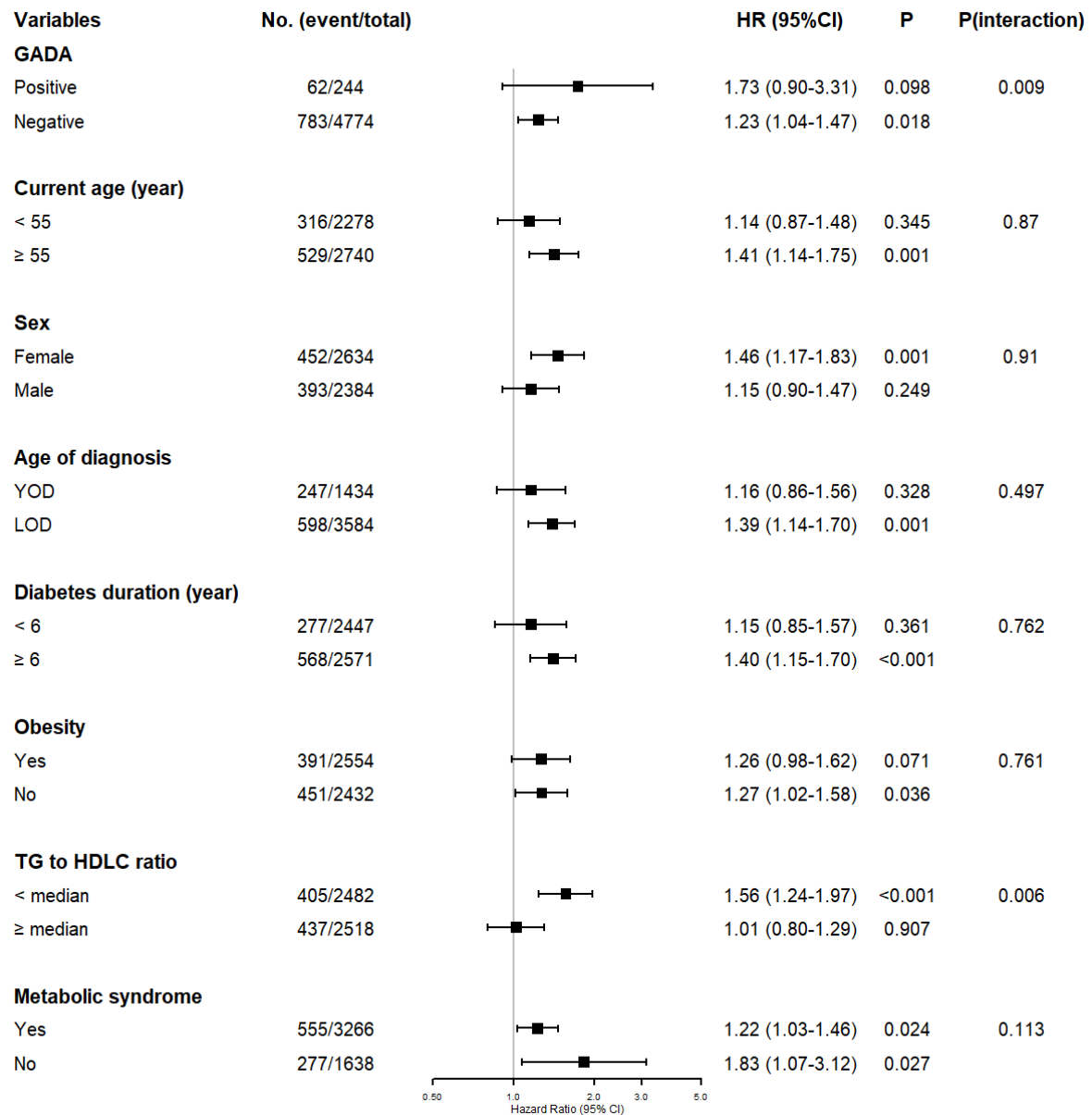| Variables	No. (event/total)		HR (95%CI)	P	P(interaction)
C-peptide (pmol/L)					
< 200	317/1408		1.86 (1.29-2.66)	<0.001	0.009
≥ 200	528/3610		0.89 (0.55-1.45)	0.642	
Current age (year)					
< 55	316/2278		1.69 (1.19-2.42)	0.004	0.027
≥ 55	529/2740		0.98 (0.61-1.58)	0.934	
Sex					
Female	452/2634		1.37 (0.94-2.01)	0.101	0.599
Male	393/2384		1.42 (0.93-2.16)	0.102	
Age of diagnosis					
YOD	247/1434		1.46 (0.97-2.19)	0.073	0.954
LOD	598/3584		1.40 (0.95-2.07)	0.09	
Diabetes duration (year)					
< 6	277/2447		1.90 (1.25-2.87)	0.002	0.018
≥ 6	568/2571		1.07 (0.72-1.60)	0.724	
Obesity					
Yes	391/2554		0.96 (0.55-1.68)	0.886	0.049
No	451/2432		1.56 (1.12-2.18)	0.009	
TG to HDLC ratio					
< median	405/2482		1.71 (1.24-2.35)	<0.001	0.001
≥ median	437/2518		0.65 (0.32-1.31)	0.23	
Metabolic syndrome					
Yes	555/3266		0.99 (0.69-1.43)	0.962	<0.001
No	277/1638		3.13 (1.80-5.46)	<0.001	

Hazard Ratio (95% CI): 0.30 0.50 1.0 2.0 3.0

Notes: (1) The reference group in subgroup analysis is patients with GADA-. The HRs of GADA+ for severe hypoglycemia were adjusted for age, sex, diabetes duration, year of assessment, HbA1c, BMI, TG to HDLc ratio, eGFR, baseline history of CVD, and baseline treatment of glucose lowering drugs and insulin.

Figure S7. Subgroup analysis of the associations between C-peptide levels stratified by 200 pmol/L and severe hypoglycemia
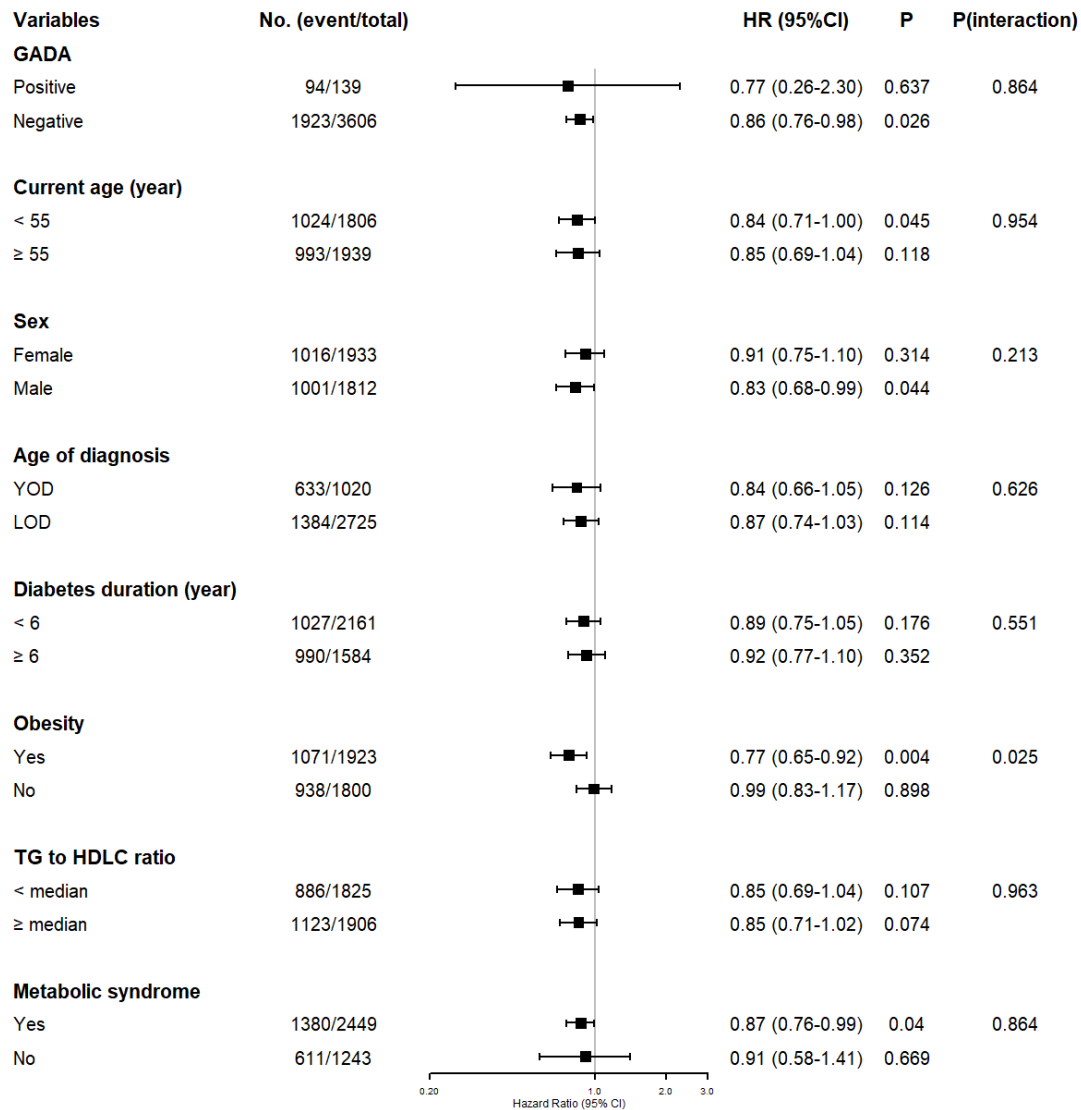
Variables	No. (event/total)	HR (95%CI)	P	P(interaction)
GADA				
Positive	62/244	1.73 (0.90-3.31)	0.098	0.009
Negative	783/4774	1.23 (1.04-1.47)	0.018	
Current age (year)				
< 55	316/2278	1.14 (0.87-1.48)	0.345	0.87
≥ 55	529/2740	1.41 (1.14-1.75)	0.001	
Sex				
Female	452/2634	1.46 (1.17-1.83)	0.001	0.91
Male	393/2384	1.15 (0.90-1.47)	0.249	
Age of diagnosis				
YOD	247/1434	1.16 (0.86-1.56)	0.328	0.497
LOD	598/3584	1.39 (1.14-1.70)	0.001	
Diabetes duration (year)				
< 6	277/2447	1.15 (0.85-1.57)	0.361	0.762
≥ 6	568/2571	1.40 (1.15-1.70)	<0.001	
Obesity				
Yes	391/2554	1.26 (0.98-1.62)	0.071	0.761
No	451/2432	1.27 (1.02-1.58)	0.036	
TG to HDLC ratio				
< median	405/2482	1.56 (1.24-1.97)	<0.001	0.006
≥ median	437/2518	1.01 (0.80-1.29)	0.907	
Metabolic syndrome				
Yes	555/3266	1.22 (1.03-1.46)	0.024	0.113
No	277/1638	1.83 (1.07-3.12)	0.027	

Hazard Ratio (95% CI)
0.50 1.0 2.0 3.0 5.0

Notes: (1) The reference group in subgroup analysis is patients with high CP (CP ≥ 200 pmol/L). The HRs of low CP (CP < 200 pmol/L) for severe hypoglycemia were adjusted for age, sex, diabetes duration, year of assessment, HbA1c, BMI, TG to HDLc ratio, eGFR, baseline history of CVD, and baseline treatment of glucose lowering drugs and insulin.

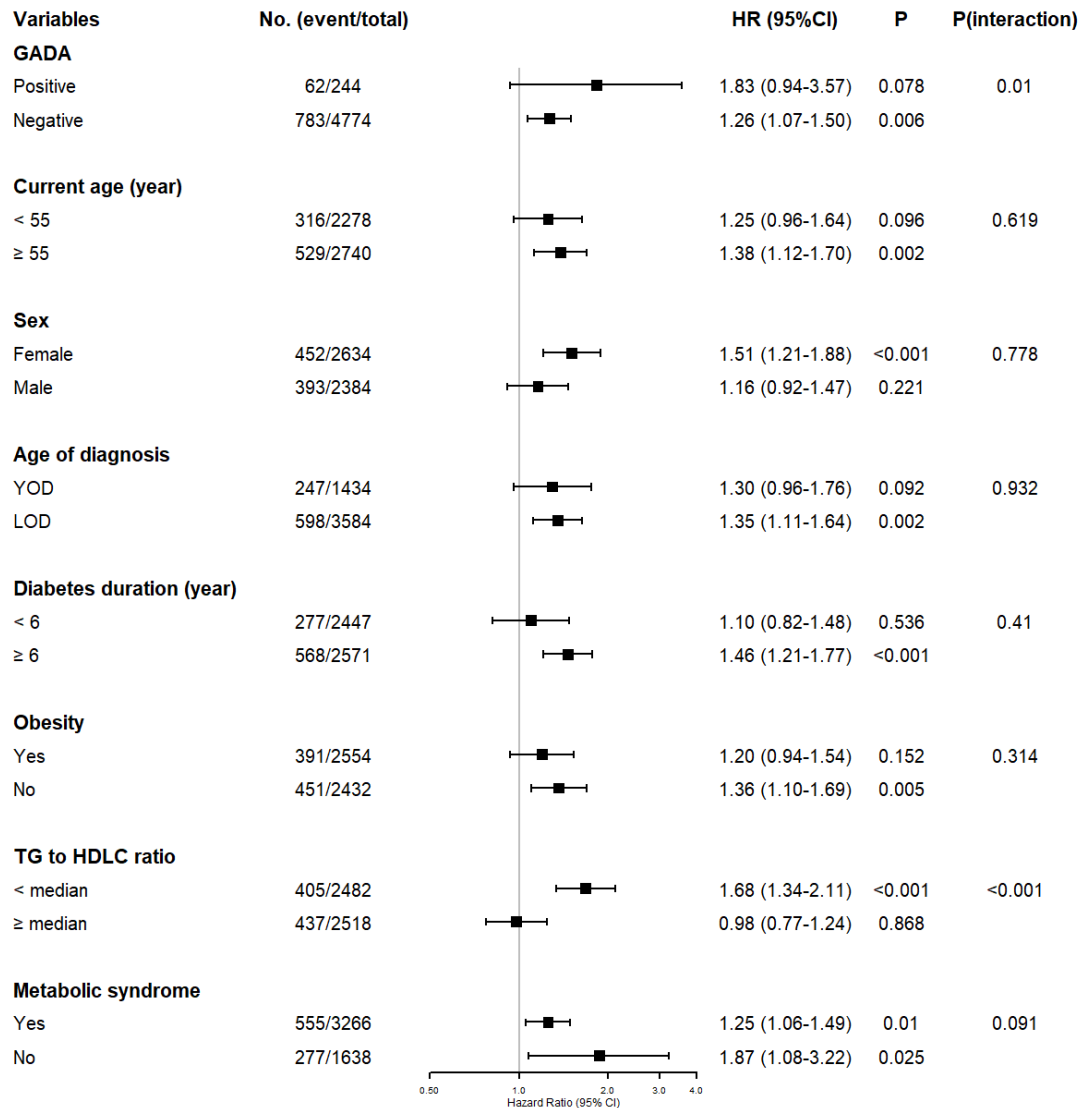Figure S8. Mean HbA1c changes from baseline to 6 and 12 months after insulin initiation
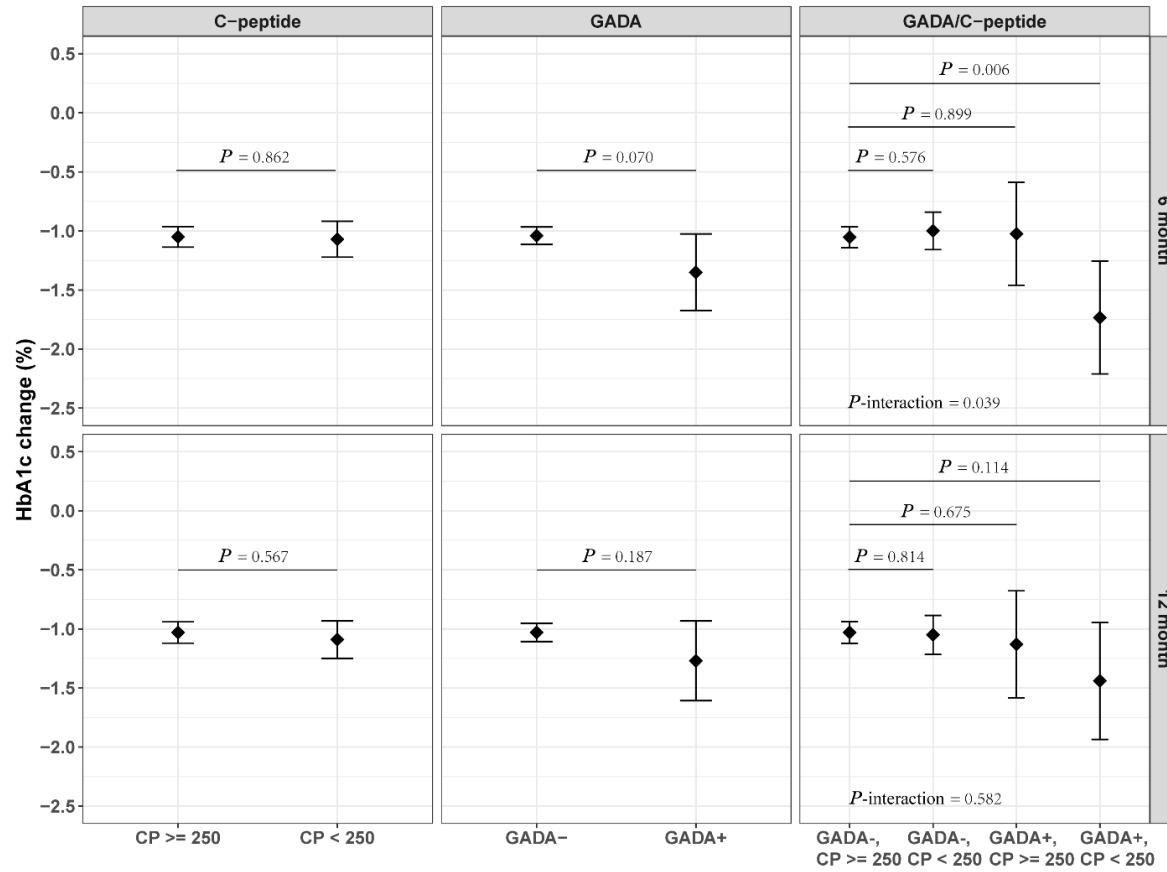
Notes: (1) Mean HbA1c changes at 6 months and 12 months after insulin initiation were adjusted for baseline HbA1c, age, sex, diabetes duration, and year of assessment. (2) The unit for CP is pmol/L. P-values were generated from the linear regression model with adjustments for covariates. The reference group was CP $\geq$ 250 pmol/L, GADA-, GADA- and CP $\geq$ 250 pmol/L, respectively.

Figure S9. Subgroup analysis of the associations between C-peptide levels stratified by 250 pmol/L and incident insulin therapy

Variables	No. (event/total)		HR (95%CI)	P	P(interaction)
GADA					
Positive	94/139		0.77 (0.26-2.30)	0.637	0.864
Negative	1923/3606		0.86 (0.76-0.98)	0.026	
Current age (year)					
< 55	1024/1806		0.84 (0.71-1.00)	0.045	0.954
≥ 55	993/1939		0.85 (0.69-1.04)	0.118	
Sex					
Female	1016/1933		0.91 (0.75-1.10)	0.314	0.213
Male	1001/1812		0.83 (0.68-0.99)	0.044	
Age of diagnosis					
YOD	633/1020		0.84 (0.66-1.05)	0.126	0.626
LOD	1384/2725		0.87 (0.74-1.03)	0.114	
Diabetes duration (year)					
< 6	1027/2161		0.89 (0.75-1.05)	0.176	0.551
≥ 6	990/1584		0.92 (0.77-1.10)	0.352	
Obesity					
Yes	1071/1923		0.77 (0.65-0.92)	0.004	0.025
No	938/1800		0.99 (0.83-1.17)	0.898	
TG to HDLC ratio					
< median	886/1825		0.85 (0.69-1.04)	0.107	0.963
≥ median	1123/1906		0.85 (0.71-1.02)	0.074	
Metabolic syndrome					
Yes	1380/2449		0.87 (0.76-0.99)	0.04	0.864
No	611/1243		0.91 (0.58-1.41)	0.669	

0.20 1.0 2.0 3.0
Hazard Ratio (95% CI)

Notes: (1) The reference group in subgroup analysis is patients with high CP (CP ≥ 250 pmol/L). The HRs of low CP (CP < 250 pmol/L) for incident insulin therapy were adjusted for age, sex, diabetes duration, year of assessment, HbA1c, BMI, TG to HDLc ratio, eGFR, and baseline treatment of oral glucose lowering drugs.

Figure S10. Subgroup analysis of the associations between C-peptide levels stratified by 250 pmol/L and severe hypoglycemia

Variables	No. (event/total)		HR (95%CI)	P	P(interaction)
GADA					
Positive	62/244		1.83 (0.94-3.57)	0.078	0.01
Negative	783/4774		1.26 (1.07-1.50)	0.006	
Current age (year)					
< 55	316/2278		1.25 (0.96-1.64)	0.096	0.619
≥ 55	529/2740		1.38 (1.12-1.70)	0.002	
Sex					
Female	452/2634		1.51 (1.21-1.88)	<0.001	0.778
Male	393/2384		1.16 (0.92-1.47)	0.221	
Age of diagnosis					
YOD	247/1434		1.30 (0.96-1.76)	0.092	0.932
LOD	598/3584		1.35 (1.11-1.64)	0.002	
Diabetes duration (year)					
< 6	277/2447		1.10 (0.82-1.48)	0.536	0.41
≥ 6	568/2571		1.46 (1.21-1.77)	<0.001	
Obesity					
Yes	391/2554		1.20 (0.94-1.54)	0.152	0.314
No	451/2432		1.36 (1.10-1.69)	0.005	
TG to HDLC ratio					
< median	405/2482		1.68 (1.34-2.11)	<0.001	<0.001
≥ median	437/2518		0.98 (0.77-1.24)	0.868	
Metabolic syndrome					
Yes	555/3266		1.25 (1.06-1.49)	0.01	0.091
No	277/1638		1.87 (1.08-3.22)	0.025	

Hazard Ratio (95% CI) 0.50 1.0 2.0 3.0 4.0

Notes: (1) The reference group in subgroup analysis is patients with high CP (CP ≥ 250 pmol/L). The HRs of low CP (CP < 250 pmol/L) for severe hypoglycemia were adjusted for age, sex, diabetes duration, year of assessment, HbA1c, BMI, TG to HDLc ratio, eGFR, baseline history of CVD, and baseline treatment of glucose lowering drugs and insulin.

Figure S11. Mean HbA1c changes from baseline to 6 and 12 months after insulin initiation in patients without advanced CKD at baseline
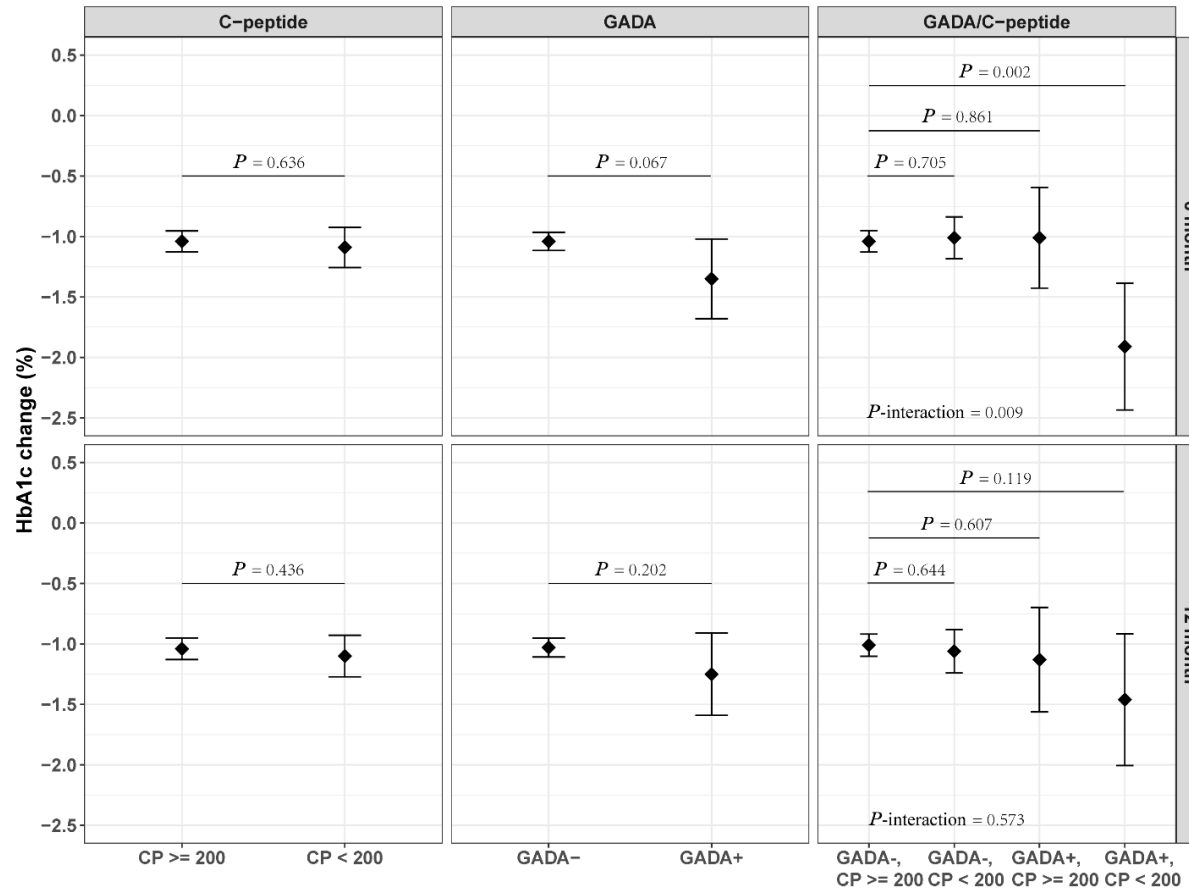
Notes: (1) Mean HbA1c changes at 6 months and 12 months after insulin initiation were adjusted for baseline HbA1c, age, sex, diabetes duration, and year of assessment. (2) The unit for CP is pmol/L. P-values were generated from the linear regression model with adjustments for covariates. The reference group was CP ⩾ 200 pmol/L, GADA-, GADA- and CP ⩾ 200 pmol/L, respectively.

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Figure S12 Mean HbA1c changes from the date of initiation to 6 and 12 months after insulin initiation in patients initiated with basal insulin only regimen
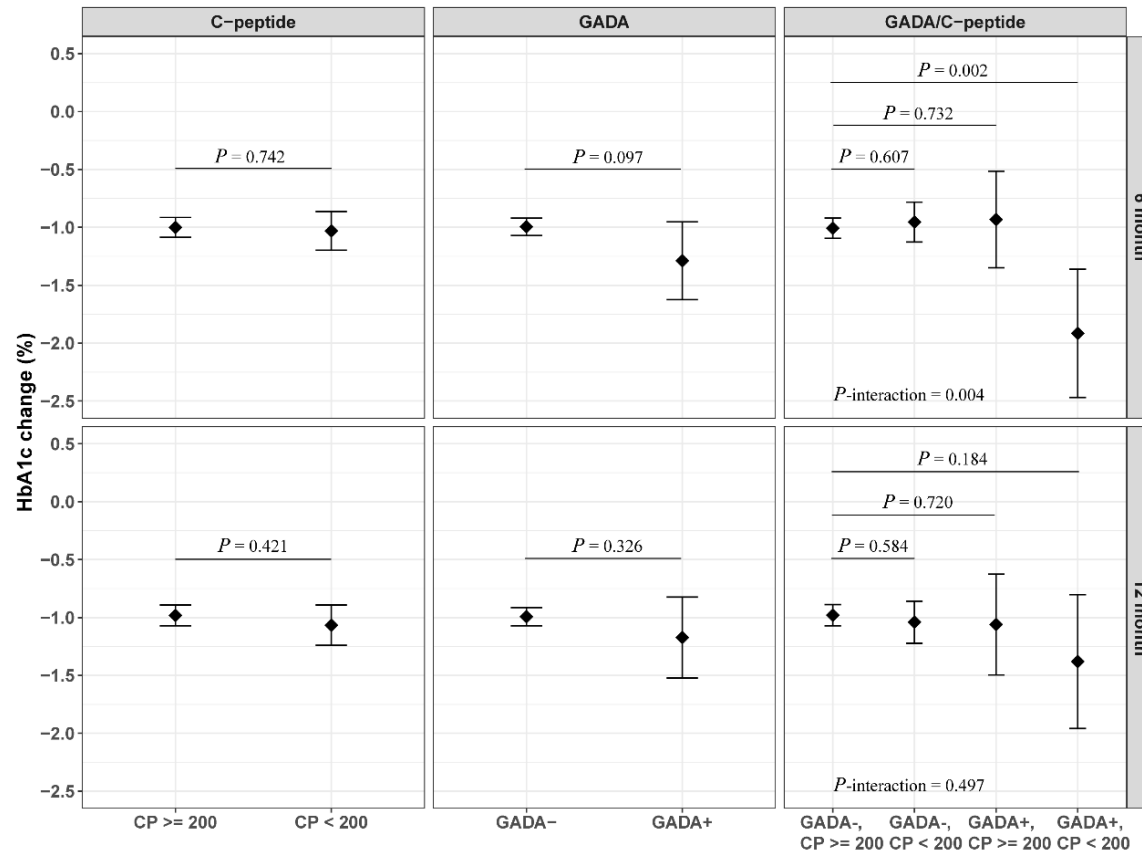
Notes: (1) Mean HbA1c changes at 6 months and 12 months after insulin initiation were adjusted for baseline HbA1c, age, sex, diabetes duration, and year of assessment. (2) The unit for CP is pmol/L. P-values were generated from the linear regression model with adjustments for covariates. The reference group was CP $\geqslant$ 200 pmol/L, GADA-, GADA- and CP $\geqslant$ 200 pmol/L, respectively.

Table S1. Baseline characteristics of patients with and without CP or GADA measurements

		With measurement	Without measurement	*P*
Number		5354	4462	
Age (year)		56.00 (14.27)	58.66 (13.46)	<0.001
Men, n (%)		2543 (47.6)	2124 (47.6)	0.976
Duration of diabetes (year)		6.0 [2.0, 12.0]	6.0 [1.0, 11.0]	<0.001
Age of diagnosis (year)		47.8 (13.8)	51.4 (13.0)	<0.001
Young-onset diabetes, n (%)		1592 (29.8)	656 (15.3)	<0.001
Family history of diabetes, n (%)		2432 (45.5)	1624 (36.4)	<0.001
Smoking, n (%)	Current	666 (12.5)	572 (12.9)	0.020
	Ex	839 (15.7)	783 (17.7)	
	Never	3828 (71.8)	3072 (69.4)	
Waist circumference (cm)	Men	89.3 (10.3)	87.8 (10.0)	<0.001
	Women	83.8 (10.4)	83.9 (10.1)	0.718
Body mass index (kg/m^2)		25.5 (4.3)	25.0 (4.0)	<0.001
Fasting plasma glucose (mmol/l)		8.4 (3.2)	8.8 (3.4)	<0.001
HbA1c (%)		7.6 (1.7)	7.7 (1.9)	0.004
Systolic blood pressure (mmHg)		132.6 (19.6)	137.1 (21.6)	<0.001
Diastolic blood pressure (mmHg)		73.7 (10.4)	76.7 (11.3)	<0.001
Total cholesterol (mmol/l)		5.0 (1.1)	5.3 (1.2)	<0.001
HDL-cholesterol (mmol/l)		1.4 (0.4)	1.3 (0.4)	<0.001
LDL-cholesterol (mmol/l)		2.8 (0.9)	3.2 (1.0)	<0.001
Triglycerides (mmol/l)		1.4 [1.0, 2.0]	1.4 [1.0, 2.1]	0.888
Urinary ACR (mg/mmol/L)		1.9 [0.7, 10.1]	2.4 [0.9, 13.5]	<0.001
eGFR (ml/min/1.73 m^2)		80.3 (26.1)	78.9 (25.6)	0.008
History of vascular complications at baseline				
Retinopathy, n (%)		1304 (27.2)	1188 (26.6)	0.577
Neuropathy, n (%)		929 (17.4)	1130 (25.3)	<0.001
Albuminuria, n (%)		2170 (41.4)	1945 (45.9)	<0.001
Chronic kidney disease, n (%)		1161 (21.7)	1053 (23.6)	0.027
End-stage kidney disease, n (%)		60 (1.1)	101 (2.3)	<0.001
Myocardial infarction, n (%)		136 (2.5)	343 (7.7)	<0.001
Congestive heart failure, n (%)		129 (2.4)	117 (2.6)	0.550
Coronary heart disease, n (%)		467 (8.7)	351 (7.9)	0.132
Peripheral vascular disease, n (%)		258 (4.8)	319 (7.1)	<0.001
Stroke, n (%)		184 (3.4)	144 (3.2)	0.597
Cardiovascular disease, n (%)		810 (15.1)	725 (16.2)	0.142
Cancer, n (%)		220 (4.1)	73 (1.6)	<0.001
Treatment at baseline				
Glucose lowering oral drugs, n (%)		3648 (74.6)	2756 (61.8)	<0.001
Insulin, n (%)		1108 (22.6)	787 (17.6)	<0.001
Lipid lowering drugs, n (%)		1281 (24.0)	604 (13.5)	<0.001
BP lowering drugs, n (%)		2671 (50.1)	1954 (43.8)	<0.001
RAS inhibitors, n (%)		1390 (29.0)	827 (18.5)	<0.001

Notes: (1) Data are expressed as mean (SD) or number (%) median [IQR]. (2) Abbreviations: ACR; albumin creatinine ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; RAS, renin angiotensin system; TG, triglycerides.

Table S2. Baseline characteristics of patients stratified by GADA status

		GADA+	GADA-	*P*
Number		257	4973	
Age (year)		50.2 (13.4)	56.81 (13.81)	<0.001
Men, n (%)		95 (37.0)	2396 (48.2)	0.001
Duration of diabetes (year)		5.0 [2.0, 12.0]	6.0 [1.0, 12.0]	0.958
Age of diagnosis (year)		42.3 (12.2)	48.7 (13.2)	<0.001
Young-onset diabetes, n (%)		127 (49.4)	1368 (27.5)	<0.001
Year of assessment (year)		2003 [2000, 2006]	2004 [2001, 2006]	0.253
Family history of diabetes, n (%)		125 (48.6)	2272 (45.7)	0.389
Smoking, n (%)	Current	34 (13.3)	623 (12.6)	0.013
	Ex	24 (9.4)	806 (16.2)	
	Never	198 (77.3)	3531 (71.2)	
Alcohol drinking, n (%)	Current	20 (7.8)	561 (11.3)	0.019
	Ex	18 (7.1)	546 (11.0)	
	Never	217 (85.1)	3837 (77.6)	
Waist circumference (cm)	Men	85.2 (11.5)	89.7 (10.0)	<0.001
	Women	78.9 (11.1)	84.4 (10.1)	<0.001
Body mass index (kg/m^2)		24.0 (4.8)	25.7 (4.2)	<0.001
Waist-hip-ratio		0.9 (0.1)	0.9 (0.1)	<0.001
Fasting plasma glucose (mmol/l)		9.3 (4.0)	8.3 (3.1)	<0.001
HbA1c (%)		8.3 (2.3)	7.6 (1.7)	<0.001
Systolic blood pressure (mmHg)		125.4 (19.5)	133.4 (19.4)	<0.001
Diastolic blood pressure (mmHg)		72.1 (11.3)	73.8 (10.3)	0.010
Total cholesterol (mmol/l)		5.1 (1.2)	5.0 (1.0)	0.451
HDL-cholesterol (mmol/l)		1.5 (0.5)	1.4 (0.4)	<0.001
LDL-cholesterol (mmol/l)		2.9 (0.9)	2.8 (0.9)	0.645
Triglycerides (mmol/l)		1.1 [0.7, 1.5]	1.4 [1.0, 2.1]	<0.001
Ratio of TG to HDL-C		0.8 [0.4, 1.2]	1.1 [0.7, 1.8]	<0.001
C-peptide (pmol/L)		366.5 (354.5)	517.4 (405.5)	<0.001
Urinary ACR (mg/mmol/L)		1.5 [0.7, 5.8]	2.0 [0.7, 10.8]	0.046
eGFR (ml/min/1.73 m^2)		88.8 (23.1)	79.2 (25.9)	<0.001
History of vascular complications at baseline				
Severe hypoglycemia, n (%)		13 (5.1)	199 (4.0)	0.499
Retinopathy, n (%)		43 (19.4)	1251 (27.7)	0.009
Neuropathy, n (%)		29 (11.4)	899 (18.1)	0.008
Albuminuria, n (%)		86 (34.3)	2066 (42.4)	0.014
Chronic kidney disease, n (%)		27 (10.5)	1131 (22.7)	<0.001
End-stage kidney disease, n (%)		0 (0.0)	60 (1.2)	0.141
Myocardial infarction, n (%)		7 (2.7)	128 (2.6)	1.000
Congestive heart failure, n (%)		5 (1.9)	123 (2.5)	0.744
Coronary heart disease, n (%)		19 (7.4)	447 (9.0)	0.445
Peripheral vascular disease, n (%)		12 (4.7)	242 (4.9)	1.000
Stroke, n (%)		0 (0.0)	183 (3.7)	0.003
Cardiovascular disease, n (%)		29 (11.3)	775 (15.6)	0.076
Cancer, n (%)		6 (2.3)	212 (4.3)	0.178
Treatment at baseline				
Glucose lowering oral drugs, n (%)		159 (68.8)	3480 (75.6)	0.026
Insulin, n (%)		118 (45.9)	1367 (27.5)	<0.001
Lipid lowering drugs, n (%)		37 (14.5)	1240 (25.0)	<0.001
BP lowering drugs, n (%)		100 (39.1)	2563 (51.6)	<0.001
RAS inhibitors, n (%)		65 (29.3)	1318 (29.1)	1.000

Notes: (1) Data are expressed as mean (SD) or number (%) median [IQR]. (2) Abbreviations: ACR; albumin creatinine ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; RAS, renin angiotensin system; TG, triglycerides.

Table S3. Baseline characteristics of patients stratified by C-peptide of 200 pmol/L

		CP < 200 pmol/L	CP ⩾ 200 pmol/L	*P*
Number		1494	3736	
Age (year)		51.7 (14.5)	58.4 (13.1)	<0.001
Men, n (%)		685 (45.9)	1806 (48.3)	0.110
Duration of diabetes (year)		8.0 [2.0, 15.0]	5.0 [1.0, 11.0]	<0.001
Age of diagnosis (year)		41.9 (12.4)	50.9 (12.6)	<0.001
Young-onset diabetes, n (%)		788 (52.7)	707 (18.9)	<0.001
Year of assessment (year)		2001 [1999, 2005]	2004 [2002, 2006]	<0.001
Family history of diabetes, n (%)		693 (46.4)	1704 (45.6)	0.633
Smoking, n (%)	Current	208 (14.0)	449 (12.1)	0.090
	Ex	220 (14.8)	610 (16.4)	
	Never	1063 (71.3)	2666 (71.6)	
Alcohol drinking, n (%)	Current	164 (11.1)	417 (11.2)	0.984
	Ex	161 (10.8)	403 (10.8)	
	Never	1159 (78.1)	2895 (77.9)	
Waist circumference (cm)	Men	87.2 (10.9)	90.4 (9.7)	<0.001
	Women	82.6 (11.1)	84.7 (9.9)	<0.001
Body mass index (kg/m^2)		25.1 (4.6)	25.8 (4.1)	<0.001
Waist-hip-ratio		0.9 (0.1)	0.9 (0.1)	<0.001
Fasting plasma glucose (mmol/l)		8.4 (3.5)	8.4 (3.0)	0.875
HbA1c (%)		7.8 (1.9)	7.5 (1.7)	<0.001
Systolic blood pressure (mmHg)		130.3 (19.6)	134.1 (19.3)	<0.001
Diastolic blood pressure (mmHg)		73.1 (10.4)	74.0 (10.4)	0.005
Total cholesterol (mmol/l)		5.0 (1.1)	5.0 (1.1)	0.502
HDL-cholesterol (mmol/l)		1.4 (0.4)	1.4 (0.4)	0.055
LDL-cholesterol (mmol/l)		2.9 (0.9)	2.8 (0.9)	0.011
Triglycerides (mmol/l)		1.2 [0.8, 1.8]	1.5 [1.0, 2.1]	<0.001
Ratio of TG to HDL-C		0.9 [0.6, 1.6]	1.1 [0.7, 1.8]	<0.001
C-peptide (pmol/L)		111.6 (27.8)	669.3 (373.9)	<0.001
Urinary ACR (mg/mmol/L)		1.9 [0.7, 10.4]	2.0 [0.7, 10.4]	0.665
eGFR (ml/min/1.73 m^2)		86.2 (26.7)	77.1 (25.0)	<0.001
History of vascular complications at baseline				
Severe hypoglycemia, n (%)		86 (5.8)	126 (3.4)	<0.001
Retinopathy, n (%)		374 (28.4)	920 (26.8)	0.294
Neuropathy, n (%)		289 (19.5)	639 (17.1)	0.049
Albuminuria, n (%)		583 (40.3)	1569 (42.6)	0.150
Chronic kidney disease, n (%)		256 (17.1)	902 (24.1)	<0.001
End-stage kidney disease, n (%)		17 (1.1)	43 (1.2)	1.000
Myocardial infarction, n (%)		34 (2.3)	101 (2.7)	0.433
Congestive heart failure, n (%)		28 (1.9)	100 (2.7)	0.110
Coronary heart disease, n (%)		103 (6.9)	363 (9.7)	0.001
Peripheral vascular disease, n (%)		84 (5.6)	170 (4.6)	0.119
Stroke, n (%)		40 (2.7)	143 (3.8)	0.050
Cardiovascular disease, n (%)		190 (12.7)	614 (16.4)	0.001
Cancer, n (%)		48 (3.2)	170 (4.6)	0.035
Treatment at baseline				
Glucose lowering oral drugs, n (%)		896 (64.9)	2743 (79.4)	<0.001
Insulin, n (%)		602 (40.3)	883 (23.6)	<0.001
Lipid lowering drugs, n (%)		283 (19.0)	994 (26.6)	<0.001
BP lowering drugs, n (%)		593 (39.9)	2070 (55.5)	<0.001
RAS inhibitors, n (%)		343 (26.0)	1040 (30.3)	0.004

Notes: (1) Data are expressed as mean (SD) or number (%) median [IQR]. (2) Abbreviations: ACR; albumin creatinine ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; RAS, renin angiotensin system; TG, triglycerides.

Table S4. Baseline characteristics of patients stratified by C-peptide of 250 pmol/L

		CP < 250 pmol/L	CP≥ 250 pmol/L	*P*
Number		1494	3736	
Age (year)		51.7 (14.5)	58.4 (13.1)	<0.001
Men, n (%)		685 (45.9)	1806 (48.3)	0.110
Duration of diabetes (year)		8.0 [2.0, 15.0]	5.0 [1.0, 11.0]	<0.001
Age of diagnosis (year)		41.94 (12.42)	50.92 (12.58)	<0.001
Young-onset diabetes, n (%)		788 (52.7)	707 (18.9)	<0.001
Year of assessment (year)		2001 [1999, 2005]	2004 [2002, 2006]	<0.001
Family history of diabetes, n (%)		693 (46.4)	1704 (45.6)	0.633
Smoking, n (%)	Current	208 (14.0)	449 (12.1)	0.090
	Ex	220 (14.8)	610 (16.4)	
	Never	1063 (71.3)	2666 (71.6)	
Alcohol drinking, n (%)	Current	164 (11.1)	417 (11.2)	0.984
	Ex	161 (10.8)	403 (10.8)	
	Never	1159 (78.1)	2895 (77.9)	
Waist circumference (cm)	Men	87.2 (10.9)	90.4 (9.7)	<0.001
	Women	82.6 (11.1)	84.7 (9.9)	<0.001
Body mass index (kg/m^2)		25.1 (4.6)	25.8 (4.1)	<0.001
Waist-hip-ratio		0.9 (0.1)	0.9 (0.1)	<0.001
Fasting plasma glucose (mmol/l)		8.4 (3.5)	8.4 (3.0)	0.875
HbA1c (%)		7.8 (1.9)	7.5 (1.7)	<0.001
Systolic blood pressure (mmHg)		130.3 (19.6)	134.1 (19.3)	<0.001
Diastolic blood pressure (mmHg)		73.1 (10.4)	74.0 (10.4)	0.005
Total cholesterol (mmol/l)		5.0 (1.1)	5.0 (1.1)	0.502
HDL-cholesterol (mmol/l)		1.4 (0.4)	1.4 (0.4)	0.055
LDL-cholesterol (mmol/l)		2.9 (0.9)	2.8 (0.9)	0.011
Triglycerides (mmol/l)		1.2 [0.8, 1.8]	1.5 [1.0, 2.1]	<0.001
Ratio of TG to HDL-C		0.9 [0.6, 1.6]	1.1 [0.7, 1.8]	<0.001
C-peptide (pmol/L)		111.6 (27.8)	669.3 (373.9)	<0.001
Urinary ACR (mg/mmol/L)		1.9 [0.7, 10.4]	2.0 [0.7, 10.4]	0.665
eGFR (ml/min/1.73 m^2)		86.2 (26.7)	77.1 (25.0)	<0.001
History of vascular complications at baseline				
Severe hypoglycemia, n (%)		86 (5.8)	126 (3.4)	<0.001
Retinopathy, n (%)		374 (28.4)	920 (26.8)	0.294
Neuropathy, n (%)		289 (19.5)	639 (17.1)	0.049
Albuminuria, n (%)		583 (40.3)	1569 (42.6)	0.150
Chronic kidney disease, n (%)		256 (17.1)	902 (24.1)	<0.001
End-stage kidney disease, n (%)		17 (1.1)	43 (1.2)	1.000
Myocardial infarction, n (%)		34 (2.3)	101 (2.7)	0.433
Congestive heart failure, n (%)		28 (1.9)	100 (2.7)	0.110
Coronary heart disease, n (%)		103 (6.9)	363 (9.7)	0.001
Peripheral vascular disease, n (%)		84 (5.6)	170 (4.6)	0.119
Stroke, n (%)		40 (2.7)	143 (3.8)	0.050
Cardiovascular disease, n (%)		190 (12.7)	614 (16.4)	0.001
Cancer, n (%)		48 (3.2)	170 (4.6)	0.035
Treatment at baseline				
Glucose lowering oral drugs, n (%)		896 (64.9)	2743 (79.4)	<0.001
Insulin, n (%)		602 (40.3)	883 (23.6)	<0.001
Lipid lowering drugs, n (%)		283 (19.0)	994 (26.6)	<0.001
BP lowering drugs, n (%)		593 (39.9)	2070 (55.5)	<0.001
RAS inhibitors, n (%)		343 (26.0)	1040 (30.3)	0.004

Notes: (1) Data are expressed as mean (SD) or number (%) median [IQR]. (2) Abbreviations: ACR; albumin creatinine ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; RAS, renin angiotensin system; TG, triglycerides.

Table S5. Baseline characteristics of patients stratified by C-peptide level of 250 pmol/L and GADA positivity

| | | Completeness (%) | GADA+ | | GADA- | | P* | P# | P |
			CP < 250 pmol/L	CP ≥ 250 pmol/L	CP < 250 pmol/L	CP ≥ 250 pmol/L			
Number			131	126	1584	3389			
Age (year)		100	47.5 (12.6)	53.0 (13.6)	52.8 (14.5)	58.7 (13.1)	0.001	<0.001	<0.001
Men, n (%)		100	51 (38.9)	44 (34.9)	752 (47.5)	1644 (48.5)	0.592	0.516	0.004
Duration of diabetes (year)		100	6.0 [2.0, 12.0]	5.0 [2.0, 12.0]	8.0 [2.0, 15.0]	5.0 [1.0, 11.0]	0.551	<0.001	<0.001
Age of diagnosis (year)		100	39.3 (11.5)	45.5 (12.2)	42.9 (12.6)	51.4 (12.5)	<0.001	<0.001	<0.001
Young-onset diabetes, n (%)		100	79 (60.3)	48 (38.1)	771 (48.7)	597 (17.6)	0.001	<0.001	<0.001
Year of assessment (year)		100	2001 [2000, 2005]	2004 [2001, 2006]	2001 [1999, 2005]	2004 [2002, 2006]	<0.001	<0.001	<0.001
Family history of diabetes, n (%)		100	79 (60.3)	48 (38.1)	771 (48.7)	597 (17.6)	0.761	0.470	<0.001
Smoking, n (%)	Current	99.73	16 (12.3)	18 (14.3)	224 (14.2)	399 (11.8)	0.459	0.047	0.015
	Ex		15 (11.5)	9 (7.1)	243 (15.4)	563 (16.7)			
	Never		99 (76.2)	99 (78.6)	1112 (70.4)	2419 (71.5)			
Alcohol drinking, n (%)	Current	99.41	10 (7.8)	10 (7.9)	184 (11.7)	377 (11.2)	0.651	0.846	0.180
	Ex		11 (8.5)	7 (5.6)	175 (11.1)	371 (11.0)			
	Never		108 (83.7)	109 (86.5)	1213 (77.2)	2624 (77.8)			
Waist circumference (cm)	Men		81.0 (10.7)	90.1 (10.5)	87.6 (10.8)	90.7 (9.5)	<0.001	<0.001	<0.001
	Women		75.1 (10.3)	82.6 (10.6)	83.3 (11.0)	84.9 (9.7)	<0.001	<0.001	<0.001
Body mass index (kg/m^2)		99.29	22.6 (4.4)	25.5 (4.8)	25.2 (4.5)	25.9 (4.0)	<0.001	<0.001	<0.001
Waist-hip-ratio		99.37	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	<0.001	<0.001	<0.001
Fasting plasma glucose (mmol/l)		99.85	9.9 (4.6)	8.7 (3.2)	8.3 (3.3)	8.4 (3.0)	0.018	0.175	<0.001
HbA1c (%)		99.62	8.8 (2.6)	7.8 (1.7)	7.7 (1.8)	7.5 (1.7)	<0.001	<0.001	<0.001
Systolic blood pressure (mmHg)		99.92	121.5 (19.3)	129.5 (19.0)	131.2 (19.6)	134.4 (19.2)	0.001	<0.001	<0.001
Diastolic blood pressure (mmHg)		99.90	70.0 (11.0)	74.3 (11.3)	73.3 (10.3)	74.1 (10.3)	0.002	0.007	<0.001
Total cholesterol (mmol/l)		98.41	5.2 (1.2)	4.9 (1.1)	5.0 (1.0)	5.0 (1.1)	0.021	0.630	0.067
HDL-cholesterol (mmol/l)		99.66	1.7 (0.6)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	<0.001	0.125	<0.001
LDL-cholesterol (mmol/l)		96.62	2.9 (1.0)	2.8 (0.9)	2.9 (0.9)	2.8 (0.9)	0.256	0.053	0.149
Triglycerides (mmol/l)		99.79	0.9 [0.6, 1.3]	1.2 [0.9, 1.6]	1.2 [0.9, 1.8]	1.5 [1.1, 2.2]	<0.001	<0.001	<0.001
Ratio of TG to HDL-C		99.66	0.6 [0.3, 1.0]	0.9 [0.6, 1.3]	0.9 [0.6, 1.6]	1.2 [0.8, 1.9]	<0.001	<0.001	<0.001
C-peptide (pmol/L)		79.29	117.3 (40.3)	625.6 (350.7)	127.0 (46.9)	699.9 (368.4)	<0.001	<0.001	<0.001
Urinary ACR (mg/mmol/L)		98.05	1.5 [0.7, 4.3]	1.6 [0.8, 5.8]	1.9 [0.7, 11.2]	2.0 [0.7, 10.5]	0.503	0.995	0.233

eGFR (ml/min/1.73 m^2)	99.79	91.5 (21.8)	86.1 (24.2)	85.1 (27.0)	76.5 (24.9)	0.064	<0.001	<0.001
History of vascular complications at baseline								
Severe hypoglycemia, n (%)	100	8 (6.1)	5 (4.0)	93 (5.9)	106 (3.1)	0.619	<0.001	<0.001
Retinopathy, n (%)	90.75	22 (20.6)	21 (18.3)	423 (30.2)	828 (26.5)	0.792	0.010	0.003
Neuropathy, n (%)	99.60	18 (14.0)	11 (8.7)	309 (19.6)	590 (17.5)	0.264	0.068	0.006
Albuminuria, n (%)	98.05	38 (29.9)	48 (38.7)	634 (41.4)	1432 (42.8)	0.182	0.380	0.026
Chronic kidney disease, n (%)	100	13 (9.9)	14 (11.1)	290 (18.3)	841 (24.8)	0.915	<0.001	<0.001
End-stage kidney disease, n (%)	100	0 (0.0)	0 (0.0)	19 (1.2)	41 (1.2)	-	1.000	0.371
Myocardial infarction, n (%)	100	1 (0.8)	6 (4.8)	36 (2.3)	92 (2.7)	0.113	0.412	0.176
Congestive heart failure, n (%)	100	4 (3.1)	1 (0.8)	27 (1.7)	96 (2.8)	0.390	0.022	0.060
Coronary heart disease, n (%)	100	6 (4.6)	13 (10.3)	114 (7.2)	333 (9.8)	0.129	0.003	0.006
Peripheral vascular disease, n (%)	100	8 (6.1)	4 (3.2)	89 (5.6)	153 (4.5)	0.413	0.106	0.255
Stroke, n (%)	100	0 (0.0)	0 (0.0)	49 (3.1)	134 (4.0)	-	0.155	0.007
Cardiovascular disease, n (%)	100	12 (9.2)	17 (13.5)	213 (13.4)	562 (16.6)	0.368	0.005	0.006
Cancer, n (%)	100	2 (1.5)	4 (3.2)	60 (3.8)	152 (4.5)	0.645	0.290	0.259
Treatment at baseline								
Glucose lowering oral drugs, n (%)	92.49	70 (60.9)	89 (76.7)	965 (66.2)	2515 (79.9)	0.014	<0.001	<0.001
Insulin, n (%)	100	74 (56.5)	44 (34.9)	620 (39.1)	747 (22.0)	0.001	<0.001	<0.001
Lipid lowering drugs, n (%)	99.75	11 (8.5)	26 (20.6)	313 (19.8)	927 (27.4)	0.010	<0.001	<0.001
BP lowering drugs, n (%)	99.79	35 (26.9)	65 (51.6)	656 (41.5)	1907 (56.4)	<0.001	<0.001	<0.001
RAS inhibitors, n (%)	90.75	24 (22.4)	41 (35.7)	371 (26.5)	947 (30.3)	0.044	0.011	0.010

Notes: (1) Data are expressed as mean (SD) or number (%) median [IQR]. (2) Abbreviations: ACR; albumin creatinine ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate; RAS, renin angiotensin system; TG, triglycerides. (3) *P* value was calculated by ANOVA for comparisons across four groups.

Table S6. Associations with incident insulin use and severe hypoglycemia in patients diagnosed with type 2 diabetes stratified by C-peptide level of 250 pmol/L and GADA status.

	Model 1		Model 2		Model 3		Model 4	
Insulin initiation								
	HR	P	HR	P	HR	P	HR	P
CP<250 vs. CP≥250 (pmol/L)	0.94 (0.85-1.04)	0.220	0.82 (0.74-0.92)	<0.001	0.88 (0.77-0.99)	0.041		
GADA+ vs. GADA-	1.61 (1.31-1.98)	<0.001	1.63 (1.32-2.02)	<0.001	1.46 (1.15-1.84)	0.002		
Severe hypoglycaemia								
	HR	P	HR	P	HR	P	HR	P
CP<250 vs. CP≥250 (pmol/L)	1.41 (1.23-1.62)	<0.001	1.43 (1.23-1.66)	<0.001	1.41 (1.21-1.64)	<0.001	1.31 (1.12-1.54)	<0.001
GADA+ vs. GADA-	1.55 (1.19-2.00)	<0.001	1.80 (1.38-2.33)	<0.001	1.57 (1.20-2.05)	<0.001	1.38 (1.04-1.83)	0.024

Notes: (1) We excluded patients with history of severe hypoglycemia for analysis of severe hypoglycemia while analysis of insulin initiation excluded patients treated with insulin at baseline; (2) In associations with incident insulin therapy, model 1 was crude model, model 2 was adjusted for age, sex, diabetes duration, and year of assessment, model 3 was adjusted for variables in model 2 and HbA1c, BMI, TG to HDLc ratio, eGFR, and baseline treatment of oral glucose lowering drugs. In associations with severe hypoglycemia, model 1 was crude model, model 2 was adjusted for age, sex, diabetes duration, and year of assessment, model 3 was adjusted for variables in model 2 and HbA1c, BMI, and TG to HDLc ratio, model 4 was adjusted for variables in model 3 and eGFR, baseline history of CVD, baseline treatment of glucose lowering drugs and insulin.

Table S7. Associations with insulin initiation and severe hypoglycemia in patients diagnosed with type 2 diabetes without advanced CKD at baseline stratified by C-peptide level of 200 pmol/L and GADA status.

	Model 1		Model 2		Model 3		Model 4	
Insulin initiation								
	HR	P	HR	P	HR	P		
CP<200 vs. CP≥200 (pmol/L)	0.94 (0.85-1.04)	0.207	0.81 (0.72-0.91)	<0.001	0.88 (0.77-1.00)	0.054		
GADA+ vs. GADA-	1.60 (1.30-1.97)	<0.001	1.61 (1.31-2.00)	<0.001	1.42 (1.12-1.81)	0.004		
Severe hypoglycaemia								
	HR	P	HR	P	HR	P	HR	P
CP<200 vs. CP≥200 (pmol/L)	1.39 (1.20-1.60)	<0.001	1.39 (1.19-1.63)	<0.001	1.36 (1.16-1.60)	<0.001	1.26 (1.06-1.49)	0.007
GADA+ vs. GADA-	1.55 (1.19-2.01)	0.001	1.78 (1.37-2.33)	<0.001	1.56 (1.19-2.05)	0.001	1.39 (1.05-1.85)	0.023

Notes: (1) We excluded patients with history of severe hypoglycemia for analysis of severe hypoglycemia while analysis of insulin initiation excluded patients treated with insulin at baseline; (2) In associations with incident insulin therapy, model 1 was crude model, model 2 was adjusted for age, sex, diabetes duration, and year of assessment, model 3 was adjusted for variables in model 2 and HbA1c, BMI, TG to HDLc ratio, eGFR, and baseline treatment of oral glucose lowering drugs. In associations with severe hypoglycemia, model 1 was crude model, model 2 was adjusted for age, sex, diabetes duration, and year of assessment, model 3 was adjusted for variables in model 2 and HbA1c, BMI, and TG to HDLc ratio, model 4 was adjusted for variables in model 3 and eGFR, baseline history of CVD, baseline treatment of glucose lowering drugs and insulin.

Table S8. Associations with insulin initiation and severe hypoglycemia in patients stratified by CP and GADA status in patients diagnosed with type 2 diabetes with available CP and GADA results after excluding patients with low fasting plasma glucose and/or hypoglycemia at baseline.

	Model 1		Model 2		Model 3		Model 4	
Exclude patients with baseline FBG < 4 mmol/L								
Insulin initiation								
	HR	P	HR	P	HR	P	HR	P
CP<200 vs. CP≥200 (pmol/L)	0.93 (0.84-1.03)	0.150	0.81 (0.72-0.91)	<0.001	0.88 (0.77-1.00)	0.049		
GADA+ vs. GADA-	1.60 (1.30-1.97)	<0.001	1.62 (1.31-2.00)	<0.001	1.43 (1.13-1.82)	0.003		
Severe hypoglycaemia								
	HR	P	HR	P	HR	P	HR	P
CP<200 vs. CP≥200 (pmol/L)	1.33 (1.15-1.54)	<0.001	1.39 (1.19-1.63)	<0.001	1.36 (1.16-1.59)	<0.001	1.29 (1.09-1.52)	0.003
GADA+ vs. GADA-	1.39 (1.06-1.83)	0.018	1.62 (1.23-2.14)	<0.001	1.42 (1.07-1.88)	0.015	1.24 (0.92-1.67)	0.156
Exclude patients with hypoglycemia history								
Insulin initiation								
	HR	P	HR	P	HR	P	HR	P
CP<200 vs. CP≥200 (pmol/L)	0.93 (0.84-1.03)	0.144	0.80 (0.71-0.90)	<0.001	0.87 (0.76-0.99)	0.034		
GADA+ vs. GADA-	1.61 (1.31-1.98)	<0.001	1.63 (1.32-2.02)	<0.001	1.48 (1.17-1.88)	0.001		

Notes: (1) We excluded patients with history of severe hypoglycemia for analysis of severe hypoglycemia while analysis of insulin initiation excluded patients treated with insulin at baseline; (2) For the associations with incident insulin therapy, model 1 was the crude model, model 2 was adjusted for age, sex, diabetes duration, and year of assessment, model 3 was adjusted for variables in model 2 and HbA1c, BMI, TG to HDLc ratio, eGFR, and baseline treatment of oral glucose lowering drugs. For the associations with severe hypoglycemia, model 1 was the crude model, model 2 was adjusted for age, sex, diabetes duration, and year of assessment, model 3 was adjusted for variables in model 2 and HbA1c, BMI, and TG to HDLc ratio, model 4 was adjusted for variables in model 3 and eGFR, baseline history of CVD, baseline treatment of glucose lowering drugs and insulin.

Table S9. Associations with insulin initiation and insulin requirement in patients stratified by CP and GADA status in patients diagnosed with type 2 diabetes with available data.

	Model 1		Model 2		Model 3	
Insulin initiation						
	HR	P	HR	P	HR	P
CP<200 vs. CP≥200 (pmol/L)	0.93 (0.84-1.03)	0.160	0.81 (0.72-0.91)	<0.001	0.88 (0.77-1.00)	0.051
GADA+ vs. GADA-	1.61 (1.31-1.98)	<0.001	1.63 (1.32-2.02)	<0.001	1.46 (1.15-1.84)	0.002
Insulin requirement						
	HR	P	HR	P	HR	P
CP<200 vs. CP≥200 (pmol/L)	1.08 (0.99-1.19)	0.097	0.88 (0.79, 0.98)	0.016	0.93 (0.82, 1.04)	0.201
CP<250 vs. CP≥250 (pmol/L)	1.08 (0.99-1.18)	0.082	0.89 (0.80, 0.98)	0.023	0.95 (0.85, 1.06)	0.337
GADA+ vs. GADA-	1.44 (1.18-1.76)	<0.001	1.40 (1.14-1.71)	0.001	1.44 (1.17-1.77)	<0.001

Notes: (1) Model 1 was the crude model, model 2 was adjusted for age, sex, diabetes duration, and year of assessment, model 3 was adjusted for variables in model 2 and HbA1c, BMI, TG to HDLc ratio, eGFR, and baseline treatment with oral glucose lowering drugs.

Table S10. Associations with severe hypoglycemia with adjustment for baseline insulin use with regimens in patients diagnosed with type 2 diabetes stratified by CP and GADA.

	Model 1		Model 2		Model 3		Model 4	
Severe hypoglycaemia								
	HR	P	HR	P	HR	P	HR	P
CP<200 vs. CP≥200 (pmol/L)	1.30 (1.12-1.50)	<0.001	1.39 (1.18-1.63)	<0.001	1.37 (1.17-1.61)	<0.001	1.29 (1.09-1.53)	0.003
GADA+ vs. GADA-	1.53 (1.17-2.01)	0.002	1.79 (1.36-2.34)	<0.001	1.58 (1.19-2.08)	<0.001	1.39 (1.04-1.87)	0.027

Notes: (1) Among 5018 patients free of history of severe hypoglycaemia, 1358 were treated with insulin at baseline. Amongst them, 926 (68.2%) were treated with basal insulin only, 82 (6.0%) with basal-bolus insulin regimen, 67 (4.9%) with prandial insulin only or prandial plus premixed insulin, 178 (13.1%) with premixed insulin, 105 (7.7%) without regimen information. (2) Model 1 was crude model, model 2 was adjusted for age, sex, diabetes duration, and year of assessment, model 3 was adjusted for variables in model 2 and HbA1c, BMI, and TG to HDLc ratio, model 4 was adjusted for variables in model 3 and eGFR, baseline history of CVD, baseline treatment of glucose lowering drugs, history of insulin use stratified by regimens.

Table S11. Subgroup analysis of associations of GADA positivity and C-peptide levels with insulin initiation and severe hypoglycemia stratified by the median of glucose:CP ratio.

Outcomes	Subgroup	Variable	HR	P	P (interaction)
Insulin initiation					
	Glucose:CP ratio				
	Below median	GADA+ vs. GADA-	1.49 (0.93-2.38)	0.099	0.537
	Above median	GADA+ vs. GADA-	1.80 (1.20-2.72)	0.005	
	Below median	Per 1-unit decrease of CP (nmol/L)	0.73 (0.59-0.90)	0.003	0.326
	Above median	Per 1-unit decrease of CP (nmol/L)	0.74 (0.44-1.25)	0.259	
Severe hypoglycaemia					
	Glucose:CP ratio				
	Below median	GADA+ vs. GADA-	1.14 (0.56-2.32)	0.720	0.750
	Above median	GADA+ vs. GADA-	0.89 (0.54-1.49)	0.669	
	Below median	Per 1-unit decrease of CP (nmol/L)	0.92 (0.63-1.33)	0.659	0.036
	Above median	Per 1-unit decrease of CP (nmol/L)	1.37 (0.73-2.56)	0.333	

Notes: (1) In associations with incident insulin therapy, the model was adjusted for age, sex, diabetes duration, year of assessment, HbA1c, BMI, TG to HDLc ratio, eGFR, baseline treatment of oral glucose lowering drugs. In associations with severe hypoglycemia, the model was adjusted for age, sex, diabetes duration, year of assessment, HbA1c, BMI, TG to HDLc ratio, eGFR, baseline history of CVD, baseline treatment of glucose lowering drugs and insulin.