The association of basal insulin treatment versus standard care with outcomes in anti-GAD positive and –negative subjects. A post-hoc analysis of the ORIGIN-trial.

Short title: Anti-GAD positivity and cardiovascular outcomes

Kåre I. Birkeland
Department of transplantation medicine, Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway

Valdemar Grill
Department of Endocrinology, St. Olav's Hospital, Trondheim, Norway

Cecilie Wium
Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway

Matthew J. McQueen, Department of Pathology and Molecular Medicine, Population Health Research Institute, McMaster University Hamilton Health Sciences, Hamilton, Ontario, Canada

Patricio Lopez-Jaramillo, Research Institute, FOSCAL, Bucaramanga, Colombia and Universidad Tecnológica Equinoccial, Facultad de Ciencias de la Salud Eugenio Espejo, Quito, Ecuador

Shun Fu Lee, Population Health Research institute, McMaster University, Hamilton Health Sciences, Hamilton, Ontario, Canada

Hertzel C. Gerstein
Department of Medicine, Population Health Research institute, McMaster University,

Hamilton Health Sciences, Hamilton, Ontario, Canada

Corresponding author: Kåre I. Birkeland, Department of transplantation medicine, Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway

Telephone: +47 23071181 or +47 92830675

email: k.i.birkeland@medisin.uio.no

Postal address: Oslo University Hospital. P.O. BOX 4950, Nydalen, 0424, OSLO, NORWAY

Word count: 1 767

Word count abstract: 158

Tables: 2 + 4 Supplementary

Figures: None

Abstract

We compared cardiovascular and other outcomes in patients with dysglycaemia with or without anti-GAD antibodies participating in the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial. Of the 12 537 participants, 8162 had anti-GAD measured at baseline and 267 were anti-GAD positive. The effects of insulin glargine versus standard care and of n-3 fatty acids supplements versus placebo were compared by testing the interaction of the treatment effects and anti-GAD status. The effect of glargine on development of new diabetes was assessed in participants without previous diabetes at baseline. The overall incidence of outcomes did not differ between anti-GAD positive and anti-GAD negative subjects. The incidence of the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke did not differ between anti-GAD positive participants randomized to insulin glargine or to standard care, with a hazard ratio (HR) [95% confidence interval (CI)] of 0.80 [0.44-1.44] or in anti-GAD negative participants with a HR of 1.07 [0.96-1.20] (P for interaction=0.20).

Trial Registration: clinicaltrials.gov Identifier: NCT00069784

Keywords: anti-GAD, type 2 diabetes, CVD

Abbreviations:

ACE	Angiotensin converting enzyme
ARB	Angiotensin 2 receptor blocker
CVD	Cardiovascular disease
GAD	Glutamic acid dehydrogenase

Diabetes is a heterogeneous metabolic disorder with varying degrees of insulin resistance and dysfunction of insulin secretion. Type 1 diabetes typically occurs due to autoimmune damage to the insulin secreting islet cells, and affected patients often have circulating antibodies directed towards islet cell antigens, most often glutamic acid decarboxylase (anti-GAD antibodies). Type 2 diabetes are not due to autoimmunity, however a subset of subjects with phenotypically type 2 diabetes have anti-GAD antibodies in their serum. Compared to seronegative individuals, those with anti-GAD antibodies have more pronounced beta cell dysfunction and less insulin resistance (1). Limited data suggest that cardiovascular comorbidity and mortality in such individuals are comparable to that of other people with type 2 diabetes (2-6). However, the effect of different treatment regimens on clinical outcomes in the subgroup that are anti-GAD positive remains poorly studied.

The ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial allocated 12,537 participants with either prediabetes or diabetes to receive either titrated basal insulin glargine targeting a normal fasting plasma glucose ≤5.3 mmol/l or standard care; 12 536 of these individuals were also allocated to either 1 g of ethyl esters of n-3 fatty acids or placebo.

A subset of 8162 of the participants had serum levels of anti-GAD measured at baseline. Here we report cardiovascular, microvascular and glycaemic outcomes in anti-GAD positive and negative subjects.

MATERIALS AND METHODS

The detailed design of the ORIGIN trial and the main results have been published previously (7-11). Episodes of hypoglycemia confirmed by a self-measured glucose level of 3.0 mmol/l or less were prospectively recorded. All participants gave written informed consent, and a subset also provided consent for the storage and subsequent analyses of blood samples drawn at the time of randomization.

ORIGIN was designed and conducted by an international steering committee of academic investigators lead by Prof. Hertzel C. Gerstein. It was funded by Sanofi, which also provided regulatory support, site monitoring and insulin glargine (Lantus). Pronova BioPharma Norge AS supplied the n-3 fatty acid supplements (Omacor) and placebo. The study was approved by the ethics committee at each center, and all participants gave written informed consent Eligible participants were randomized to the two interventions using a 2 x 2 factorial design

and then seen at the study center after 0.5, 1, 2 and 4 months and thereafter every 4 months until the study ended after a median (interquartile range) follow-up of 6.2 (5.8-6.8) years.

Outcomes

The two co-primary outcomes were 1) a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke and 2) a composite of any of these events, a revascularization procedure, or hospitalization for heart failure. Non-severe hypoglycemic episodes since the previous visit were recorded at each visit and patients with HbA1C levels ≤6% (42 mmol/mol) at the end of the study were also considered.

Laboratory methods

Anti-GAD was assayed at the Clinical Research Laboratory and Biobank at the Population Health Research Institute in Hamilton, Canada. All assays were done blinded to treatment allocation and other clinical characteristics, using the commercially available Kronus anti-GAD ELISA kit (Star Idaho 83669, USA). Results were reported as international units/ml and were considered negative if the concentration was < 5 IU/ml. This assay had a coefficient of variation of 2.89% at a mean level of 54.2 IU/ml, and 0.56% at a mean level of 2.06 IU/ml. C-peptide was measured in fasting samples using a multiplex assay (Myriad RBM Inc., USA) as previously reported (12).

Statistical analyses

All statistical analyses were done using SAS 9.4 for UNIX (SAS Institute Inc., Cary, North Carolina, USA). The effect of each intervention on outcomes was analyzed using Cox regression models stratified according to the factorial allocation, baseline diabetes status and prior cardiovascular event (8). Whether the effect of the intervention differed according to anti-GAD antibody positivity was assessed by including the anti-GAD status in the Cox model as well as an interaction term between the status and treatment allocation.

The relationship between anti-GAD status and an achieved fasting plasma glucose of ≤5.3 mmol/l after two years of treatment was analyzed using logistic regression with adjustment for age, sex and the variables with p-values (P) <0.1 in the univariate analysis. Finally, the effect of antibody positivity on the dose of insulin required to achieve normal glycaemia at 2 years in the subgroup of participants who were allocated to insulin glargine was evaluated

using the similar approach with the linear regression. The nominal level of significance for all the analyses was p value less than 0.05.

For participants without diabetes at baseline, the effect of the glargine on the development of new diabetes in anti-GAD positive and negative individuals were assessed using a Cochran–Mantel–Haenszel (CMH) test stratified by factorial allocation and adjusted for a history of a prior cardiovascular event. For consistency, the odds ratios (OR) with 95% CI were calculated based on the CMH test, but the interaction between allocation to glargine and both the n-3 fatty acid allocation and the anti-GAD status was assessed using generalized linear models.

RESULTS

The mean (SD) age of the 8162 participants included in this study was 63.7 (8.0) years, 33.8% were female, and 81.5% had prior diabetes (Table 1). The mean levels of blood pressure and lipids at baseline did not differ between anti-GAD positive and negative participants (Table 1). The use of ACE-inhibitors/angiotensin 2-receptor blockers was higher among anti-GAD positive participants. The participants included in this sub-study of the ORIGIN trial did not differ substantially in baseline characteristics compared to those not included (Supplementary Tables 1 and 2).

Compared to 7895 anti-GAD-negative participants, the 267 anti-GAD-positive participants had a higher prevalence of diagnosed diabetes at baseline (86.5% vs 81.3%, p=0.031) and more thyroid disease (10.9% vs 7.4%, p= 0.034).

Cardiovascular and microvascular outcomes overall and according to glargine and n-3 fatty acid allocation

The overall incidence of the first co-primary outcome did not differ significantly between anti-GAD positive and negative patients (3.06/100 patient-years vs 2.92/100 patient-years (Table 2.) Neither did the incidence of this outcome differ between anti-GAD positive participants randomized to insulin glargine or to standard glucose lowering treatment, with a HR [95% confidence interval] 0.80 [0.44-1.44] (Table 2), or to n-3 fatty acids or placebo with a HR 0.98 [0.54-1.78] (Supplementary Table 3). Furthermore, the incidence of the second co-primary outcome or all-cause death did not differ between anti-GAD positive and negative individuals, and neither between anti-GAD positive participants randomized to insulin

glargine or to standard treatment, or to participants randomized to n-3 fatty acids or placebo (Tables 2 and Supplementary Table 3).

The overall incidence of microvascular outcomes was 2.34/100 patient-years in anti-GAD positive participants and 3.93/100 patient-years in anti-GAD negative participants. The HR for the combined microvascular endpoint in anti-GAD positive participants randomized to glargine vs standard treatment was 1.02 [0.50-2.09].

Effects on glycaemic control

The incidence of achieving HbA1c ≤6.0% (42 mmol/mol) at study end did not differ between anti-GAD-positive individuals randomized to insulin glargine or standard care (Table 2).

The number of non-severe, symptomatic hypoglycaemic episodes was not different between anti-GAD positive or negative participants (7.20 vs 5.99/100 patient-years).

Between randomization and approximately one month after all study interventions were stopped at the end of the trial (when an oral glucose tolerance test was administered to people not diagnosed with diabetes by that time), both anti-GAD positive and negative participants who had been allocated to insulin glargine had a lower incidence of diabetes compared to controls (24.5% vs 31.6%, p=0.014) with no difference between groups (P for interaction=0.16). This effect was attenuated when tested approximately two months later (Supplementary Table 4, data not shown).

DISCUSSION

The distinction between type 1 and type 2 diabetes has usually been based upon age of onset, the severity of beta cell failure and insulin resistance, and the presence of diabetes-associated auto-antibodies. Of interest, in the present study we observed no differences in duration of diabetes, age at diagnosis or ethnic distribution between anti-GAD negative and positive individuals, but more anti-GAD-positive participants had diabetes at inclusion.

The major findings in the present study were that the overall incidence of cardiovascular outcomes was similar in anti-GAD positive and negative patients, and that incidence of major cardiovascular events did not differ between anti GAD-positive participants randomized to insulin glargine or standard glucose lowering treatment, or to n-3 fatty acids or placebo.

We confirm the results from previously published observational studies that report at least as high rates of cardiovascular endpoints and mortality in anti-GAD-positive individuals as in the typical form of anti-GAD-negative patients with phenotypically type 2 diabetes (2-5). This may be a reminder of the importance of hyperglycemia per se as a risk factor for cardiovascular disease.

As previously reported from the full ORIGIN cohort, we found a reduced incidence of new diabetes in the group treated with insulin glargine when OGTT was performed one month after stopping treatment in subjects without diabetes at baseline. The effect was found in both anti-GAD positive and negative individuals. The mean fasting levels of C-peptide at baseline did not differ significantly between the groups, indicating the participants with signs of autoimmune diabetes still had significant endogenous insulin secretion.

The prevalence of anti-GAD antibodies in our cohort was 3.2% and lower than in many previously reported studies, where numbers usually range from 5-14% (3, 15, 16). This may partly be due to the selection of study participants in ORIGIN. Participants were recruited globally, were 50 years or older with vascular disease, were required to be insulin-naïve and had short duration of diabetes or only prediabetes at baseline. This probably resulted in a selected group of anti-GAD positive participants that may differ from an unselected group in a population-based sample.

Strengths of the present study include the randomized controlled design testing relevant therapeutic options a relatively long follow-up. Possible weaknesses are the post-hoc nature, the low number of anti-GAD-positive participants and therefore wide confidence intervals to our effect estimates and limited power to detect effects of interventions in anti-GAD positive subjects, and the afore-mentioned possible selection bias. We also chose to measure only anti-GAD among several autoantibodies known to be associated with autoimmune diabetes. Furthermore, we cannot exclude that the findings may be different in subgroups of patients i.e. with high or low levels of C-peptide or low anti-GAD titers. Due to the limited number of anti-GAD positive individuals in our study, this could not be explored further here.

In conclusion, we report that anti-GAD positive participants included in the ORIGIN study had a similar incidence of cardiovascular outcomes as anti-GAD negative subjects, and that

early insulin treatment had a neutral effect compared with standard anti-hyperglycaemic treatment on important outcomes in anti-GAD-positive individuals.

Acknowledgements. K.I.B. and H.C.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding. The ORIGIN trial was funded by Sanofi, who also provided regulatory support, site monitoring and insulin glargine. Pronova Bio Pharma Norge supplied the n-3 fatty acids supplements and placebo.

Duality of Interest. KIB or his employer has received lecture and consultancy fees from Boehringer-Ingelheim, Novo Nordisk, Sanofi, MSD, Astra Zeneca and Lilly, for use in research. CW has received lecture and consultancy fees from Boehringer-Ingelheim, Novo Nordisk, Sanofi, MSD, Astra Zeneca, Lilly, GlaxoSmithKline and Bristol-Myers Squibb. HCG is supported by the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care and has received research grant support from Sanofi, Lilly, AstraZeneca and Merck, honoraria for speaking from Sanofi, Novo Nordisk, Abbot and AstraZeneca, and consulting fees from Sanofi, Lilly, AstraZeneca, Merck, Novo Nordisk, Abbot, Amgen, and Boehringer Ingelheim.

Author Contributions. K.I.B. and H.C.G. developed the study concept and design, performed the analysis and interpretation of data, drafted the manuscript, performed critical revision of the manuscript for important intellectual content, and performed statistical analysis. V.G., C.W., M.J.M., P.L-J., S.F.L. performed critical revision of the manuscript for important intellectual content.

References

1. Isomaa B, Almgren P, Henricsson M, Taskinen MR, Tuomi T, Groop L, et al. Chronic complications in patients with slowly progressing autoimmune type 1 diabetes (LADA). Diabetes Care. 1999;22(8):1347-53.

2. Laugsand LE, Janszky I, Vatten LJ, Dalen H, Midthjell K, Grill V, et al. Autoimmune diabetes in adults and risk of myocardial infarction: the HUNT study in Norway. J Intern Med. 2016.
3. Olsson L, Grill V, Midthjell K, Ahlbom A, Andersson T, Carlsson S. Mortality in adult-onset autoimmune diabetes is associated with poor glycemic control: results from the HUNT Study. Diabetes Care. 2013;36(12):3971-8.
4. Myhill P, Davis WA, Bruce DG, Mackay IR, Zimmet P, Davis TM. Chronic complications and mortality in community-based patients with latent autoimmune diabetes in adults: the Fremantle Diabetes Study. Diabet Med. 2008;25(10):1245-50.
5. Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. Diabetes Care. 2008;31(4):714-9.
6. Hernández M, López C, Real J, Valls J, Ortega-Martinez de Victoria E, Vázquez F, Rubinat E, Granado-Casas M, Alonso N, Molí T, Betriu A, Lecube A, Fernández E, Leslie RD, Mauricio D. Preclinical carotid atherosclerosis in patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes and classical type 1 diabetes. Cardiovasc Diabetol. 2017 Jul 28;16(1):94.
7. Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). American heart journal. 2008;155(1):26-32, .e1-6.
8. Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, Maggioni AP, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367(4):319-28.
9. Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012;367(4):309-18.
10. Gilbert RE, Mann JF, Hanefeld M, Spinas G, Bosch J, Yusuf S, et al. Basal insulin glargine and microvascular outcomes in dysglycaemic individuals: results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial. Diabetologia. 2014;57(7):1325-31.
11. Bordeleau L, Yakubovich N, Dagenais GR, Rosenstock J, Probstfield J, Chang Yu P, et al. The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. Diabetes Care. 2014;37(5):1360-6.
12. Chow LS, Chen H, Miller ME, Marcovina SM, Seaquist ER. Biomarkers related to severe hypoglycaemia and lack of good glycaemic control in ACCORD. Diabetologia. 2015;58(6):1160-6.
13. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay I, et al. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. Lancet. 1997;350:1288-93.
14. Niskanen LK, Tuomi T, Karjalainen J, Groop LC, Uusitupa MI. GAD antibodies in NIDDM. Ten-year follow-up from the diagnosis. Diabetes Care. 1995;18(12):1557-65.
15. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. Lancet. 2014;383(9922):1084-94.

307 **Table 1: Baseline Characteristics of Study Participants**

Variable	All Participants (n=8162)	Anti-GAD Positive (n=267)	Anti-GAD Negative (n=7895)	P
Age, years	63.7 (8.0)	64.0 (8.0)	63.7 (8.0)	0.566
Females	2757 [33.8]	99 [37.1]	2658 [33.7]	0.246
Prior Diabetes	6649 [81.5]	231[86.5]	6418[81.3]	0.031
Duration of diabetes, years	5.2 (5.8)	5.3 (5.7)	5.2 (5.8)	0.838
New diabetes	533 [6.5]	10 [3.7]	523 [6.6]	0.061
Prior CVD	4840 [59.3]	155 [58.1]	4685 [59.3]	0.671
Thyroid disease	612 [7.5]	29 [10.9]	583 [7.4]	0.034
Ethnic Background				
White	4940 [60.5]	159 [59.6]	4781 [60.6]	0.737
Black	353 [4.3]	11 [4.1]	342 [4.3]	0.866
South Asian	439 [5.4]	11 [4.1]	428 [5.4]	0.353
Other Asian	38 [0.5]	2 [0.7]	36 [0.5]	0.489
Latin	2191[26.9]	78 [29.2]	2113[26.8]	0.376
Other	199 [2.4]	6 [2.2]	193 [2.4]	0.837
Prior Gestational Diabetes	103 [3.7]	2 [2.0]	101 [3.8]	0.359
Hypertension	6456 [79.1]	216 [80.9]	6240 [79.0]	0.464
Smoker	1007 [12.3]	26 [9.7]	981 [12.4]	0.189
Alcohol > 2 /week	2014 [24.7]	65 [24.3]	1949 [24.7]	0.898
Education Level				
Education < 8 y	3132 [38.4]	103 [38.6]	3029 [38.4]	0.947
Education 9-12 y	2150 [26.5]	59 [22.1]	2091 [26.5]	0.109
Education > 12 y	2878 [35.1]	105 [39.3]	2773 [35.1]	0.158
BMI (kg/m2)	30.1(5.3)	29.6(4.9)	30.1(5.3)	0.140
Systolic BP (mmHg)	146.3 (21.8	146.6 (21.3)	146.3 (21.8)	0.797
Diastolic BP (mmHg)	84.4 (12.1)	84.8 (12.9)	84.4 (12.1)	0.668
Creatinine (μmol/l)	89.3 (22.2)	88.2 (20.8)	89.3 (22.2)	0.394
ACR > 30 mg/g	1550 [19.3]	55 [20.8]	1495 [19.1]	0.511
HDL-cholesterol, mmol/l	1.18 (0.32)	1.18 (0.32)	1.18 (0.32)	0.896
Triglycerides, mmol/l*	1.60 (1.14- 2.20)	1.56 (1.13- 2.10)	1.60 (1.12- 2.20)	0.536
LDL-cholesterol, mmol/l	2.89 (1.02)	2.84 (1.00)	2.90 (1.02)	0.369

Variable	All Participants (n=8162)	Anti-GAD Positive (n=267)	Anti-GAD Negative (n=7895)	P
Total cholesterol, mmol/l	4.87 (1.15)	4.78 (1.12)	4.88 (1.15)	0.186
HbA1c, %	6.50 (0.94)	6.46 (0.93)	6.50 (0.95)	0.538
HbA1c, mmol/mol	47 (10.3)	47 (10.2)	47 (10.4)	0.538
F-Plasma Glucose, mmol/l	7.3 (2.0)	7.3 (1.9)	7.3 (2.0)	0.763
Statin users	4488 [55.0]	140 [52.4]	4348 [55.1]	0.393
ACE/ARB users	5635[69.0]	199[74.5]	5436[68.9]	0.049
Beta Blocker users	4398 [53.9]	143 [53.6]	4255 [53.9]	0.912
Thiazide users	1502 [18.4]	53 [19.9]	1449 [18.4]	0.535
C peptide (nmol/l)**	0.25 (0.86)	0.17 (0.82)	0.25 (0.86)	0.092

Values are mean (SD) or n [%]. P are comparison between anti-GAD positive and –negative groups. * values are median (25-75%-tile) ** Values were log-transformed before calculating the mean.

Table 2: Effect of Glargine versus Standard Care (STD) in anti-GAD Positive and anti-GAD Negative Participants Based on Survival Models

	Overall	Glargine	STD			
	N(N/100py)	N(N/100py)	N(N/100py)	HR(95%CI)	P	P*
N	8162	4074	4088			.
Person Years	48394	24131	24263			.
First Co-primary	1358 (2.93)	699 (3.06)	659 (2.83)	1.06(0.95-1.18)	0.295	0.200
anti-GAD positive	46 (3.06)	20 (2.53)	26 (3.65)	0.80 (0.44-1.44)	0.454	.
anti-GAD negative	1312 (2.92)	679 (3.04)	633 (2.81)	1.07 (0.96-1.20)	0.204	.
Second Co-primary	2361 (5.56)	1201 (5.68)	1160 (5.43)	1.04(0.96-1.13)	0.360	0.329
anti-GAD positive	75 (5.41)	35 (4.78)	40 (6.10)	0.87 (0.55-1.38)	0.550	.
anti-GAD negative	2286 (5.56)	1166 (5.71)	1120 (5.41)	1.05 (0.96-1.14)	0.281	.
Total Mortality	1295 (2.68)	645 (2.67)	650 (2.68)	0.99 (0.89-1.11)	0.916	0.761
anti-GAD positive	40 (2.52)	21 (2.57)	19 (2.47)	1.17 (0.61-2.22)	0.642	.
anti-GAD negative	1255 (2.68)	624 (2.68)	631 (2.69)	0.99 (0.89-1.11)	0.874	.
Microvascular Outcome	1733 (3.87)	863 (3.89)	870 (3.89)	1.00 (0.91-1.10)	0.955	0.827
anti-GAD positive	35 (2.34)	19 (2.45)	16 (2.21)	1.02 (0.50-2.09)	0.959	.
anti-GAD negative	1698 (3.93)	844 (3.91)	854 (3.94)	1.00 (0.91-1.10)	0.957	.
Non severe hypo	2363 (6.03)	1786 (10.5)	577 (2.61)	3.82 (3.48-4.20)	<0.001	0.307
anti-GAD positive	90 (7.20)	65 (11.5)	25 (3.66)	3.16 (1.97-5.06)	<0.001	.
anti-GAD negative	2273 (5.99)	1721 (10.4)	552 (2.58)	3.85 (3.50-4.24)	<0.001	.
HbA1c<=6% (42 mmol/mol)	2891 (9.30)	1450 (9.37)	1441 (9.22)	1.02 (0.92-1.12)	0.741	0.950
anti-GAD positive	103 (10.5)	53 (10.2)	50 (10.8)	0.95 (0.56-1.60)	0.841	.
anti-GAD negative	2788 (9.26)	1397 (9.34)	1391 (9.17)	1.02 (0.92-1.12)	0.746	.

P* is the p-value for the interaction of glargine allocation and anti-GAD-status, py=patient-years.
The first co-primary was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke and the second co-primary was a composite of any of these events, a revascularization procedure, or hospitalization for heart failure.