Combined oral triglyceride and glucose tolerance test after acute ischemic stroke to predict recurrent vascular events: the Berlin "Cream&Sugar" study

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Stroke

CLINICAL AND POPULATION SCIENCES

Combined Oral Triglyceride and Glucose Tolerance Test After Acute Ischemic Stroke to Predict Recurrent Vascular Events: The Berlin "Cream&Sugar" Study

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BACKGROUND: Elevated triglyceride and glucose levels are associated with an increased cardiovascular disease risk including ischemic stroke. It is not known whether the response to a combined oral triglyceride and glucose challenge after ischemic stroke improves identification of patients with increased risk for recurrent vascular events.

METHODS: The prospective, observational Berlin "Cream&Sugar" study was conducted at 3 different university hospital sites of the Charité–Universitätsmedizin Berlin, Germany, between January 24, 2009 and July 31, 2017. Patients with first-ever ischemic stroke were recruited 3 to 7 days after stroke. An oral triglyceride tolerance test (OTTT) and consecutive blood tests before (t_0) as well as 3 (t_1), 4 (t_2), and 5 hours (t_3) after OTTT were performed in fasting patients. An oral glucose tolerance test was performed in all nondiabetic patients 3 hours after the start of OTTT. Outcomes of the study were recurrent fatal or nonfatal stroke as well as a composite vascular end point including stroke, transient ischemic attack, myocardial infarction, coronary revascularization, and cardiovascular death assessed 1 year after stroke. Cox regression models were used to estimate hazard ratios and corresponding 95% CIs between patients with high versus low levels of triglyceride and glucose levels.

RESULTS: Overall 755 patients were included; 523 patients completed OTTT and 1-year follow-up. Patients were largely minor strokes patients with a median National Institutes of Health Stroke Scale score of 1 (0–3). Comparing highest versus lowest quartiles of triglyceride levels, neither fasting (adjusted hazard ratio$_{t0}$, 1.24 [95% CI, 0.45–3.42]) nor postprandial triglyceride levels (adjusted hazard ratio$_{t3}$, 0.44 [95% CI, 0.16–1.25]) were associated with recurrent stroke. With regard to recurrent vascular events, results were similar for fasting triglycerides (adjusted hazard ratio$_{t0}$, 1.09 [95% CI, 0.49–2.43]), however, higher postprandial triglyceride levels were significantly associated with a lower risk for recurrent vascular events (adjusted hazard ratio$_{t3}$, 0.42 [95% CI, 0.18–0.95]). No associations were observed between fasting and post–oral glucose tolerance test blood glucose levels and recurrent vascular risk. All findings were irrespective of the diabetic status of patients.

CONCLUSIONS: In this cohort of patients with first-ever, minor ischemic stroke, fasting triglyceride or glucose levels were not associated with recurrent stroke at one year after stroke. However, higher postprandial triglyceride levels were associated with a lower risk of recurrent vascular events which requires further validation in future studies. Overall, our results do not support the routine use of a combined OTTT/oral glucose tolerance test to improve risk prediction for recurrent stroke.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiovascular disease ■ glucose ■ ischemic stroke ■ risk factor ■ triglyceride

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Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
HR	hazard ratio
OGTT	oral glucose tolerance test
OTTT	oral triglyceride tolerance test
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels

Metabolic impairments, such as hypercholesterolemia and diabetes, are independent risk factors for cardiovascular diseases including ischemic stroke.[1] The association between elevated triglyceride levels and the risk of ischemic stroke is less clear.[2–4] Evidence from large epidemiological studies of the general population show that elevated levels of fasting and especially nonfasting triglycerides might be associated with increased risk of ischemic stroke.[5–7] However, in patients with first-ever ischemic stroke included in the SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), high triglyceride levels were associated with recurrent major cardiovascular events, but not with recurrent stroke.[8] In contrast to triglycerides, elevated blood glucose as well as newly diagnosed diabetes are associated with increased residual vascular risk among patients with ischemic stroke.[9,10]

A previous study comprising patients with stable coronary artery disease reported an independent association between elevated fasting triglyceride values and future cardiovascular events but found no clear association between triglyceride values following a combined oral triglyceride tolerance test (OTTT)/oral glucose tolerance test (OGTT) and vascular risk.[11] This raises the question of whether there is utility of a combined OTTT and OGTT in patients with ischemic stroke for future vascular risk prediction. Not only is the strength of the relationship unclear but also which parameters of a combined OTTT/OGTT procedure are best to predict vascular risk remains unknown.

Therefore, we performed the Berlin "Cream&Sugar" study aiming to explore the value of a sequential OTTT/OGTT in patients with first-ever ischemic stroke to predict the risk of recurrent ischemic stroke as well as combined recurrent vascular events 1 year after stroke.

METHODS

Study Design and Patient Selection

The data that support the findings of this study are available from the corresponding author upon reasonable request. This article adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.[12] The Berlin "Cream&Sugar" study is a prospective observational study that was performed between January 24, 2009 and July 31, 2017 at 3 different university hospital sites of the Charité–Universitätsmedizin Berlin. The study was registered online (NCT01378468) and the study protocol including power calculations was published previously.[13] In brief, the Berlin "Cream&Sugar" study recruited patients with first-ever acute ischemic stroke 3 to 7 days after symptom onset of stroke. Ischemic stroke was defined as a focal neurological deficit lasting for at least 24 hours without signs of hemorrhage on cerebral imaging and no other cause explaining respective symptoms. Recruiting sites continuously screened newly admitted stroke patients for eligibility. Eligible patients were ≥18 years of age. Main exclusion criteria of the study were aphasia hampering informed consent, dysphagia not allowing to participate in oral tolerance testing, pregnancy, renal or hepatic failure as well as pancreatitis, malabsorption, or lactose intolerance. The full list of inclusion and exclusion criteria are listed in Table S1. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Charité–Universitätsmedizin Berlin (EA4/100/08). Written informed consent was given by all patients.

Oral Triglyceride and Glucose Tolerance Testing

Patients were asked to fast overnight until the patients received a phlebotomy at 8 AM (baseline=t_0) to determine fasting levels of blood parameters including glucose and triglycerides. Subsequently, an OTTT was performed with 250 mL of cream (32% fat) swallowed within 30 minutes. Consecutive blood draws were performed 3 (t_1), 4 (t_2), and 5 hours (t_3) after OTTT to determine metabolic changes over time. In patients without known diabetes, an additional OGTT was performed with 75 g of glucose 3 hours after start of OTTT (t_1). Oral input after OTTT/OGTT was not allowed until after the last blood draw. For more detailed information we refer to the published study protocol.[13]

Outcome Assessment

Patients were followed-up 1 year after stroke via a standardized telephone interview performed by trained personnel. Primary outcome of the study was recurrent fatal and nonfatal ischemic stroke. Secondary outcome of the study was the composite of vascular end points including recurrent ischemic stroke, transient ischemic attack, myocardial infarction, coronary revascularization, and cardiovascular death. Hospital discharge letters were acquired from the patient, general practitioners, or the Charité clinical database confirming potential end points. If patients were not reached via telephone, patients were contacted via mail. If patients remained lost to follow-up, local authorities were contacted to receive information on whether the patient died during follow-up or the address had changed. If patients were deceased, the date of death was obtained for end point verification.

Statistical Analysis

Patients with a complete OTTT and valid blood tests, that is, at least 2 blood tests of which one was before the OTTT (fasting state), were eligible for analyses. For each analysis, complete case analysis was used. For descriptive analyses, we performed univariate analyses using the Mann-Whitney *U* test for the comparison

of medians for nonparametric data. The χ^2 or Kruskal-Wallis test was used for the comparisons of categorical variables between groups, as appropriate. Kaplan-Meier survival analysis was performed using time to event data. Cox proportional-hazards regression analyses were used to estimate crude hazard ratios (HR) with 95% CI. We assessed the association of the outcome variables (recurrent stroke and recurrent vascular events) with the following types of triglyceride and glucose exposure measures obtained from the OTTT/OGTT measurement based on the current recommendations of the European Atherosclerosis Society, European Federation of Clinical Chemistry and Laboratory Medicine[14] and American Diabetes Association.[15]

Elevated fasting triglyceride levels comparing levels >150 mg/dL versus levels ≤150 mg/dL and elevated fasting glucose levels comparing <100 mg/dL versus ≥100 mg/dL (prediabetes cutoff) and <126 mg/dL versus ≥126 mg/dL (diabetes cutoff). Elevated nonfasting levels at t_3 were defined as triglyceride levels >175 mg/dL and glucose levels ≥140 mg/dL (prediabetes cutoff) and ≥200 mg/dL (diabetes cutoff), respectively. For analysis of nonfasting glucose levels, only patients with an OGTT were included. We also analyzed the obtained values in various other ways, all representing a different element of the body's response to the triglyceride/glucose challenge. To further investigate extreme values, we categorized patients by comparing the highest quartile (Q4) versus lowest quartile (Q1) of triglyceride and glucose response. To avoid the loss of information by categorization, we also modeled the relative increase in risk per 1 mmol/L increase of triglyceride levels (=88.57 mg/dL) and glucose levels (=18.02 mg/dL), respectively.

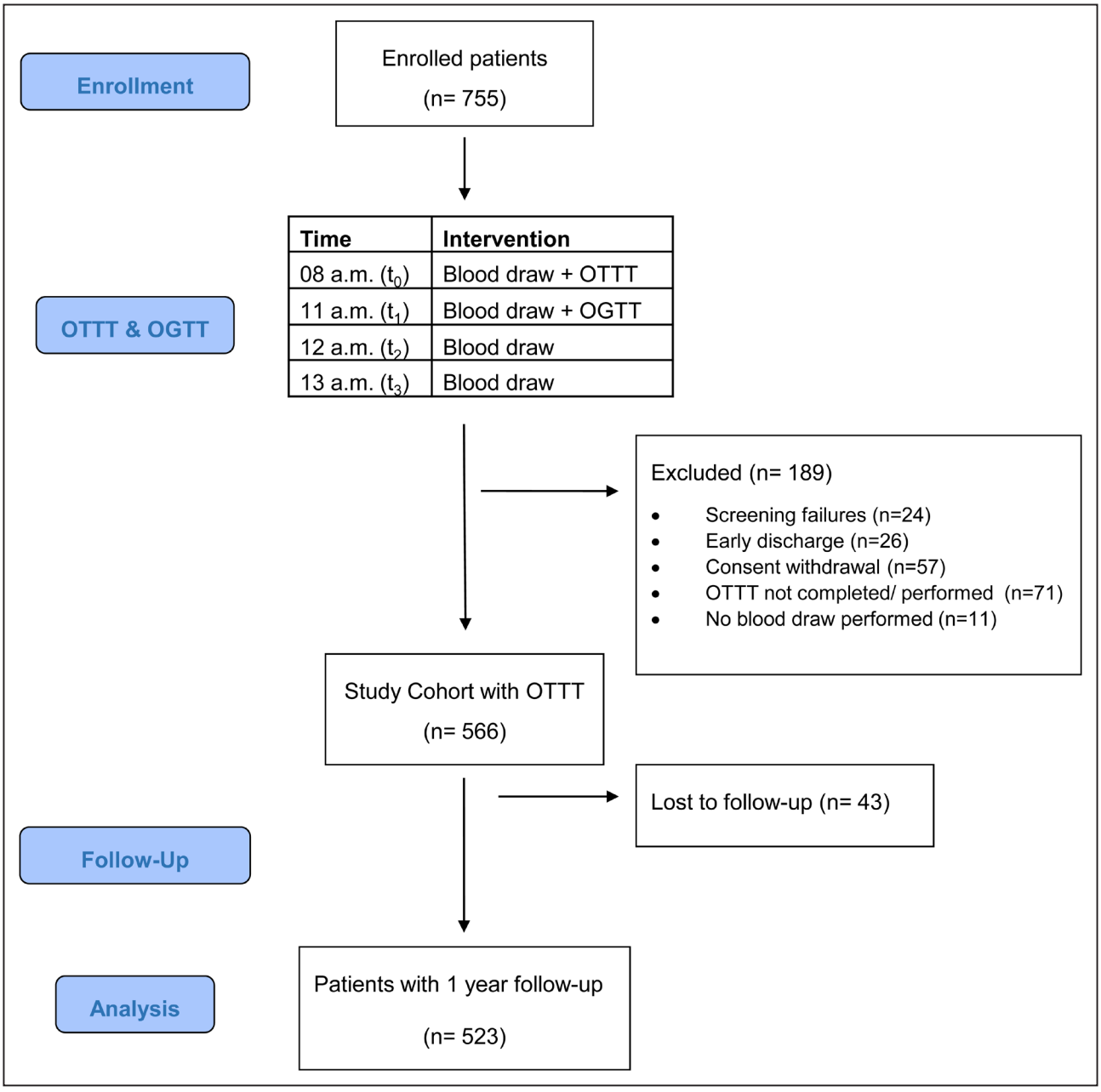

Figure 1. Flowchart of the Berlin "Cream&Sugar" Study.
OGTT indicates oral glucose tolerance test; and OTTT, oral triglyceride tolerance test.

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We performed further exploratory analyses to assess the relevance of the cumulative exposure and dynamic changes over time. We calculated the area under the curve (area under the curve in mg·dL^{-1}·h^{-1}) of the OTTT for each individual between t_0 and the other time points (t_1, t_2, and t_3). We subsequently compared the risk of vascular events from those in the highest tertile (T3) versus the lowest tertile (T1) to understand whether extreme differences in the speed of which the body handles the metabolic challenge are related to future risk. This speed is also captured in our analyses where patients were categorized according to the moment of maximum triglyceride level after OTTT, that is, peak levels at t_2 or t_3 (with t_1 as reference).

Finally, we assessed the relative and absolute change of triglyceride levels over time from baseline (t_0) to t_1, t_2, and t_3, respectively. The highest tertile of patients with a high change in triglyceride levels (high responders) were compared to the bottom tertile of patients (low responders).

We assessed these various measures in different multivariable models with the first model (model 1) also including age (continuous) and sex (male/female). The second model (model 2) additionally included diagnosis of diabetes (yes/no [y/n]). The third model (model 3) included variables of the model 2 as well as presence of arterial hypertension (y/n), atrial fibrillation (y/n), National Institutes of Health Stroke Scale (continuous), hypercholesterolemia (y/n), peripheral artery disease (y/n), coronary artery disease (y/n), and smoking status (active/previous/never). All analyses comparing high versus low responders of absolute change from baseline triglyceride levels were additionally adjusted for baseline triglyceride levels. Subgroup analyses were done in groups with and without OGTT. Additional sensitivity analyses were conducted after excluding patients with cardioembolic and lacunar strokes. Statistical analyses were performed with IBM SPSS Statistics 27 (SPSS Inc, Chicago) and R statistical software.

RESULTS

Baseline Characteristics of the Study Cohort

A total of 755 patients were enrolled in the study. Of those, 566 patients (75%) had completed the OTTT with available blood triglyceride levels to be eligible for analysis (Figure 1). Incomplete OTTT, withdrawal of consent, and early discharge were the main reasons for exclusion from analysis. Seventy-one patients (12.5%) reported adverse events following OTTT. Main adverse events were diarrhea (n=30), nausea (n=29), bloating (n=11), and other complaints (n=16).

At baseline, the mean age of patients was 64.8 (SD 13.6) years, and 69% were male with a median (interquartile range) National Institutes of Health Stroke Scale score of 1 (0–3) on admission. Median fasting glucose was 96 (88–110) mg/dL, and a history of diabetes was present in 23% of patients. Median fasting triglyceride concentration was 117 (89–151) mg/dL, and 25% of patients had fasting triglycerides above 150 mg/dL (Table 1). As expected, patients in the top quartile of fasting triglyceride levels were more likely to have a history of coronary artery disease, diabetes, and hypercholesterolemia

Table 1. Baseline Characteristics of the Berlin "Cream&Sugar" Study Cohort

Variable	All patients (n=566)
Age, mean (SD)	64.8 (13.6)
Sex, male % (n)	69.3 (392)
NIHSS, median [IQR], missing=9	1 [0–3]
TOAST, missing=3	
Large artery atherosclerosis, % (n)	37.4 (212)
Cardioembolic, % (n)	22.4 (127)
Small vessel occlusion, % (n)	15.0 (85)
Other cause, % (n)	4.4 (25)
Unknown cause, % (n)	17.0 (96)
Competing cause, % (n)	3.2 (18)
Arterial hypertension, % (n)	71.6 (405)
Atrial fibrillation, % (n), missing=2	18.3 (103)
Diabetes, % (n)	22.6 (128)
Peripheral artery disease, % (n), missing=11	6.1 (34)
Coronary artery disease, % (n), missing=12	11.7 (65)
Hypercholesterolemia, % (n)	45.9 (260)
Smoking (active), % (n)	31.1 (176)
Smoking (previous smoker), % (n)	21.6 (122)
Fasting triglyceride level, median [IQR]	116.5 [89.25–151]
Fasting triglyceride level >150 mg/dL, % (n)	25.1 (142)
Fasting total cholesterol, median [IQR], missing=8	178 [153–205.75]
Fasting LDL-cholesterol, median [IQR], missing=1	109 [86–133]
Fasting HDL-cholesterol, median [IQR], missing=1	46 [40–57]
Post-OTTT triglyceride maximum,median [IQR]	228 [164–314.5]
Triglyceride maximum time point, h, median [IQR]	4 [4–5]
3 h–OTTT triglyceride, median [IQR], missing=14	189 [139–252]
3 h–OTTT triglyceride >175 mg/dL, % (n), missing=14	57.4 (317)
4 h–OTTT triglyceride, median [IQR], missing=32	220 [155.25–304]
4 h–OTTT triglyceride >175 mg/dL, % (n), missing=32	67.6 (361)
5 h–OTTT triglyceride, median [IQR], missing=29	208 [149–294]
5 h–OTTT triglyceride >175 mg/dL, % (n), missing=29	62.2 (334)
3 h–OTTT triglyceride AUC (mg/dL/3 h), median [IQR], missing=14	463.5 [351–599.25]
4 h–OTTT triglyceride AUC (mg/dL/4 h), median [IQR], missing=43	672.5 [499–876.5]
5 h–OTTT triglyceride AUC (mg/dL/5 h), median [IQR], missing=60	891 [652.75–1177.25]
Fasting glucose, median [IQR], missing=4	96 [88–110]
2 h-OGTT [5 h–OTTT] glucose, median [IQR], missing=27	131 [104–169]
2 h-OGTT [5 h–OTTT] glucose in patients with OGTT, median [IQR], missing=18	140.5 [116–180]
	n=411
2 h-OGTT [5 h–OTTT] glucose in patients without OGTT, median [IQR], missing=10	106 [92–126]
	n=155
HbA1c, median [IQR], missing=8	5.7 [5.3–6.2]
Lipoprotein (a), median [IQR], missing=55	15.6 [5.6–43.75]
hs-CRP, mg/L, median [IQR], missing=7	4.9 [1.8–16.0]
Previous statin intake, %(n), missing=6	79.6 (446)

Values are given as mean (SD) or median [IQR] for continuous data and as percentage (n) for categorical data. AUC indicates area under the curve; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; OGTT, oral glucose tolerance test; OTTT, oral triglyceride tolerance test; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

(Table S2). After OTTT, median triglyceride levels of patients were 189 mg/dL, 220 mg/dL, and 208 mg/dL at t_1, t_2, and t_3, respectively. At 5 hours after OTTT (t_3), 62% of patients demonstrated triglyceride levels >175 mg/dL. The full baseline characteristics are listed in Table 1.

Follow-up data at 1 year after index stroke was available for 523 patients (92%) and 43 patients (8%) were lost to follow-up. Within 1 year after index stroke, 54 patients (10%) had reached a study end point. Of those, 40 patients experienced a recurrent ischemic stroke or transient ischemic attack (31 and 9, respectively), 5 patients had a myocardial infarction, and 2 patients underwent coronary revascularization. Seven patients died from a cardiovascular cause.

Association of Triglyceride Levels and Study Outcomes

Comparing the highest versus lowest quartile of fasting triglyceride levels, higher fasting levels were not associated with recurrent ischemic stroke (fully adjusted HR [aHR], 1.24 [95% CI, 0.45–3.42]) within 1 year after first ischemic stroke. Similar results were observed comparing patients with fasting triglycerides >150 mg/dL versus ≤150 mg/dL or when using per 1 mmol/L increase in triglycerides (see Table 2). Following OTTT, patients in the top quartile versus patients in the lowest quartile of triglyceride levels at t_3 had a lower effect estimate of experiencing a recurrent ischemic stroke (aHR, 0.44 [95%

Table 2. Association of Fasting and Post-OTTT Triglyceride Levels and Vascular Outcomes at 1 Year After Stroke

Variable	N	Follow-up patient years	Recurrent stroke					Recurrent vascular events				
			Number of events	Crude HR (95% CI)	aHR1 (95% CI)	aHR2 (95% CI)	aHR3 (95% CI)	Number of events	Crude HR (95% CI)	aHR1 (95% CI)	aHR2 (95% CI)	aHR3 (95% CI)
Fasting (t_0)												
>150 mg/dL	129	116.2	11	1.73 [0.83–3.61]	1.76 [0.84–3.69]	1.66 [0.78–3.51]	1.47 [0.67–3.21]	17	1.45 [0.82–2.57]	1.50 [0.84–2.68]	1.44 [0.80–2.59]	1.23 [0.67–2.25]
≤150 mg/dL	394	370.0	20					37				
Q4 (149–416 mg/dL)	130	117.2	11	1.63 [0.63–4.20]	1.69 [0.65–4.37]	1.54 [0.58–4.08]	1.24 [0.45–3.42]	17	1.47 [0.70–3.08]	1.57 [0.75–3.30]	1.48 [0.69–3.16]	1.09 [0.49–2.43]
Q1 (33–89 mg/dL)	132	122.9	7					12				
Per 1 mmol/L	523	486.2	31	1.14 [0.92–1.42]	1.14 [0.92–1.41]	1.12 [0.90–1.40]	1.08 [0.85–1.37]	54	1.09 [0.92–1.3]	1.09 [0.92–1.30]	1.08 [0.91–1.29]	1.02 [0.84–1.23]
5 h post-OTTT (t_3)												
>175 mg/dL	307	287.2	18	0.99 [0.47–2.10]	0.99 [0.46–2.12]	0.92 [0.43–1.98]	0.82 [0.37–1.81]	29	0.84 [0.48–1.47]	0.84 [0.47–1.48]	0.79 [0.45–1.41]	0.64 [0.35–1.17]
≤175 mg/dL	188	173.5	11					21				
Q4 (294–794 mg/dL)	124	116.2	7	0.68 [0.26–1.79]	0.67 [0.25–1.78]	0.60 [0.22–1.61]	0.44 [0.16–1.25]	11	0.67 [0.31–1.44]	0.67 [0.31–1.45]	0.62 [0.28–1.34]	0.42 [0.18–0.95]
Q1 (32–146 mg/dL)	124	112.9	10					16				
Per 1 mmol/L	495	460.8	29	1.03 [0.93–1.15]	1.03 [0.93–1.15]	1.02 [0.91–1.13]	1.00 [0.89–1.12]	50	0.99 [0.91–1.08]	0.99 [0.91–1.08]	0.98 [0.90–1.07]	0.95 [0.86–1.05]
AUC												
T3 3 h-AUC, mg/(d·3 h)	168	151.4	13	1.34 [0.59–3.06]	1.46 [0.63–3.38]	1.35 [0.58–3.17]	1.15 [0.47–2.79]	22	1.49 [0.79–2.82]	1.70 [0.89–3.26]	1.63 [0.85–3.16]	1.29 [0.65–2.57]
T1 3 h-AUC, mg/(dL·3 h)	170	158.9	10					16				
T3 4 h-AUC, mg/(dL·4 h)	161	145.3	12	1.55 [0.63–3.78]	1.65 [0.67–4.07]	1.47 [0.59–3.70]	1.31 [0.50–3.46]	22	1.52 [0.79–2.92]	1.68 [0.86–3.26]	1.56 [0.79–3.08]	1.26 [0.61–2.59]
T1 4 h-AUC, mg/(dL·4 h)	162	151.8	8					14				
T3 5 h-AUC, mg/(dL·5 h)	155	142.0	10	1.27 [0.50–3.22]	1.33 [0.52–3.39]	1.18 [0.45–3.05]	1.01 [0.37–2.76]	18	1.22 [0.62–2.43]	1.31 [0.65–2.61]	1.19 [0.59–2.40]	0.92 [0.44–1.95]
T1 5 h-AUC, mg/(dL·5 h)	156	145.8	8					15				
Triglyceride peak												
Peak level at 3 h–OTTT	79	70.4	7	1 (ref)	1 (ref)	1 (ref)	1 (ref)	11	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Peak level at 4 h–OTTT	254	237.5	15	0.65 [0.26–1.59]	0.65 [0.27–1.61]	0.71 [0.28–1.76]	0.67 [0.27–1.69]	25	0.68 [0.34–1.39]	0.69 [0.34–1.42]	0.73 [0.36–1.50]	0.72 [0.35–1.49]
Peak level at 5 h–OTTT	190	178.4	9	0.52 [0.19–1.39]	0.45 [0.16–1.21]	0.45 [0.17–1.22]	0.41 [0.15–1.14]	18	0.65 [0.31–1.39]	0.55 [0.26–1.17]	0.55 [0.26–1.17]	0.53 [0.24–1.14]

aHR1: adjusted for age and sex. aHR 2: adjusted for age, sex, and diabetes. aHR3: adjusted for age, sex, diabetes, arterial hypertension, atrial fibrillation, NIHSS, hypercholesterolemia, peripheral artery disease, coronary artery disease, and active smoking. aHR indicates adjusted hazard ratio; AUC indicates area under the curve; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; and OTTT, oral triglyceride tolerance test.

CI, 0.16–1.25]). Kaplan-Meier curves of the primary end point are depicted in Figure 2. Moreover, no meaningful differences were observed comparing groups of other triglyceride exposure variables, such as area under the curve or time point of triglyceride peak level (Table 2).

Results for the composite end points were similar for fasting triglyceride levels: No association was observed with the composite vascular end point at one year after stroke (aHR, 1.09 [95% CI, 0.49–2.43]). In contrast to fasting levels, higher postprandial triglyceride levels at t_3 were associated with lower risk of reaching the composite vascular end point 1 year after stroke (aHR, 0.42 [95% CI, 0.18–0.95]). For Kaplan-Meier curves depicting recurrent vascular event–free survival, see Figure S1. Most importantly, effect estimates were similar in subgroup analyses exploring the association of triglyceride levels 5 hours post-OTTT and outcomes in patients with and without OGTT at t_1, indicating similar effects in diabetic and nondiabetic patients (Table S3). Furthermore, results were similar in a sensitivity analysis excluding cardioembolic and lacunar stroke patients (Table S4).

Glucose Levels and Vascular Outcome

Overall, higher levels of fasting glucose did not result in a higher risk of recurrent stroke or vascular events (Table 3). More specifically, a pathological OGTT (≥200 mg/dL) in nondiabetic patients was not associated with a higher risk of recurrent stroke or vascular events within one year after first-ever ischemic stroke (aHR, 1.68 [95% CI, 0.59–4.77] and aHR, 1.01 [95% CI, 0.41–2.49], respectively).

Dynamic Changes of Triglycerides After OTTT and Vascular Outcome

We explored the association of the absolute and relative changes in triglyceride levels after OTTT and recurrent vascular events, as displayed in Table 4. Comparing the top versus the bottom tertile, patients with a high relative change in triglyceride levels (high responders) between t_0 (fasting) and t_3 (5 hours post-OTTT) had a significantly lower risk of recurrent vascular events compared with patients with a low relative change in triglycerides (low responders) with a fully adjusted HR of 0.33 (95% CI, 0.15–0.72). Similar results were found for absolute changes in triglyceride levels. Interestingly, the lower vascular risk seemed to build up over time, with respect to observed effect estimates at t_1 (aHR, 0.91 [95% CI, 0.44–1.87] and at t_2 (aHR, 0.51 [95% CI, 0.24–1.08]; see Table S5). Respective Kaplan-Meier Curves are depicted in Figure S2. The observed effect estimates were similar in subgroup analyses for patients with and without OGTT performed at t_1 (Table S6). When comparing baseline characteristics of both groups, high responders were younger, less likely to suffer from arterial hypertension or atrial fibrillation, and more likely to be male and actively smoking compared to low responders (Table S7).

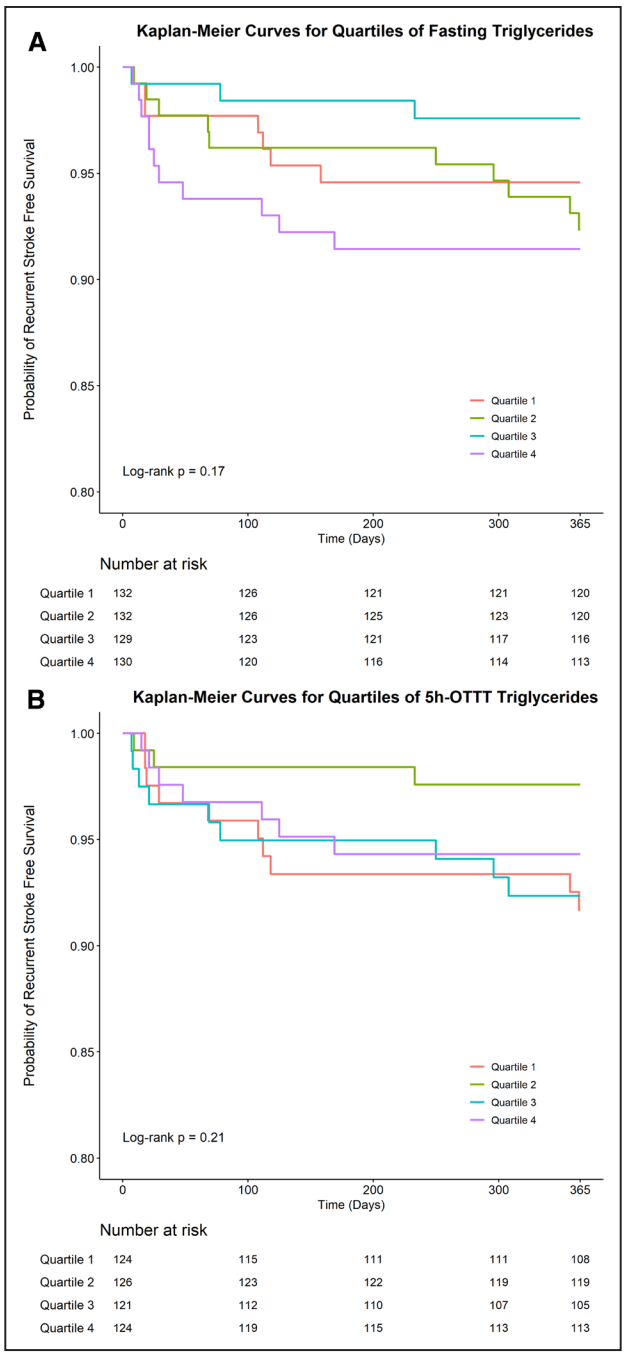

Figure 2. Kaplan-Meier curves for recurrent stroke after index ischemic stroke.
A, Patients stratified in quartiles of fasting triglyceride. **B**, Quartiles of triglycerides 5 h post-oral triglyceride tolerance test (OTTT).

DISCUSSION

The Berlin "Cream&Sugar" study is the first prospective observational study of acute patients with first-ever, minor ischemic stroke that investigated the value of a combined OTTT and OGTT in relation to vascular

Table 3. Association of Fasting and Postchallenge Glucose Levels With Risk of Recurrent Ischemic Stroke and Vascular Events at 1 Year After Stroke

Variable	N	Follow-up patient-years	Recurrent stroke					Recurrent vascular events				
			Number of events	Crude HR	aHR 1 (95% CI)	aHR 2 (95% CI)	aHR 3 (95% CI)	Number of events	Crude HR	aHR 1 (95% CI)	aHR 2 (95% CI)	aHR 3 (95% CI)
Fasting (all patients)												
≥100 mg/dL	219	200.8	16	1.48 [0.73–3.00]	1.30 [0.63–2.65]	1.07 [0.46–2.50]	1.12 [0.48–2.57]	25	1.20 [0.70–2.05]	1.01 [0.59–1.73]	0.83 [0.43–1.59]	0.86 [0.46–1.61]
<100 mg/dL	300	281.4	15					29				
≥126 mg/dL	72	67.5	3	0.65 [0.20–2.15]	0.61 [0.18–2.00]	0.30 [0.08–1.14]	0.31 [0.08–1.20]	8	1.06 [0.50–2.25]	0.97 [0.46–2.06]	0.66 [0.26–1.66]	0.74 [0.29–1.90]
<126 mg/dL	447	414.7	28					46				
Q4 (110–294 mg/dL)	125	112.4	11	2.05 [0.76–5.55]	1.70 [0.62–4.66]	1.37 [0.39–4.79]	1.63 [0.47–5.68]	18	1.69 [0.81–3.50]	1.33 [0.64–2.77]	1.15 [0.45–2.89]	1.45 [0.58–3.62]
Q1 (37–88 mg/dL)	135	127.9	6					12				
Per 1 mmol/L	519	482.2	31	1.07 [0.90–1.27]	1.05 [0.88–1.26]	0.97 [0.76–1.23]	1.00 [0.78–1.27]	54	1.08 [0.96–1.23]	1.06 [0.93–1.22]	1.03 [0.86–1.23]	1.07 [0.89–1.28]
5 h post-OTTT=2 h post-OGTT (in nondiabetic patients with OGTT; n=385)												
≥140 mg/dL	190	175.0	13	1.55 [0.64–3.75]	1.34 [0.55–3.26]	…	1.44 [0.59–3.54]	21	1.34 [0.69–2.60]	1.14 [0.58–2.22]	…	1.16 [0.59–2.29]
<140 mg/dL	179	168.0	8					15				
≥200 mg/dL	55	51.8	5	1.74 [0.64–4.74]	1.59 [0.58–4.36]	…	1.68 [0.59–4.77]	6	1.11 [0.46–2.68]	1.02 [0.42–2.45]	…	1.01 [0.41–2.49]
<200 mg/dL	314	291.2	16					30				
Q4 (180–373 mg/dL)	89	82.4	5	1.77 [0.42–7.40]	1.49 [0.35–6.28]	…	1.61 [0.37–6.91]	11	1.46 [0.59–3.63]	1.20 [0.48–3.01]	…	1.23 [0.48–3.16]
Q1 (64–117 mg/dL)	95	88.3	3					7				
Per 1 mmol/L	369	343.0	21	1.10 [0.95–1.28]	1.08 [0.92–1.26]	…	1.09 [0.93–1.27]	36	1.07 [0.95–1.21]	1.05 [0.93–1.18]	…	1.05 [0.93–1.20]

aHR1: adjusted for age and sex. aHR 2: adjusted for age, sex, and diabetes. aHR3: adjusted for age, sex, diabetes, arterial hypertension, atrial fibrillation, NIHSS, hypercholesterolemia, peripheral artery disease, coronary artery disease, and active smoking. aHR indicates adjusted hazard ratio; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; OGTT, oral glucose tolerance test; and OTTT, oral triglyceride tolerance test.

outcomes after stroke. The study results demonstrate that performing a combined OTTT/OGTT within the first 7 days after minor stroke is feasible and about 10% of patients reported minor adverse events following testing. In line with previous reports, patients with higher fasting triglyceride levels demonstrated more cardiovascular risk factors and higher triglyceride levels following OTTT.[16] However, the study could not demonstrate a clear picture that fasting or postchallenge levels of triglycerides or glucose are strongly associated with vascular risk 1 year after stroke. This leads to the conclusion that the use of a combined OTTT/OGTT early after stroke is not likely to be useful for improving vascular risk prediction.

Our findings are in contrast with the results from a previous study by Werner et al[11] involving 514 patients with stable coronary artery disease in which an independent association between fasting triglyceride levels and vascular outcomes was observed. Patients in the highest tertile of fasting triglycerides demonstrated an ≈2-fold higher risk for a combined cardiovascular outcome within 48 months. If anything, our data comparing quartiles of fasting triglyceride levels suggest an effect in the same direction, but the effect size is smaller and very imprecise (aHR, 1.09 [95% CI, 0.49–2.43]). These different observations emphasize that hypertriglyceridemia most likely represents a stronger risk factor for cardiovascular disease outcomes in myocardial infarction patients compared to patients with ischemic stroke.[17–19] By inference, the results also underscore that atherosclerosis constitutes only one of multiple causes ischemic stroke.[20]

The accumulation of triglyceride-rich lipoproteins and their remnants in the postprandial state play a crucial role in the pathophysiology of atherosclerosis.[21] Nonfasting lipids have gained much attention due to considerable amount of evidence mainly derived from epidemiological studies that pointed towards an association with increased risk of cardiovascular and cerebrovascular disease.[5,6,22,23] In contrast to these observations, results from Werner et al[11] demonstrated that postchallenge triglycerides after an OTTT are not strongly linked to vascular risk. Furthermore, the results from our study indicate that high triglyceride levels after OTTT are associated with a lower risk of recurrent vascular events one year after stroke. Among patients with established cardiovascular disease, nonfasting lipids may not similarly contribute to future risk stratification for recurrent cardiovascular events as opposed to the general population. Moreover, and perhaps most significantly, postprandial triglycerides following an OTTT and randomly sampled, nonfasting triglyceride levels cannot be treated equivalent and possibly explains part of the discrepant findings.

Table 4. Dynamic Changes of Triglycerides and Risk of Recurrent Vascular Events

Variable	N	Follow-up patient-years	No. of events	Crude HR	HR1 (95% CI)	HR2 (95% CI)	HR 3 (95% CI)
T3 Δ5h-OTTT (123 to 528 mg/dL)	165	154.8	15	0.63 [0.33 to 1.21]	0.50 [0.24 to 1.05]	0.50 [0.24 to 1.03]	0.45 [0.21 to 0.96]
T1 Δ5h-OTTT (−83 to 60.7 mg/dL)	165	149.2	23				
T3 r5h-OTTT (2.0 to 5.8)	165	159.4	9	0.35 [0.16 to 0.76]	0.37 [0.17 to 0.80]	0.36 [0.17 to 0.78]	0.33 [0.15 to 0.72]
T1 r5h-OTTT (0.4 to 1.5)	165	148.1	24				

aHR1: adjusted for age and sex. aHR 2: adjusted for age, sex, and diabetes. aHR3: adjusted for age, sex, diabetes, arterial hypertension, atrial fibrillation, NIHSS, hypercholesterolemia, peripheral artery disease, coronary artery disease, and active smoking. HRs for Δ5h-OTTT were also adjusted for the baseline triglyceride. Δ5h-OTTT and r5h-OTTT indicates absolute and relative change of triglyceride levels between fasting and 5 h post-OTTT, respectively; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; OTTT, oral triglyceride tolerance test; T1, tertile 1; and T3, tertile 3.

We observed that patients who reached their peak triglyceride level following OTTT at t_2 or t_3, had numerically fewer end points, compared to patients who reached their peak triglyceride level already at t_1 (Table 2). Exploratory analysis of dynamic changes over time exhibited a reduced vascular risk for high responders to OTTT, indicating that patients with a greater absolute or relative increase in triglyceride levels following OTTT have a lower risk of recurrent vascular events. This inverse association was strongest for triglyceride levels assessed 5 hours after OTTT. At this stage, a potential pathophysiological explanation of this rather counterintuitive observation remains speculative: Patients with a sustained increase in postprandial triglyceride levels might be characterized by other vascular risk factors. Indeed, high responders suffered less frequently from arterial hypertension or atrial fibrillation (Table S5) possibly explaining the lower vascular event rate of this patient group. Our regression models might have failed to remove all of these observed and unobserved differences. Given the exploratory nature of this analysis, these results should be interpreted with caution.

Similar to OTTT, a pathological OGTT among nondiabetic patients did not show an association with study outcomes. In a previous analysis of 13 European cohort studies of individuals who received an OGTT, Hyvärinen et al[24] found that fasting glucose and postchallenge glucose levels predicted stroke mortality in nondiabetic individuals. In a more recent study from China with >1500 stroke patients who received an OGTT within 14 days of stroke onset, newly diagnosed diabetes based on OGTT results was found to be an independent risk factor for stroke recurrence and mortality at 1 year after stroke.[10] Despite sharing a similar study design and methodology, our results do not seem to confirm these observations. The smaller sample size of our study and the use of a combined OTTT/OGTT instead of OGTT alone may have prevented the detection of independent associations with study outcomes.

There are some limitations that should be considered when interpreting study findings. First, the study largely comprises patients with minor stroke due to the necessity of unimpaired swallowing and the necessity to obtain informed consent. Therefore, results cannot be generalized to all stroke patients. Second, the power of the study was limited. The rate of recurrent stroke in our study was lower than expected. This resulted in wide confidence intervals in most analyses. Therefore, results from fully adjusted regression models should be interpreted with caution. Merging cohorts of similar methodology and patients with cardiovascular disease could provide sufficient power for more detailed analyses in future. Lastly, a sequential OTTT/OGTT was performed in nondiabetic patients only and could limit the interpretation of an OTTT of the entire cohort. However, previous results of Werner et al[11] indicate that the OGTT does not affect the course of triglyceride levels after OTTT. Moreover, we have performed subgroup analyses stratified by diabetes status and OGTT, respectively, indicating similar results in diabetic and nondiabetic stroke patients.

CONCLUSIONS

In this cohort of patients with first-ever, minor ischemic stroke receiving a combined OTTT/OGTT fasting triglyceride or glucose levels were not associated with recurrent stroke within one year after stroke. The association of higher postprandial triglyceride levels with lower risk of cardiovascular events requires further validation in other stroke cohorts. Overall, our results do not support the routine use of a combined OTTT/OGTT early after stroke to improve risk prediction for recurrent stroke.

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Supplemental Material

STROBE Statement Checklist
Figures S1–S2
Tables S1–S7

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