frontiers in
NEUROLOGY

OPINION ARTICLE
published: 30 November 2010
doi: 10.3389/fneur.2010.00148

Triglycerides and stroke risk prediction: lessons from a prospective cohort study in German primary care patients

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Triglyceride levels and their role in ischemic stroke are the topic of intense research (Leonards et al., 2010). Large-scale epidemiological studies with more than 10,000 participants each were able to detect an association between triglycerides and stroke risk (Bansal et al., 2007; Freiberg et al., 2008). Specifically, such studies have revealed a relationship between non-fasting triglyceride levels and ischemic stroke risk. However, the results of studies in smaller cohorts remain inconclusive (Leonards et al., 2010). Are large studies necessary to detect an effect of non-fasting triglycerides because triglycerides exhibit a relatively weak influence on stroke risk or are there other factors involved?

Even in a primary care cohort of 6,621 unselected patients, taken from the prospective cohort DETECT study (diabetes cardiovascular risk-evaluation: targets and essential data for commitment of treatment), we struggled to replicate findings from the larger studies (Bansal et al., 2007; Freiberg et al., 2008). Details of the DETECT study design can be found elsewhere (Pieper et al., 2005; Wittchen et al., 2005; Schneider et al., 2008). Briefly, however, triglyceride levels were measured in venous blood samples taken at time of patient enrolment using a Roche Modular automatic analyzer (Roche Diagnostics Scandinavian, Bromma, Sweden). Fasting was defined as having eaten no earlier than 8 h prior to phlebotomy. The endpoint chosen for this analysis was incident ischemic stroke as reported by physicians and/or patients occurring in the 4–5 years follow-up period.

Consistent with Freiberg et al. (2008), triglyceride levels were stratified into quintiles (<89, 89–176, 177–265, 266–353, and ≥354 mg/dL). Hazard ratios (HRs) were then calculated by Cox proportional hazard model for individual strata of triglycerides and verified by Schoenfeld residuals. Additionally, HRs were calculated for dimensional triglyceride levels (increase of 1 SD) and scaled to an increase of 89 mg/dL for interpretation to follow (Freiberg et al., 2008). Also for reasons of comparison, age, total cholesterol, alcohol consumption, smoking, hypertension, atrial fibrillation, lipid lowering therapy, diabetes, BMI, and HDL were included in triglyceride analyses (Freiberg et al., 2008). Because of the low incidence base rate of 97 strokes (23 in women), we applied a forward stepping algorithm to minimize covariates and avoided overadjustment (Triglyceride Cononary Disease Consortium and Emerging Risk Factors Collaboration, 2010) using a minimum triglyceride HR change of 5% as an inclusion criterion of a covariate into the model. All statistical analyses were conducted with the software package STATA 10.2 (Stata Corp.).

We found in the unadjusted model and models adjusted for age only, a significant association of fasting triglyceride levels with ischemic stroke in women (HR 1.2, 95% CI 1.2–1.4, $p < 0.01$) but not in men (HR 1.0, 95% CI 0.8–1.1, $p > 0.5$). This finding concurred with two long term cohort studies from Japan (Iso et al., 2007) and Norway (Njolstad et al., 1996) suggesting a possible gender difference in triglycerides' predictive role for stroke. No significant association between fasting or non-fasting triglycerides and stroke was found however after multiple adjustments (**Table 1**).

Our study may have been underpowered and the low number of events was a major limitation. A *post hoc* power analysis revealed a 13.1% chance of incorrectly rejecting the null hypothesis at a 95% confidence interval. Based on these findings, one may conclude that if any the relationship between triglycerides and stroke is relatively weak and possibly limited to females.

Overall, however, the association of fasting and non-fasting triglyceride levels with stroke remains inconclusive. Despite several proposed mechanisms describing how triglycerides might possibly increase the risk of stroke (Papagianni et al., 2004; Karepov et al., 2008), the observed associations between triglycerides and vascular events do not provide much support of a causal relationship (Third Report of the National Cholesterol Education, 2002). On the other hand, a generalized lack of standardization could explain the discrepancies between our results and other studies. Neither time points of blood draws after the last meal nor the content of that meal have been standardized in most of the studies discussed here. We therefore advocate a more standardized approach to future research in an effort to garner meaningful outcomes without needing to include tens of thousands of participants. A prospective study (Ebinger et al., 2010), using a novel oral triglyceride tolerance test (blood draws after a 10 h fast and 3 h after intake of 250 mL of 32% fat cream) to test this theory and thereby circumvent the possible problems associated with a lack of standardization is currently under way.

ACKNOWLEDGMENTS

Diabetes cardiovascular risk-evaluation: targets and essential data for commitment of treatment (DETECT) is a cross-sectional and prospective-longitudinal, nationwide clinical epidemiological study. DETECT is supported by an unrestricted educational grant of Pfizer GmbH, Karlsruhe, Germany. Principal investigator: Prof. Dr. H.-U. Wittchen; Staff members: Dr. H. Glaesmer, E. Katze, Dipl.-Math. J. Klotsche, Dipl.-Psych. L. Pieper, Dipl.-Psych. A. Bayer, Dipl.-Psych.

Table 1 | Increase of the hazard with every increase of dimensional triglyceride levels by 89 mg/dL and 1 SD in both fasting and non-fasting men and women.

Gender	Analyses	Increase of triglyceride level by 89 mg/dL			Increase of triglyceride level by 1 SD		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Fasting women	Adjustment 1†	**1.2**	1.1–1.4	0.001	**1.3**	1.1–1.6	0.001
	Adjustment 2‡	**1.2**	1.1–1.4	0.002	**1.3**	1.1–1.6	0.002
	Adjustment 3¶	1.1	1.0–1.3	0.162	1.2	0.9–1.5	0.162
Fasting men	Adjustment 1†	1.0	0.8–1.1	0.574	0.9	0.7–1.2	0.574
	Adjustment 2‡	1.0	0.9–1.2	0.869	1.0	0.8–1.2	0.869
	Adjustment 3¶	1.0	0.8–1.2	0.722	0.9	0.7–1.3	0.722
Non-fasting women	Adjustment 1†	1.0	0.7–1.2	0.779	0.9	0.6–1.4	0.779
	Adjustment 2‡	0.9	0.6–1.2	0.403	0.8	0.5–1.4	0.403
	Adjustment 3¶	0.7	0.5–1.1	0.137	0.6	0.3–1.2	0.137
Non-fasting men	Adjustment 1†	0.9	0.7–1.1	0.269	0.8	0.6–1.2	0.269
	Adjustment 2‡	0.9	0.7–1.2	0.625	0.9	0.6–1.3	0.625
	Adjustment 3¶	0.8	0.5–1.2	0.307	0.7	0.3–1.4	0.307

CI, confidence interval; HR, hazard ratio estimated by Cox proportional hazard model.
†Crude, ‡age, ¶fasting women: age, cholesterol, lipid lowering therapy, HDL; fasting men: age, cholesterol, HDL,diabetes; non-fasting women: age, cholesterol, HDL, diabetes, BMI; non-fasting men: age, cholesterol, lipid lowering therapy, diabetes, hypertension, BMI.
Bold print indicates that the p-value for the corresponding HR is <0.05.

A. Neumann. Steering Committee: Prof. Dr. H. Lehnert (Magdeburg, Coventry), Prof. Dr. G.K. Stalla (Munich), Prof. Dr. M.A. Zeiher (Frankfurt), Professor Dr. M. Wehling (Mannheim); Advisory Board: Prof. Dr. W. März (Graz/Heidelberg), Prof. Dr. S. Silber (Munich), Prof. Dr. Dr. U. Koch (Hamburg), PD Dr. D. Pittrow (Munich, Dresden). The research leading to these results has received funding from the Federal Ministry of Education and Research via the grant Center for Stroke Research Berlin (01 EO 0801), the Volkswagen Foundation (Lichtenberg program to Matthias Endres), DFG (NeuroCure), and European Union (European Stroke Network).

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Received: 09 October 2010; accepted: 05 November 2010; published online: 30 November 2010.
Citation: Ebinger M, Sievers C, Klotsche J, Schneider HJ, Leonards CO, Pieper L, Wittchen H-U, Stalla GK and Endres M (2010) Triglycerides and stroke risk prediction: lessons from a prospective cohort study in German primary care patients. Front. Neur. ***1****:148. doi: 10.3389/fneur.2010.00148*
This article was submitted to Frontiers in Stroke, a specialty of Frontiers in Neurology.