The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2020; 27: 144-154. http://doi.org/10.5551/jat.49304

Association of Non-LDL Indices with Recurrent Stroke Risk while on Lipid-Modifying Therapy

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Aims: Low-density lipoprotein (LDL)-lowering statin therapy is an established secondary stroke prevention strategy. However, the differential impact of key non-LDL levels on recurrent stroke risk, while on lipid-modifying therapy (LT), remains unclear.

Methods: We analyzed the dataset of a multicenter trial involving 3640 recent (<4 months) noncardioembolic stroke patients followed for 2 years. Participants were categorized into four groups of presumed improving lipid profile: level 0, no LT prescribed; level I, LT use with low high-density lipoprotein cholesterol (HDL-C) (<40 mg/dL for men; <50 mg/dL for women); level II, LT use with high HDL-C (≥ 40 mg/dL and ≥ 50 mg/dL, respectively); and level III, level II with low triglycerides (<150 mg/dL). Independent associations of LT category with stroke, major vascular events (MVEs; stroke/coronary heart disease/vascular death), and all-cause death were assessed.

Results: LTs were mostly statins (>95%). The unadjusted recurrent stroke rate declined with LT category level (9.2% for level 0; 8.4% for level I; 7.5% for level II; and 5.7% for level III). Compared with level 0, the adjusted hazard ratio of stroke for level I was 0.78 (95% confidence interval (CI), 0.59–1.03), level II 0.80 (0.54–1.18), and level III 0.63 (0.43–0.91). Multivariable analyses of MVEs and all-cause death followed a similar pattern of declining risk with higher LT category level.

Conclusions: Compared with the nonuse of LT, there may be a hierarchy of residual vascular risk after stroke by non-LDL type and target, while on LT. Particularly, stroke patients with low HDL-C levels on LT may benefit from additional therapeutic strategies to improve their outcomes.

Key words: Lipid, Statin, Stroke, HDL, Triglycerides, Dyslipidemia

Introduction

Primarily through their effects on lowering low-density lipoprotein cholesterol (LDL-C), statins have a proven role in preventing primary and secondary vascular events, and expert consensus guidelines endorse intensive LDL-lowering therapy for the secondary prevention of stroke[1, 2]. However, intensive LDL-lowering with high dose statins, or statins plus other agents (ezetimibe or PCSK9 inhibitors), may not be enough to ward off the vascular risk linked to adverse serum lipid derangements. For instance, other serum lipid indices such as low high-density lipoprotein cholesterol (HDL-C) levels and high triglyceride levels have been independently linked to an increased risk of major cardiovascular events[3]. In particular, the presence of atherogenic dyslipidemia, that is, the simultaneous occurrence of both HDL-C (≤ 40 mg/dL) and high triglycerides (≥ 150 mg/dL), was related to greater residual vascular risk among stroke and transient ischemic attack (TIA) patients receiving statin treatment[4], and an elevated baseline triglyceride/HDL-C ratio may confer higher vascular risk after an index stroke[5].

Further clarification of the residual vascular risk after a stroke linked to expert consensus guideline sec-

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Received: February 12, 2019 Accepted for publication: April 18, 2019

ondary serum lipid targets, that is, non-LDL-C parameters, while on lipid-modifying therapy (LT), could foster the development of interventions aimed at reducing such a risk. Comparing the presumably different serum lipid profiles may highlight variations in risk burden after stroke that may facilitate strategies for targeting patients at especially high vascular risk. The aim of this study was to investigate the associations of key non-LDL-C parameters with recurrent vascular events after stroke, while on LT.

Methods

Study Subjects and Database

We reviewed data from the Vitamin Intervention for Stroke Prevention (VISP) trial[6]. The methods and main results of this trial have been previously reported[6]. Briefly, VISP enrolled 3680 subjects aged ≥ 35 years to determine whether high doses of multivitamin (folic acid, pyridoxine, and cobalamin) given to lower the total homocysteine levels would reduce the risk of recurrent stroke and major vascular events in subjects with a noncardioembolic stroke within 120 days[6]. Demographic, clinical, and laboratory data were collected at baseline, with subsequent clinical and laboratory information obtained at follow-up visits of 1, 6, 12, 18, and 24 months (lipid profile at 1, 12, and 24 months or the final visit)[6]. For each patient, hypertension, diabetes mellitus, and body mass index (BMI), which was calculated as the weight in kilograms divided by the square of height in meters, were retrieved at the baseline visit. We also assessed the use of secondary prevention medications, including antihypertensive, antithrombotic (antiplatelet/anticoagulation), and LT; all of them were collected at every 6-month interval follow-up visit. The trial was approved by the ethics committee or the institutional review board at each national or local site, and all the participants provided written informed consent before enrolment[6].

Categories of Lipid-Modifying Therapy and Non-LDL Levels (LT Categories)

LT included statins mostly (>95%), ezetimibe, fenofibrate, niacin, and omega-3 fatty acids. The study participants were categorized into four groups according to their presumed appropriateness level for LT and mean non-LDL levels during the follow-up: level 0, no LT prescribed; level I, LT with low HDL-C (<40 mg/dL for men; <50 mg/dL for women) regardless of triglyceride levels; level II, LT with high HDL-C (≥ 40 mg/dL for men; ≥ 50 mg/dL for women) and high triglycerides (≥ 150 mg/dL); and level III, LT with high HDL-C and low triglycerides (<150 mg/dL). The primary reason for focusing on HDL-C more than triglycerides was based on a review of the literature, which demonstrated a strong association of low HDL-C levels with stroke risk in the elderly[7, 8] and the development of symptomatic intracranial atherosclerotic stenosis[9], which is associated with a higher risk of recurrent stroke compared with other stroke subtypes[10]; moreover, we did not find published data showing a clear link between high serum triglyceride levels and the risk of vascular events after a stroke. The cut-off values of HDL-C and triglycerides were determined on the basis of the sex-specific criteria of the metabolic syndrome[11, 12]. The mean follow-up lipid profile, including HDL-C and triglycerides from the baseline to the final visit, was calculated for each participant.

Assessment of Endpoints

The primary outcome for this analysis was ischemic stroke. The secondary outcome was a composite of ischemic stroke, coronary heart disease (CHD), or vascular death as major vascular events (MVEs). The tertiary outcome was all-cause death. Each adjudicated endpoint in VISP was verified through the consensus of a review committee[6].

Statistics

Comparisons across the LT categories were examined using the one-way analysis of variance, followed by the Dunnett *post hoc* test for multiple comparisons, for continuous variables and the χ^2 test for categorical variables. Participants with no outcome events were censored at the last follow-up examination, at the last visit until they died, or when they experienced an endpoint. A total of 1077 patients had relatively few follow-up lipid data since randomization: 715 (19.6%) had one or two follow-up lipid data and 362 (9.9%) had no follow-up. For the latter patients, baseline lipid was used as the proxy. Participants with no LT (level 0) were the referent group for the purposes of comparison. Baseline demographic and clinical covariates were preselected on the basis of previous studies of factors that influence vascular events after ischemic stroke. Backward stepwise elimination Cox proportional hazard regression analyses were performed to estimate the risk of endpoints over 2 years after adjusting for covariates (unadjusted $p<0.10$): age, sex, ethnicity, mini-mental state examination score, BMI, systolic blood pressure, serum levels of mean total cholesterol and mean LDL-C during follow-up, hypertension, diabetes mellitus, smoking, history of CHD, history of heart failure, history of carotid artery endarterectomy, history of alcohol use, antihypertensive use, and antithrombotic use. A total of 2563 participants with

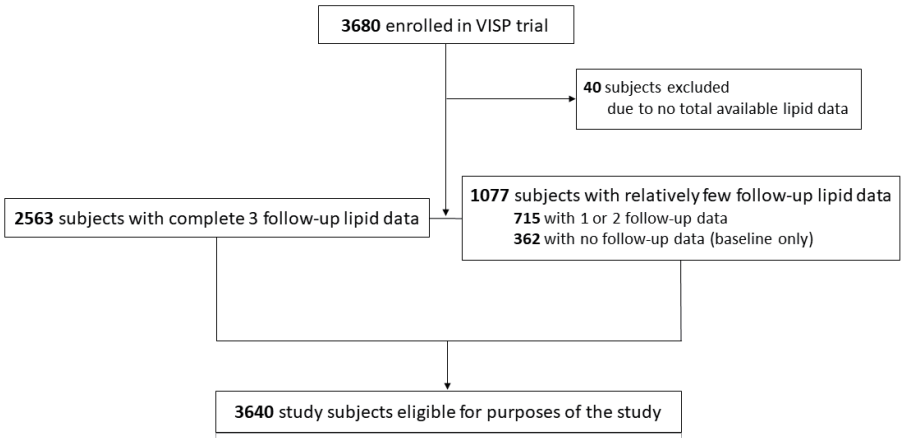

Fig. 1. Trial profile for *post hoc* analysis

complete follow-up lipid data after excluding 1077 subjects with incomplete data were also analyzed. A linear trend of adjusted hazard ratios (HRs) across the LT categories was examined using a likelihood ratio test. The interaction between demographic/clinical characteristics and LT categories in predicting the risk of outcome events was assessed by including the appropriate interaction terms in the model. The results are given by HR and its 95% confidence interval (CI). The above analyses were conducted using IBM SPSS Version 22.0 (IBM Corp., Armonk, NY), and the survival curves were fit by the log-rank tests using MedCalc software version 5.0 (Mariakerke, Belgium). A probability value of <0.05 was considered to be statistically significant.

Results

Participants' Characteristics by LT Categories

A total of 3640 participants (mean age, 66.3 ± 10.8 years; male, 62.4%; white, 79.5%) were included in this study from 3680 participants after excluding 40 subjects with no total available lipid data (**Fig. 1**). During the follow-up visits, 54.5% received LT medication, 81.3% received antihypertensive medication, and 93.4% received antithrombotic medication. Overall, 16.5% of the total participants received optimal LT (level III). The demographics and clinical features of participants by LT categories are provided in **Table 1**. Compared with participants with level 0, those receiving optimal LT were more likely to be older, had higher levels of HDL-C, showed greater frequencies of hypertension, history of CHD, history of heart failure, history of carotid artery endarterectomy, history of alcohol use, antihypertensive use, and antithrombotic use, but had lower levels of total cholesterol, LDL-C, and triglycerides, had lower systolic blood pressure and BMI, and had less frequencies of nonwhite, diabetes, and smoking.

Comparisons of Lipid Profiles by LT Categories

Table 2 shows the baseline, final, and change in the lipid levels by LT categories. At the final visit, the mean levels of lipids, including total cholesterol, LDL-C, and triglycerides, were significantly lower whereas the HDL-C levels were higher in the level III group, when compared with the level 0 group, and each of the mean lipid changes were significantly different across the LT categories. Furthermore, the frequencies of mean LDL-C <100 mg/dL and mean LDL-C $<$ 70 mg/dL at the final visit were more likely to be higher in the level I group across the LT categories.

Effect of LT on Vascular Outcomes by Non-LDL Levels

During the 2 years of follow-up, a total of 298 (8.2%) incident ischemic strokes, 608 (16.7%) MVEs, and 207 (5.7%) all-cause deaths were recorded. The results of the adjusted associations between LT categories and vascular outcomes are given in **Table 3 and Figs. 2 and 3**. The unadjusted HR for ischemic stroke for level III was 0.59 (95% CI, 0.41–0.86; $p=0.006$) vs. level 0, and this association remained stable (0.63, 0.43–0.91; $p=0.015$ and $p_{trend}=0.0371$) after multivariable adjustment. When compared with level 0, the unadjusted HR for MVEs was lower in the level II group (0.75, 0.57–1.00; $p=0.048$) and in the level III group (0.70, 0.55–0.90; $p=0.006$), and these associations remained similar after adjusting for multiple covariates (0.75, 0.56–1.01; $p=0.062$ for level II; 0.72, 0.55–0.93; $p=0.013$ for level III; $p_{trend}=0.0031$). The unadjusted HR for all-cause death was lower in the level I group (0.67, 0.48–0.93; $p=0.017$), in the level II group (0.55, 0.33–0.91; $p=0.020$), and in the level

Table 1. Baseline characteristics of study participants by lipid-modifying therapy categories*

	Lipid-modifying therapy categories†				*p*
	Level 0 (*n* = 1,657)	Level I (*n* = 969)	Level II (*n* = 413)	Level III (*n* = 601)	
Age, year	67.0 ± 11.4	65.0 ± 10.2‡	64.9 ± 10.0	67.2 ± 10.3‡	< 0.001
MMSE, score	26.8 ± 3.4	26.9 ± 3.4	27.4 ± 2.8‡	26.8 ± 3.3‡	0.020
BMI, kg/m^2	27.9 ± 5.9	29.3 ± 5.5	28.5 ± 5.8‡	27.5 ± 5.1‡	< 0.001
Systolic BP, mm Hg	141.6 ± 18.7‡	140.7 ± 18.7	140.3 ± 18.6	139.4 ± 18.8‡	0.067
Mean follow-up lipid, mg/dL					
Total cholesterol	200.3 ± 39.0‡	190.4 ± 39.4	212.6 ± 45.0	187.7 ± 32.3‡	< 0.001
LDL-C	119.8 ± 33.2	111.9 ± 34.9	117.4 ± 34.9‡	110.1 ± 27.8‡	< 0.001
HDL-C	48.3 ± 15.3	36.9 ± 6.2	53.6 ± 17.8‡	55.9 ± 13.2‡	< 0.001
Triglycerides	159.7 ± 88.4‡	213.1 ± 113.4	234.7 ± 321.6	106.1 ± 25.0‡	< 0.001
Creatinine, mg/dL	1.11 ± 0.53	1.11 ± 0.50	1.14 ± 0.80	1.10 ± 0.62	0.736
Homocystein, mmol/L	14.0 ± 5.6	14.1 ± 6.4	14.5 ± 7.2	14.1 ± 5.3	0.565
Male sex	1024 (61.8)	601 (62.0)	260 (63.0)	386 (64.2)	0.748
Non-white	303 (18.3)	104 (10.7)	32 (7.7)	100 (16.6)	< 0.001
Hypertension	1332 (80.4)	866 (89.4)	359 (86.9)	508 (84.5)	< 0.001
Diabetes mellitus	426 (25.7)	372 (38.4)	146 (35.4)	138 (23.0)	< 0.001
Current Smoking	304 (18.3)	170 (17.5)	74 (17.9)	71 (11.8)	0.003
Days from stroke to randomization	35.2 ± 13.3	35.5 ± 13.7	34.7 ± 12.9	35.7 ± 16.4	0.673
Qualifying stroke NIHSS					0.465
0	546 (33.0)	308 (31.8)	148 (35.8)	221 (36.8)	
1–4	976 (58.9)	584 (60.3)	232 (56.2)	332 (55.2)	
≥ 5	135 (8.1)	77 (7.9)	33 (8.0)	48 (8.0)	
History					
Prior stroke§	380 (22.9)	231 (23.8)	90 (21.8)	144 (24.0)	0.815
Coronary heart disease	313 (18.9)	336 (34.7)	112 (27.1)	185 (30.8)	< 0.001
Heart failure	73 (4.4)	72 (7.5)	12 (2.9)	31 (5.2)	0.001
CEA	85 (5.1)	75 (7.7)	35 (8.5)	50 (8.3)	0.005
Alcohol use	960 (59.9)	499 (52.5)	258 (63.9)	385 (65.7)	< 0.001
Antihypertensive use	1244 (75.1)	856 (88.3)	351 (85.0)	507 (84.4)	< 0.001
Antithrombotic use	1492 (90.0)	932 (96.2)	394 (95.4)	581 (96.7)	< 0.001
High-dose B vitamin	844 (50.9)	473 (48.8)	196 (47.5)	292 (48.6)	0.489

*Values are expressed as number (%) or mean ± deviation, as appropriate. MMSE, mini-mental state examination; BMI, body mass index; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; and CEA, carotid artery endarterectomy. †Level 0 indicates no lipid-modifying therapy (LT); Level I, LT with low HDL-C (< 40 mg/dL for male; < 50 mg/dL for female); Level II, LT with high HDL-C (≥ 40 mg/dL for male; ≥ 50 mg/dL for female) and high triglycerides (≥ 150 mg/dL); level III, LT with high HDL-C and low triglycerides (< 150 mg/dL). ‡Indicates significant difference between them ($p < 0.05$) by Dunnet *post hoc* tests. §Before VISP qualifying stroke.

III group (0.45, 0.28–0.72; $p = 0.001$) vs. level 0, and these associations also remained similar after multivariable adjustment (0.69, 0.48–1.00; $p = 0.048$ for level I; 0.62, 0.36–1.08; $p = 0.089$ for level II; 0.49, 0.29–0.81; $p = 0.006$ for level III; $p_{trend} = 0.0008$). Kaplan–Meier curves are shown in **Figs. 2 and 3**, where a divergence between levels II and III was not noted in the curve for MVEs (**Fig. 2B**) and that for all-cause death (**Fig. 3**). When the level I group was set as the referent group however, no significant association between the higher LT category level and either of the outcome events was observed (data not shown). **Supplemental Table 1** provides the unadjusted and adjusted associations between LT categories and vascular outcomes in 2563 patients with complete follow-up lipid data, which is a roughly similar pattern to the findings from **Table 3**. Compared with level 0, level III was linked to a lesser risk of ischemic stroke (0.56, 0.34–0.91; $p = 0.018$) and MVEs (0.72, 0.52–0.98; $p = 0.038$), but showed a trend toward a lower risk of all-cause death after multivariable adjustment. The adjusted HRs of covariates included in the

Table 2. Comparisons of lipid profiles*

Lipid, mg/dL	Lipid-modifying therapy categories†				p‡
	Level 0 (n = 1,657)	Level I (n = 969)	Level II (n = 413)	Level III (n = 601)	
Total cholesterol					
Baseline	197.8 ± 42.9	201.8 ± 48.3	222.7 ± 52.9§	199.2 ± 45.0§	< 0.001
Final	202.9 ± 41.9§	175.7 ± 41.3	199.6 ± 41.6	177.4 ± 34.5§	< 0.001
Change in level	5.5 ± 38.8§	-25.3 ± 50.9	-20.1 ± 53.2	-21.6 ± 47.7§	< 0.001
LDL-C					
Baseline	119.1 ± 38.4	122.5 ± 42.8	129.1 ± 45.1§	122.0 ± 37.9§	< 0.001
Final	121.2 ± 38.1	97.6 ± 30.8	106.5 ± 38.5§	99.5 ± 29.5§	< 0.001
Change in level	2.4 ± 40.3§	-24.6 ± 43.0	-22.3 ± 48.8	-22.7 ± 40.1§	< 0.001
Final LDL-C < 70, %	6.1	16.7	14.1	14.0	< 0.001
Final LDL-C < 100, %	27.9	58.6	48.5	54.4	< 0.001
HDL-C					
Baseline	47.1 ± 16.7	35.8 ± 7.1	50.6 ± 16.3§	53.5 ± 14.4§	< 0.001
Final	49.5 ± 15.7	38.1 ± 7.6	55.4 ± 25.6§	58.0 ± 16.0§	< 0.001
Change in level	2.1 ± 15.9§	2.3 ± 8.2	6.0 ± 27.4	4.2 ± 15.8§	< 0.001
Triglycerides					
Baseline	157.1 ± 100.8§	218.7 ± 130.9	237.1 ± 331.3	110.9 ± 37.9§	< 0.001
Final	162.6 ± 97.2§	203.4 ± 118.7	213.1 ± 94.2	103.3 ± 33.3§	< 0.001
Change in level	4.7 ± 97.1§	-11.5 ± 129.4	-5.6 ± 132.6	-9.2 ± 47.7§	0.003

*Values are mean ± standard deviation or number (%). LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. †Level 0 indicates no lipid-modifying therapy (LT); Level I, LT with low HDL-C (< 40 mg/dL for male; < 50 mg/dL for female); Level II, LT with high HDL-C (≥ 40 mg/dL for male; ≥ 50 mg/dL for female) and high triglycerides (≥ 150 mg/dL); level III, LT with high HDL-C and low triglycerides (< 150 mg/dL). ‡By one-way analysis of variance across LT categories. §Indicates significant difference between them (p < 0.05) by Dunnet *post hoc* tests.

Table 3. Effect of lipid-modifying therapy categories on vascular outcomes and all-cause death

	Lipid-modifying therapy categories			
	Level 0 (n = 1,657)	Level I (n = 969)	Level II (n = 413)	Level III (n = 601)
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Ischemic stroke				
Unadjusted	1 [Reference]	0.89 (0.68–1.17)	0.78 (0.53–1.15)	0.59 (0.41–0.86)‡
Adjusted*	1 [Reference]	0.78 (0.59–1.03)	0.80 (0.54–1.18)	0.63 (0.43–0.91)†
Events, n (%)	152 (9.2)	81 (8.4)	31 (7.5)	34 (5.7)
Major vascular events				
Unadjusted	1 [Reference]	1.04 (0.87–1.26)	0.75 (0.57–1.00)†	0.70 (0.55–0.90)‡
Adjusted*	1 [Reference]	0.94 (0.77–1.15)	0.75 (0.56–1.01)	0.72 (0.55–0.93)†
Events, n (%)	294 (17.7)	179 (18.5)	58 (14.0)	77 (12.8)
All-cause death				
Unadjusted	1 [Reference]	0.67 (0.48–0.93)†	0.55 (0.33–0.91)†	0.45 (0.28–0.72)‡
Adjusted*	1 [Reference]	0.69 (0.48–1.00)†	0.62 (0.36–1.08)	0.49 (0.29–0.81)‡
Events, n (%)	122 (7.4)	48 (5.0)	17 (4.1)	20 (3.3)

HR, hazard ratio; CI, confidence interval. *Adjusted for age, sex, ethnicity, mini-mental state examination score, body mass index, systolic blood pressure, mean total cholesterol, mean low-density lipoprotein cholesterol, hypertension, diabetes mellitus, smoking, history of coronary heart disease, history of heart failure, history of carotid artery endarterectomy, history of alcohol use, antihypertensive use, and antithrombotic use. †p < 0.05; ‡p < 0.01.

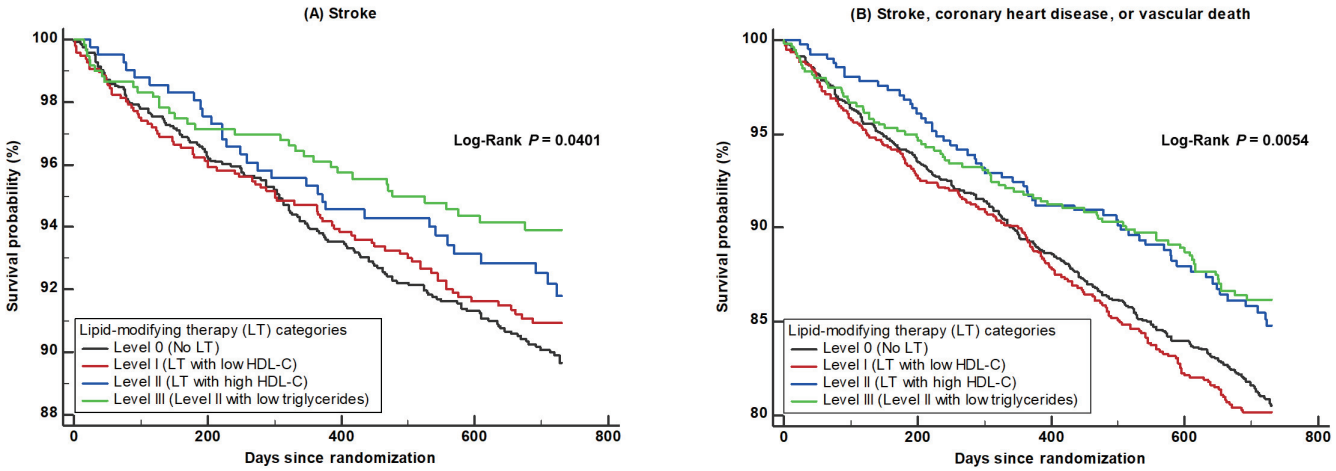

Fig. 2. Kaplan–Meier curves for the endpoints of stroke (A) and a composite of stroke, CHD, or vascular death (B) among participants over 2 years after a recent noncardioembolic stroke

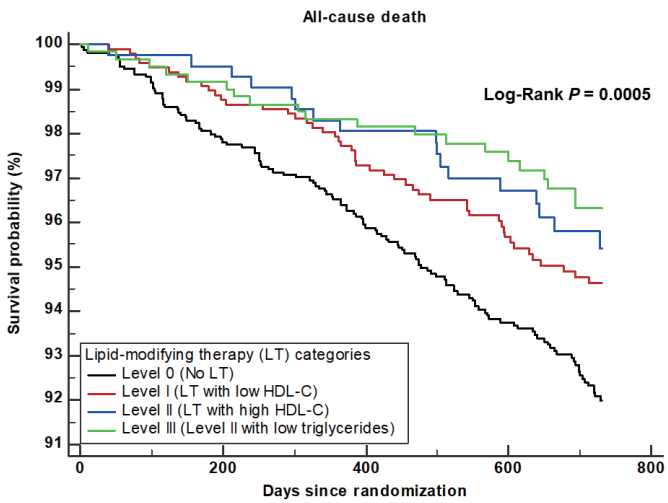

Fig. 3. Kaplan–Meier curves for the endpoints of all-cause death among participants over 2 years after a recent noncardioembolic stroke

HR, hazard ratio; CI, confidence interval.

multivariable Cox model are given in **Supplemental Table 2**. Among them, independent predictors of all the primary, secondary, and tertiary outcome events were a low mini-mental state examination score and diabetes mellitus. Hypertension was linked to an increased risk of both the primary and secondary outcome events. The interaction effect between variables and LT classes on the risk of outcomes is shown in **Supplemental Table 3**. There was a significant interaction of age with all-cause death in the level I group ($p=0.011$) and of smoking with MVEs in the level III group ($p=0.023$).

Discussion

We found that noncardioembolic stroke patients with high HDL-C and low triglycerides on LT (level III) had a 37% lower risk of recurrent stroke when compared with those not on LT (level 0). Although stroke patients with low HDL-C (level I) and high HDL-C (level II) on LT had comparatively lower rates of recurrent stroke by 22% and 20%, respectively, vs. those not on LT, these differences did not reach statistical significance. Multivariable analyses of MVEs and all-cause death followed a similar pattern of declining risk with higher LT category level. Our findings are independent of the higher frequency of having cardio-

vascular comorbidities and antihypertensive and antithrombotic medication compared with the level 0 group.

Although statin therapy exerts beneficial effects via its potent LDL-C-lowering properties, it is also well known that statins significantly lower the non-HDL-C and triglyceride levels. Indeed, statins have been shown to lower the triglyceride levels by up to 20%; however, it would appear that the higher the baseline triglyceride level, the stronger the triglyceride-lowering effect[13]. On the contrary, statin treatment may boost HDL-C levels by 4%–10%[14], and the HDL-C target level of 40 mg/dL is frequently not achieved with statins[15]. Given all the aforementioned facts, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines[16] have previously advised that lowering the LDL-C levels should be the primary target of therapy. The secondary target should be to achieve a triglyceride level <150 mg/dL, but clinical trial data are insufficient to support a specific HDL-C goal even though HDL-C <40 mg/dL is an established cardiovascular risk factor[17]. The updated American Heart Association/American Stroke Association (AHA/ASA) guidelines are consistent with these recommendations[18]. Our findings indicate that targeting triglycerides after an index ischemic stroke is probably beneficial, but the role and best strategy for addressing low HDL-C levels remain an open question.

AHA/ASA recommended a target LDL attainment of <100 mg/dL for patients with stroke or TIA presumed to be of atherosclerotic origin[18]. Our study showed that during the follow-up visits, 54.5% received LT medication, and the attained mean LDL levels at the final visit were 97.6, 106.5, and 99.5 mg/dL in levels I, II, and III, respectively (vs. 121.2 mg/dL in level 0). Suboptimal attainment (>100 mg/dL) to the recommended LDL target in level II might have attenuated the reduction power of stroke, MVEs, and all-cause death in level II.

When referenced to level I, there was no significant association between the optimal LT class and outcome events, which might be due to similarly attained LDL-C levels between level I (97.6 mg/dL) and level III (99.5 mg/dL) and the relatively higher frequency of attained LDL-C levels <100 mg/dL (58.6% vs. 54.4%, respectively) and <70 mg/dL (16.7% vs. 14.0%, respectively). Taken together, these findings provide supporting evidence for the beneficial implications of statins as an important strategy for secondary stroke prevention. As such, in a recent substudy from the Japan Statin Treatment against recurrent stroke (J-STARS), achieving LDL-C levels <120 mg/dL by pravastatin showed a significant risk reduction of recurrent stroke and TIA by 29% during the 5-year follow-up period, the risk of which was much lower by 51%, when combined with C-reactive protein (CRP) <1 mg/dL, compared with LDL-C ≥ 120 mg/dL and CRP ≥ 1 mg/dL[19].

In an attempt to modify atherogenic dyslipidemia, clinical trials of fibrates, niacin, and cholesteryl ester transfer protein inhibitors have yielded disappointing results with respect to vascular reductions[20]. However, fibrates revealed the benefit of cardiovascular risk reduction in patients with type 2 diabetes mellitus with hypertriglycemia in meta-analyses[21]. Moreover, among subjects with baseline triglycerides >2 mmol/L, the major cardiovascular events were inversely associated with the magnitude of triglyceride-lowering therapy in a metaregression analysis of the fibrate trials[22]. Our findings showed that in the level III group, the mean HDL-C and triglyceride levels were highest and lowest, respectively, from the baseline, although changes in level were more likely to be greater across the LT categories. The effect of fibrates needs to be reappraised in future among stroke patients with atherogenic dyslipidemia. In contrast to the negative findings of several trials, a high dose of icosapent ethyl (a total daily dose of 4 g) significantly reduced cardiovascular events, including stroke, by 25% in statin-treated patients with elevated triglyceride levels, among whom over 70% had established cardiovascular disease[23].

Several limitations need to be acknowledged. First, VISP was conducted over a decade ago, before the era of Get With The Guidelines (GWTG) for lipid management. The use of LT in VISP was lower than that from GWTG-Stroke from 2003 to 2012 [24] (54.5% vs. 81.1%). Furthermore, the VISP dataset did not provide index stroke subtype, culprit vascular status, or socioeconomic status, which could reflect high-risk patients. The use of fixed-dose high-intensity or moderate-intensity statin therapy for secondary stroke prevention on the basis of the 2013 ACC/AHA cholesterol guidelines[2] and the triage of high-risk patients to attain LDL target levels (<70 mg/dL)[18] should have shown more viable and beneficial results. Second, partial missing components of lipid data from the 1077 participants, besides the complete exclusion of 40 participants, might have influenced the current results, jeopardizing the precision of estimates for lipid levels and outcomes. Third, we could not measure to what extent nonstatin drugs were prescribed across the LT categories to see the modulating effect on atherogenic dyslipidemia. Finally, the *post hoc* exploratory analysis of a completed randomized trial did not allow us to establish a cause–effect relationship between LT categories and outcomes. Despite the aforementioned

limitations, this study shows potential promising associations between optimal LT category level (modifying non-LDL added to LT) and vascular outcomes in patients after a noncardioembolic stroke.

Conclusion

Our study demonstrates that LDL-lowering therapy along with high HDL-C and low triglyceride levels may be associated with a further benefit in reducing vascular outcomes, particularly recurrent stroke (vs. LDL-lowering alone) among patients with noncardioembolic stroke. Although the VISP population was not provided with the best medical management aimed at a designated LDL target to prevent recurrent stroke, our compelling findings suggest that there is a residual opportunity for advancement in the secondary prevention of stroke through the optimization of lipid profiles, especially for non-LDL-C. Our findings need to be validated through prospective studies with general stroke populations.

Funding

This study was supported by Award NS103752 from the National Institute of Neurological Disorders and Stroke.

Conflict of Interests

None of the authors have conflict of interests to disclose related to this study.

Ethical Approval

The VISP trial was approved by the ethics committee or institutional review board at each national or local site, and all participants provided written informed consent before enrolment.

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Supplemental Table 1. Effect of lipid-modifying therapy categories on vascular outcomes and all-cause death in 2563 patients with complete follow-up lipid data

	Lipid-modifying therapy categories			
	Level 0 (n = 1,132)	Level I (n = 678)	Level II (n = 302)	Level III (n = 451)
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Ischemic stroke				
Unadjusted	1 [Reference]	0.93 (0.66–1.30)	0.73 (0.44–1.19)	0.51 (0.32–0.83)‡
Adjusted*	1 [Reference]	0.89 (0.62–1.26)	0.77 (0.46–1.27)	0.56 (0.34–0.91)†
Events, n (%)	93 (8.2)	53 (7.8)	19 (6.3)	20 (4.4)
Major vascular events				
Unadjusted	1 [Reference]	1.10 (0.87–1.38)	0.68 (0.47–0.98)†	0.72 (0.54–0.98)†
Adjusted*	1 [Reference]	0.99 (0.77–1.27)	0.71 (0.49–1.04)	0.72 (0.52–0.98)†
Events, n (%)	182 (16.1)	120 (17.7)	35 (11.6)	55 (12.2)
All-cause death				
Unadjusted	1 [Reference]	0.68 (0.44–1.03)	0.30 (0.13–0.69)‡	0.51 (0.29–0.88)†
Adjusted*	1 [Reference]	0.69 (0.42–1.11)	0.44 (0.19–1.02)	0.59 (0.32–1.06)
Events, n (%)	73 (6.4)	30 (4.4)	6 (2.0)	15 (3.3)

HR, hazard ratio; CI, confidence interval. *Adjusted for age, sex, ethnicity, mini-mental state examination score, body mass index, mean low-density lipoprotein cholesterol, hypertension, diabetes mellitus, smoking, history of coronary heart disease, history of carotid artery endarterectomy, history of alcohol use, antihypertensive use, and antithrombotic use. †$p < 0.05$; ‡$p < 0.01$.

Supplemental Table 2. Adjusted hazard ratios (AHRs) of covariates included in the backward elimination Cox models of vascular outcomes and all-cause death by lipid-modifying therapy categories

Covariates	Vascular outcomes				All-cause death	
	Ischemic stroke		Major vascular events*			
	AHR (95%, CI)	p	AHR (95%, CI)	p	AHR (95%, CI)	p
Age (1-yr difference)	—	—	1.02 (1.01–1.03)	< 0.001	1.04 (1.02–1.05)	< 0.001
Male	—	—	1.28 (1.06–1.53)	0.009	1.91 (1.35–2.69)	< 0.001
MMSE, score	0.96 (0.93–0.99)	0.005	0.96 (0.94–0.98)	0.001	0.92 (0.89–0.95)	< 0.001
Hypertension	1.61 (1.09–2.40)	0.018	1.91 (1.29–2.83)	0.001	1.79 (0.95–3.35)	0.070
Diabetes	1.35 (1.05–1.74)	0.017	1.50 (1.26–1.79)	< 0.001	1.51 (1.10–2.07)	0.010
Smoking	—	—	1.30 (1.03–1.64)	0.025	—	—
Mean LDL-C	—	—	—	—	1.01 (1.00–1.01)	< 0.001
History						
CHD	—	—	1.38 (1.15–1.66)	0.001	1.63 (1.18–2.25)	0.003
Heart failure	—	—	1.56 (1.16–2.09)	0.003	2.53 (1.64–3.91)	< 0.001
CEA	—	—	1.56 (1.19–2.04)	0.001	1.58 (1.02–2.45)	0.041
Alcohol use	0.68 (0.53–0.86)	0.001	0.83 (0.70–0.99)	0.038	—	—
Antihypertensive use	—	—	0.74 (0.53–1.03)	0.070	0.55 (0.32–0.92)	0.024
Antithrombotic use	—	—	0.73 (0.55–0.98)	0.035	—	—

MMSE, mini-mental state examination; CHD, coronary heart disease; CEA, carotid artery endarterectomy; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval. *Defined as ischemic stroke, CHD or vascular death.

Supplemental Table 3. Interaction effect between variables and lipid-modifying therapy (LT) categories on outcomes

	Lipid-modifying therapy categories*		
	Level I† *p*‡	Level II† *p*‡	Level III† *p*‡
Ischemic stroke/ Major vascular events/ All-cause death			
Age, year§	0.107/ 0.651/ 0.011	0.726/ 0.850/ 0.440	0.482/ 0.329/ 0.076
Male sex	0.291/ 0.117/ 0.075	0.439/ 0.372/ 0.838	0.746/ 0.930/ 0.628
Black race	0.121/ 0.060/ 0.690	0.211/ 0.245/ 0.944	0.420/ 0.157/ 0.238
Body mass index	0.492/ 0.377/ 0.347	0.965/ 0.627/ 0.135	0.641/ 0.999/ 0.307
Hypertension	0.316/ 0.051/ 0.127	0.834/ 0.756/ 0.891	0.836/ 0.716/ 0.781
Diabetes mellitus	0.126/ 0.488/ 0.952	0.722/ 0.529/ 0.365	0.958/ 0.427/ 0.595
Smoking	0.107/ 0.249/ 0.774	0.302/ 0.231/ 0.608	0.388/ 0.023/ 0.866
History of CHD	0.208/ 0.858/ 0.506	0.841/ 0.635/ 0.712	0.773/ 0.452/ 0.506
History of HF	0.760/ 0.583/ 0.075	0.786/ 0.365/ 0.073	0.534/ 0.377/ 0.546
History of CEA	0.133/ 0.186/ 0.183	0.499/ 0.325/ 0.934	0.285/ 0.242/ 0.207
B-vitamin (high-dose)	0.570/ 0.124/ 0.241	0.261/ 0.630/ 0.353	0.381/ 0.653/ 0.648

CHD, coronary heart disease; HF, heart failure; CEA, carotid artery endarterectomy. *Level I indicates lipid-modifying therapy (LT) with low HDL-C (<40 mg/dL for male; <50 mg/dL for female); Level II, LT with high HDL-C (≥ 40 mg/dL for male; ≥ 50 mg/dL for female); level III, level II with low triglycerides (<150 mg/dL). †Referenced to Level 0 (no LT prescribed). ‡Interaction between LT categories and respective covariate. §As a continuous variable.