Stroke

ORIGINAL ARTICLE

Yield of Dual Therapy With Statin and Ezetimibe in the Treat Stroke to Target Trial

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BACKGROUND: In atherosclerotic stroke, lipid-lowering treatment with a target LDL (low-density lipoprotein) cholesterol of <70 compared with 100±10 mg/dL reduced the risk of subsequent cardiovascular events. This post hoc analysis explored the relative effects of the combination of statin and ezetimibe (dual therapy) and statin monotherapy in achieving the lower LDL cholesterol target and in reducing the risk of major vascular events, as compared with the higher target group.

METHODS: Patients with ischemic stroke in the previous 3 months or transient ischemic attack within the previous 15 days and evidence of cerebrovascular or coronary artery atherosclerosis were randomly assigned to a target LDL cholesterol of <70 or 100±10 mg/dL, using statin and/or ezetimibe as needed. The primary outcome was the composite of ischemic stroke, myocardial infarction, new symptoms requiring urgent coronary or carotid revascularization, and vascular death. Cox regression model including lipid-lowering therapy as a time varying variable, after adjustment for randomization strategy, age, sex, index event (stroke or transient ischemic attack), and time since the index event.

RESULTS: Among 2860 patients enrolled, patients who were on dual therapy during the trial in the lower target group had a higher baseline LDL cholesterol as compared to patients on statin monotherapy (141±38 versus 131±36, respectively, $P<0.001$). In patients on dual therapy and on statin monotherapy, the achieved LDL cholesterol was 66.2 and 64.1 mg/dL respectively, and the primary outcome was reduced during dual therapy as compared with the higher target group (HR, 0.60 [95% CI, 0.39–0.91]; $P=0.016$) but not during statin monotherapy (HR, 0.92 [95% CI, 0.70–1.20]; $P=0.52$), with no significant increase in intracranial bleeding.

CONCLUSIONS: In the TST trial (Treat Stroke to Target), targeting an LDL cholesterol of < 70 mg/dL with a combination of statin and ezetimibe compared with 100±10 mg/dL consistently reduced the risk of subsequent stroke.

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Key Words: ezetimibe ■ lipoproteins, LDL ■ stroke

After a transient ischemic attack (TIA) or an ischemic stroke of atherosclerotic origin, the 2021 American Heart Association (AHA)/ American Stroke Association (ASA) guidelines recommend intensive statin therapy and to lower LDL (low-density lipoprotein) cholesterol to a target level <70 mg/dL using statin, and ezetimibe as needed.[1] Recommendations in patients with stroke are based on the results of the SPARCL trial (Stroke

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Nonstandard Abbreviations and Acronyms

HDL	high-density lipoprotein
LDL	low-density lipoprotein cholesterol
PCSK9	proprotein convertase subtilsin/kexin type 9
SPARCL	Stroke Prevention by Aggressive Reduction of Cholesterol Level
TIA	transient ischemic attack
TST	Treat Stroke to Target trial
TTR	time in therapeutic range

Prevention by Aggressive Reduction in Cholesterol Level) that found a 16% relative risk reduction with atorvastatin 80 mg per day as compared with placebo in patients with stroke and no known coronary heart disease, and a subanalysis of that trial showing a relative risk reduction of 33% in patients randomized with carotid stenosis.[2,3] The AHA/ASA recommendation of a target LDL cholesterol level <70 mg/dL in patients with ischemic stroke and atherosclerotic stenosis was based on the results of the Treat Stroke to Target trial that showed a 22% reduction in major vascular events in the target LDL cholesterol group <70 mg/dL as compared with a target LDL 100±10 mg/dL.[4] Only 1 trial showed the benefit of using dual therapy with statin and ezetimibe as compared with statin monotherapy in patients with coronary atherosclerosis.[5] No trial has evaluated specifically in patients with stroke the effect of a dual therapy with statin and ezetimibe as compared with statin monotherapy to achieve the <70 mg/dL goal and to reduce major vascular events.

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In a post hoc analysis of the TST trial (Treat Stroke to Target), we aimed to evaluate the relative efficacy of dual therapy with statin and ezetimibe or statin monotherapy to achieve the target LDL cholesterol assigned by the randomization, and to reduce major vascular events, in the target LDL cholesterol group <70 mg/dL as compared with a target LDL cholesterol 100±10 mg/dL.

METHODS

Data and Resource Availability

Data are available upon reasonable request to the first and corresponding author of this article for research purpose after approbation by the Steering Committee.

Trial Design

This was a randomized, event-driven trial. The methods of patient recruitment, evaluation, and statistical assumptions have been published.[6] The protocol was approved by local institutional review boards. All patients gave written informed consent. The first author and independent academic statisticians at Bichat hospital, CHRU of Lille and Fernand Widal Hospital had full access to the trial databases, analyzed the data, prepared the first draft of the article, and made decision to submit the article for publication. There were unrestricted grants from Pfizer, AstraZeneca, and Merck for the support of the trial, and from Althera Pharmaceuticals (the maker of a dual therapy with statin and ezetimibe) for the current analysis, but there was no industry involvement in the conduct of the trial or data gathering or analysis. All authors vouch for the accuracy of the data and all analyses and for the fidelity of the trial to the protocol and reporting of adverse events. The present report is a post hoc analysis of the TST trial and the dual versus monotherapy treatment assignment was not randomized but was the choice of the investigators to get their patient to the LDL cholesterol level assigned by randomization.

Trial Participants

Patients were eligible for enrollment if they were 18 years or older (>20 years in South Korea), had an ischemic stroke <3 months previously and a modified Rankin Scale after stroke of 0 to 3 (modified Rankin Scale scores of 0 to 6, 0 indicating no symptoms, 1 no disability, 2 to 3 needing some help, 4 to 5 dependent or bedridden, and 6 death) at randomization, once investigators determined the neurological deficit was stable, or a TIA within the previous 15 days that included at least arm and leg motor deficit or speech disturbance lasting more than 10 minutes. Transient ischemic symptoms with a documented ischemic lesion on computed tomography or magnetic resonance imaging in the cerebral regions corresponding to the symptoms were defined as ischemic strokes. As recommended by the AHA/ASA guidelines,[7] all patients were screened using noninvasive imaging of the cervical vessels (carotid duplex, computed tomography angiography, MR angiography) as part of the routine evaluation of patients with suspected TIA or ischemic stroke, as well as computed tomography angiography or MR angiography of the intracranial vasculature to exclude a proximal intracranial stenosis and/or occlusion, and transesophageal echocardiography or computed tomography angiography of the aorta to detect aortic atheroma, which were obtained when the responsible clinician determined that knowledge of intracranial steno-occlusive disease or severe aortic atheroma would alter management.[7] The choice of vascular tests and the diagnosis of atherosclerotic stenosis was made and judged by the investigators and was not standardized or adjudicated. To be enrolled in the trial, patients had to have atherosclerotic disease including stenosis of an extra or intracranial cerebral artery, ipsilateral or contralateral to the region of imputed brain ischemia, or aortic arch atherosclerotic plaques ≥4 mm in thickness, or a known history of coronary artery disease. Patients also had to have an indication for statin treatment based on stroke AHA/ASA, French Agence Nationale de Sécurité du Médicament (ANSM), or South Korean recommendations.[1,8,9] According to these recommendations, patients with ischemic stroke presumed to be of atherosclerotic origin should receive statin therapy[1] and for the French and Korean recommendations should be treated to a target LDL cholesterol of 100 mg/dL. Patients were required to have a directly measured LDL cholesterol of at least 70 mg/dL (1.8 mmol per liter) if they were on statin before randomization, or at least 100 mg/dL (2.4 mmol per liter) if they had not previously received statins.

Trial Design

Eligible patients were randomly assigned in a 1:1 ratio to a target LDL cholesterol of <70 mg/dL(with no lower LDL threshold limit) or a target LDL cholesterol of 100±10 mg/dL. Investigators could use any type and any dose of statin to reach this target. Investigators were asked to perform a determination of LDL cholesterol 3 weeks after randomization to adjust the statin dose, or to add other lipid lowering agents including ezetimibe, to achieve the assigned LDL cholesterol target. Patients were followed every 6 months after randomization with measurement of LDL cholesterol. In addition to face-to-face visits with the investigators to collect trial outcomes since the previous visit, a central core of clinical research assistants based at Bichat Hospital called patients or their relatives every 6 months to acquire the results of LDL measurement at the preceding visit and to collect potential trial end points using a structured questionnaire. If the LDL cholesterol level was above or below the range assigned by randomization, the investigator was contacted to adjust the lipid lowering treatment to the target range. If a potential trial outcome was collected, the local investigator was contacted to confirm the event clinically and activate the adjudication process. Triglyceride, HDL (high-density lipoprotein) cholesterol, blood pressure in the sitting position, fasting glucose, and HbA1C were collected at every 6-month visits.

Outcomes

The primary outcome was a composite of adjudicated nonfatal cerebral infarction or stroke of undetermined source, nonfatal myocardial infarction, hospitalization for unstable angina followed by urgent coronary artery revascularization, TIA requiring urgent carotid revascularization, or cardiovascular death including unexplained sudden death. The pre specified secondary composite outcomes were myocardial infarction or urgent coronary revascularization following new symptoms; cerebral infarction or urgent carotid or cerebral artery revascularization following a TIA; cerebral infarction or TIA; any revascularization procedures both urgent and elective (coronary, cerebral or peripheral artery); vascular death; all cause death; cerebral infarction or intracranial hemorrhage; intracranial hemorrhage; newly diagnosed diabetes; composite of primary outcome and intracranial hemorrhage (the last of these was pre specified in the protocol but not included in the statistical analysis plan). All incident events that were components of these end points were adjudicated by a committee in which the members were unaware of LDL cholesterol group assignments or LDL levels achieved.

Statistical Methods

This article follows the STROBE reporting guideline. Quantitative variables were expressed as means (±SD) in case of normal distribution or median (interquartile range) otherwise. Categorical variables were expressed as counts (percentage). We assessed the effect of monotherapy or dual therapy in the lower LDL target arm as compared with the TST higher LDL target control arm on primary and secondary outcomes by using Cox' proportional hazard model including lipid-lowering therapy as a time-varying variable. For the purpose of this analysis, patients on dual therapy were those on statin plus ezetimibe at any trial visit. Patients receiving any other lipid-lowering agents in addition to statin were in the statin monotherapy group. None of the patients received PCSK9 (proprotein convertase subtilsin/kexin type 9) inhibitors. Dual therapy in the lower target group was compared with all controls, no matter the latter were on dual or monotherapy. All analyses were performed on all randomized patients and were adjusted for prespecified covariates as done in primary efficacy analysis of TST trial (age, sex, entry event [stroke or TIA], time since entry event)[4] as well as for the 2 main between-group differences (baseline dyslipidemia and baseline LDL cholesterol levels). Adjusted hazard ratios (HRs) for dual therapy and monotherapy in the lower target group relative to target LDL cholesterol of 100±10 mg/dL (control group) were derived from these models with their 95% CIs as the effect size measures. A sensitivity analysis was conducted for primary outcome by treating nonvascular death as competing event using a multivariable Fine and Gray model. Adherence to the intervention was reported as time in therapeutic range calculated alike calculation of INR range 2 to 3 in case of warfarin treatment.[10] Sensitivity analysis was performed on the French cohort.

Statistical testing was conducted at the 2-tailed α-level of 0.05. Data were analyzed using SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS

Between March 2010 and December 2018, 2873 patients were enrolled in France and South Korea. Among 2860 patients followed a median of 3.5 years (IQR, 2.0–6.7), 1430 were assigned a LDL cholesterol of 100±10 mg/dL (the control group) who achieved a mean LDL cholesterol of 96 mg/dL, and 1430 were assigned a LDL cholesterol of <70 mg/dL, who achieved a LDL cholesterol of 65 mg/dL.

The Table shows baseline characteristics according to the 4 groups. For the purpose of this Table, patients who had at least 1 visit with dual therapy were in the dual therapy groups and patients who had all their follow-up on statin or on ezetimibe only were in the statin monotherapy groups. Patients had similar age at inclusion and > 65% were male. At inclusion, patients on dual therapy groups had a higher LDL cholesterol than patients on statin monotherapy (141±38 and 145±46 mg/dL on dual therapy as compared with 131±36 and 135±37 mg/dL on statin monotherapy in the <70 and 100±10 mg/dL strategy groups, respectively). In the lower target group, *P* was 0.001 for baseline LDL cholesterol in patients on dual versus monotherapy.

During the trial, medication persistence at 6 months, 1, 2 and 3 years are presented in Tables S1 through S4. In the <70 mg/dL target group, around 20% of patients who received only statin had intense therapy (respectively, 18.9, 20.6, 23.7, and 24.0% at 6 months, 1, 2, and 3 years) against around 7% in the 100±10 mg/dL target (respectively, 6.7, 6.6, 7.6, and 8.6 at 6 months, 1, 2, and 3 years). Similar proportions were observed in the dual therapy group (Tables S1 through S4). Figure 1 shows

Table. Baseline Characteristics According to Groups

Characteristics	LDL-c <70 mg/dL		LDLc 100±10 mg/dL	
	Monotherapy (n=896)	Dual therapy (n=529)	Monotherapy (n=1283)	Dual therapy (n=141)
Age, y	66.9 (11.5)	65.6 (11.0)	67.0 (11.2)	66.9 (10.6)
Male sex, no/total no, (%)	608/896 (67.9)	360/529 (68.1)	865/1283 (67.4)	95/141 (67.4)
Body mass index, median (IQR)	25.6 (23.0–28.4)	25.6 (23.7–28.7)	25.5 (23.2–28.4)	25.6 (23.7–28.7)
Entry event				
Ischemic stroke	773/896 (86.3)	444/526 (84.4)	1109/1282 (86.5)	116/141 (82.3)
TIA	123/896 (13.7)	82/526 (15.6)	173/1282 (13.5)	25/141 (17.7)
Time since entry event, days,median (IQR)	6 (4–11)	6 (3–9)	6 (4–11)	6 (4–10)
Medical history				
Hypertension, no/total no, (%)	581/877 (66.3)	328/501 (65.5)	742/1245 (68.5)	104/137 (75.9)
Diabetes, no/total no, (%)	234/884 (26.5)	94/518 (18.2)	284/1264 (22.5)	31/138 (22.5)
Dyslipidemia, no/total no, (%)	489/827 (59.1)	389/500 (77.8)	745/1169 (63.7)	116/134 (86.6)
Former smoker, no/total no, (%)	220/884 (24.9)	129/526 (24.5)	271/1268 (21.4)	34/141 (24.1)
Current smoker, no/total no, (%)	263/884 (29.8)	183/526 (34.8)	374/1268 (29.5)	38/141 (27.0)
Stroke or TIA, no/total no, (%)	105/887 (11.8)	64/525 (12.2)	136/1259 (10.8)	16/141 (11.4)
Coronary artery disease, no/total no, (%)	160/884 (18.1)	103/525 (19.6)	193/1259 (15.3)	34/138 (24.6)
Statin naive	522/827 (63.1)	278/500 (55.6)	718/1169 (61.4)	49/134 (36.6)
Lipids, mg/dL				
LDL-c, mean (SD)	131 (36)	141 (38)	135 (37)	145 (46)
HDL-c, mean (SD)	50 (19)	50 (17)	50 (18)	49 (18)
Total cholesterol, mean (SD)	204 (46)	217 (46)	209 (49)	223 (63)
Triglycerides, median (IQR)	119 (88–161)	124 (92–172)	123 (92–162)	133 (89–193)
Systolic blood pressure, mm Hg, mean (SD)	140 (23)	140 (22)	141 (21)	140 (21)
Diastolic blood pressure, mm Hg; mean (SD)	79 (13)	80 (13)	80 (13)	78 (13)
Glucose, mg/dL, median (IQR)	5.7 (5.0–6.8)	5.5 (5.0–6.3)	5.6 (5.0–6.6)	5.6 (5.0–6.6)
Hemoglobin A1c, %, mean (SD)	6.5 (3.3)	6.2 (1.3)	6.2 (1.3)	6.3 (1.1)

IQR indicates interquartile range; and TIA, transient ischemic attack.

the distribution of dual therapy and statin monotherapy in the lower and higher target group over the course of the trial. At baseline, >95% were on statin only or ezetimibe only. After the second visit, > 30% of patients were on dual therapy in the <70 mg/dL group whereas <10% of patients were on dual therapy in the 100±10 mg/dL group (except for the last visits).

Effect on Lipid Levels

The mean LDL cholesterol level during the follow-up was 66.2 and 64.1 in the <70 mg/dL group and 95.8 and 96.5 in the 100±10 mg/dL group, respectively in the dual therapy and statin monotherapy groups (Figure 2).

Effect on Outcomes

Patients in the <70 mg/dL group who were on dual therapy had a reduced risk of having major cardiovascular event compared with all patients in the 100±10 mg/dL (HR, 0.59 [95% CI, 0.38–0.90]; *P*=0.016; Figure 3). We also found a reduced risk in cerebral infarction and urgent carotid and cerebral artery revascularization when patients were in the <70 mg/dL group on dual therapy (HR, 0.57 [95% CI, 0.33–0.97]; *P*=0.037; Figure 3). The risk of primary outcome and intracranial hemorrhage was also lower in patients in the <70 mg/dL group on dual therapy (HR, 0.62 [95% CI, 0.41–0.94]; *P*=0.023) as compared with all patients in the higher target group.

In the subgroup who spent 50% to 100% of their time in the therapeutic range (LDL cholesterol below 70 mg/dL), there was a significant 49% reduction in the primary outcome in the dual therapy (HR, 0.51 [95% CI, 0.30–0.84]; *P*=0.009) as compared with patients in the higher target group, and no significant effect in the statin monotherapy group (HR, 0.91 [95% CI, 0.66–1.26]; *P*=0.57).

In the sensitivity analysis restricted to the French cohort, with a median follow-up of 5 years, similar results were found on the primary outcome (HR, 0.58 [95% CI, 0.37–0.90]; *P*=0.016), primary outcome and intracranial hemorrhage (HR, 0.58 [95% CI, 0.38–0.90]; *P*=0.014) and on adverse events, while on dual therapy in the lower target group (Figure S1).

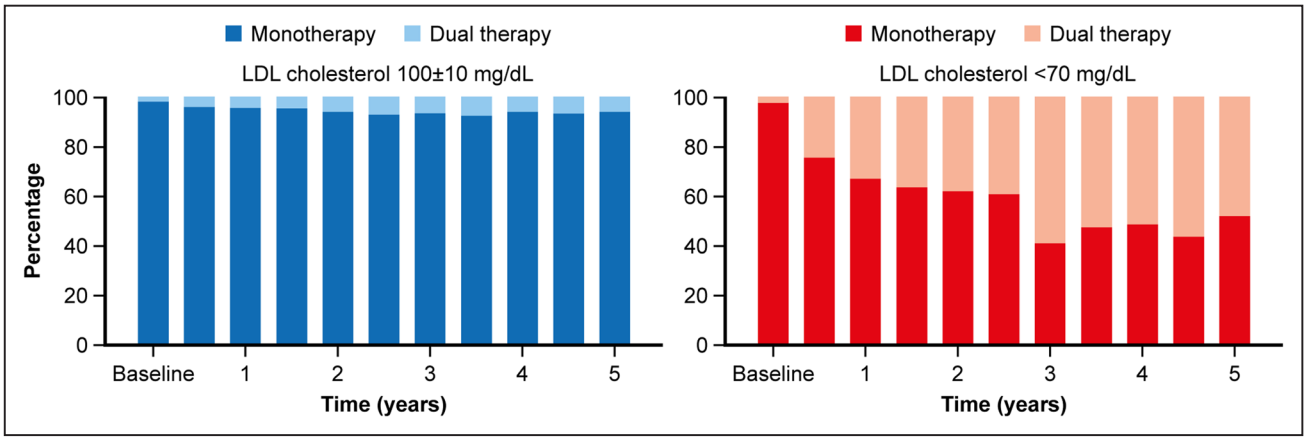

Figure 1. Evolution of prescriptions of dual therapy with statin and ezetimibe and with statin monotherapy in both randomization groups.

DISCUSSION

In this post hoc analysis of the Treat Stroke to Target trial, we found that in the lower target group, dual therapy with statin and ezetimibe significantly reduced major vascular events, and that the reduction was not significant on the statin monotherapy, as compared with all patients in the higher target group. This difference was observed although the mean LDL cholesterol achieved was very similar in both groups. Explanation for such a different effect between dual therapy and statin monotherapy groups may be a higher baseline mean LDL cholesterol level in the dual therapy group, with consequently greater reduction in LDL cholesterol from baseline. Indeed, the effect of LDL-lowering therapy has always been associated with the magnitude of the reduction in LDL cholesterol from baseline.[11,12,13]

Although, intuitively, we anticipated that patients in the lower target group on dual therapy would achieve a lower LDL cholesterol than patients on statin monotherapy, the similar LDL levels achieved in both group is finally logical. Indeed, by design, we asked investigators to titrate the dosage of statin and use ezetimibe as needed to target a LDL < 70 mg/dL to conform to the trial hypothesis. In other words, in the lower target group, there were no patients better treated (supposedly dual therapy) than

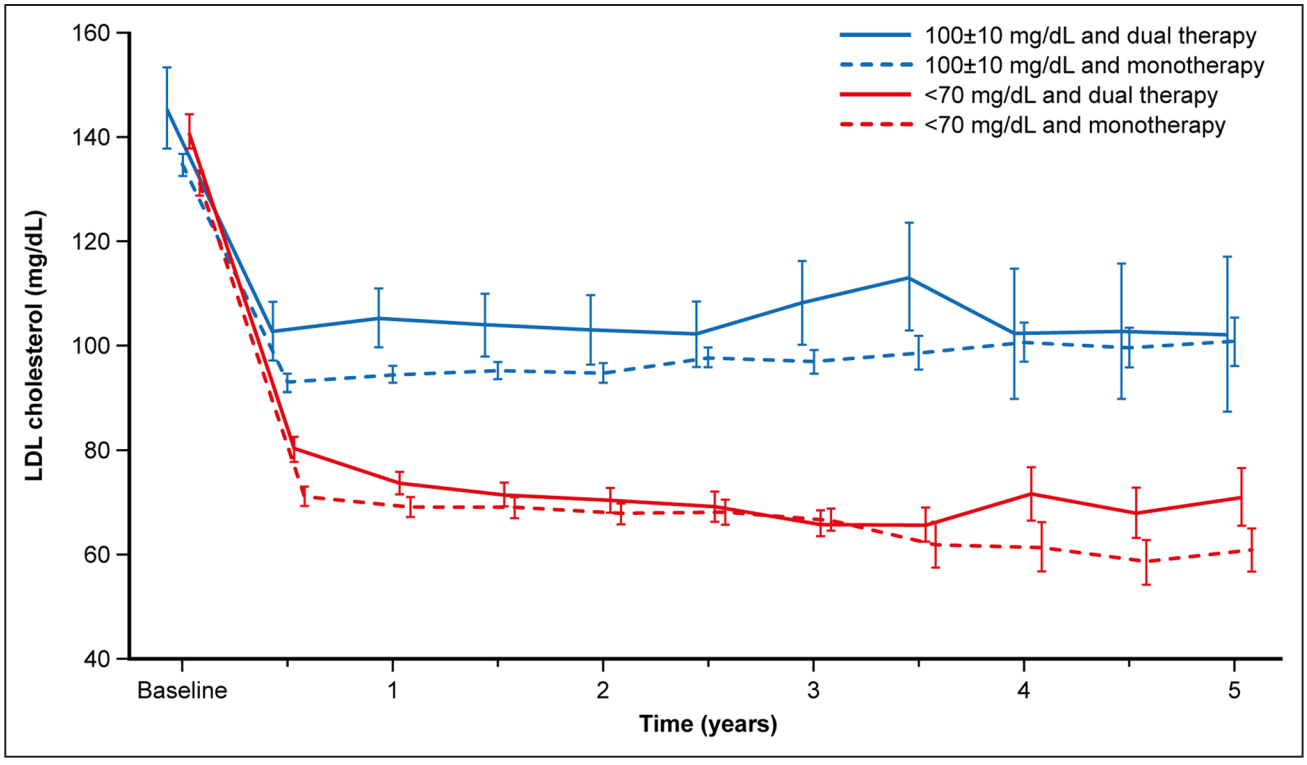

Figure 2. LDL (low-density lipoprotein) evolution according to dual therapy with statin and ezetimibe or statin monotherapy in the lower and higher target groups.

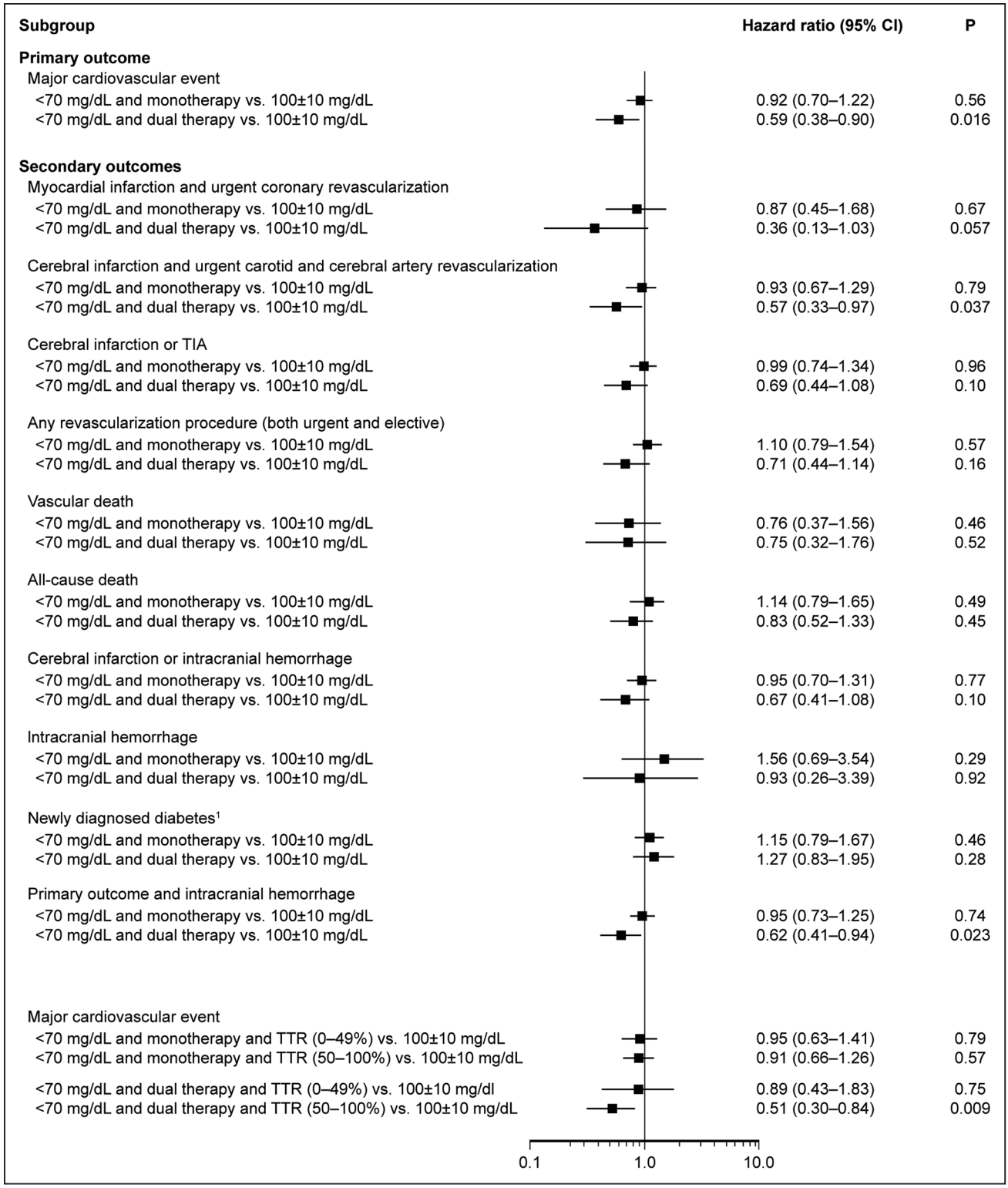

Figure 3. Hazard ratio for primary and secondary outcomes while on dual therapy with statin and ezetimibe (n=529) or on statin monotherapy (n=896) in the lower target group as compared with all patients in the control group (higher target group, n=1424), regardless the latter were on dual therapy (n=141) or on statin monotherapy (n=1283).

Patients who did not have diabetes at baseline were categorized as having newly diagnosed diabetes if they had at least 2 measures of fasting glucose of 126 mg/dL 7.0 (mmol/L) or more, or a glycated hemoglobin value of 6.5% or more at a follow-up visit. HR based on Cox model with competitive risk (Finn and Gray model) 0.88 ([95% CI, 0.68–1.15]; *P*=0.35) for target <70 mg/dL and monotherapy, and 0.58 ([95% CI, 0.38–0.89]; *P*=0.011) for target <70 mg/dL and dual therapy.

others (supposedly statin monotherapy). Interestingly, patients on dual therapy who had a time in therapeutic range <70 mg/dL between 50% and 100% had an even greater risk reduction. Hence, had all patients who were assigned a target LDL<70 mg/dL been on dual therapy, achieved LDL would likely be lower than the actual mean level observed, and would have larger percent reduction in major vascular events. This assumption should of course be trialed in future study.

Since baseline LDL cholesterol in the dual therapy group was 141±38 mg/dL and consequently all patients in the dual therapy group had a baseline LDL cholesterol above 103 mg/dL (141–38=103 mg), a practical suggestion derived from this analysis is that one could use immediate dual therapy with statin and ezetimibe in patients with a LDL cholesterol above 100 mg/dLto achieve a LDL <70 mg/dL.

In this analysis, we took advantage of LDL measurements done at every follow-up visit, to perform a time-varying analysis. The use of time-varying analysis enabled us to compare patient actually on dual therapy versus those actually on statin monotherapy, by truncating the follow-up of every individual patients at each follow-up 6-month visit in those actually on dual therapy during the last 6 months or on statin monotherapy during the last 6 months. With this method, patients contributed to the dual therapy group only during their follow-up time on dual therapy, and if for some reasons, they switched to monotherapy during their follow-up, they contributed to the statin monotherapy group for the duration they were on monotherapy, and, if they re-switched to dual therapy thereafter, they again contributed to the dual therapy group. Events occurring during these respective periods were distributed to the dual therapy or statin monotherapy according to respective groups. In addition to the post hoc nature of this analysis that has not been prespecified in the original protocol, one limitation of this analysis is that if an event occurred in someone who had been treated with monotherapy for 90% of the treatment period, and the event occurred just after switching to dual therapy, that event was attributed to dual therapy, although this can be questioned, and vice versa. One other limitation was that dual and single therapy were not randomized, so the findings should be taken with caution and be trialed in the future to be confirmed.

In conclusion, with all the limits of such analysis because dual and monotherapy were not randomized, in the TST trial, after an ischemic stroke with evidence of atherosclerosis, dual therapy with statin and ezetimibe in patients who were assigned a LDL cholesterol < 70 mg/dL, reduced major vascular events, as compared with patients who were assigned a LDL cholesterol 100±10 mg/dL. Future trial should explore the effect of new LDL cholesterol target <55 or even 40 mg/dL by systematically using dual therapy with statin plus ezetimibe or PCSK9 inhibitors.

ARTICLE INFORMATION

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Acknowledgments

The Charles Foix Group (Academic research organization for Clinical Trials in Stroke at Paris University) was responsible for study conduct. Dr Amarenco is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Amarenco designed the study, obtained funding, designed CRF, conducted the study and chaired the Steering Committee, interpreted the data, drafted the article; J. Labreuche and H. Charles did the statistical analysis, tables, and figures; Dr Vicaut supervised the statistical analysis and the methodology of the trial; all other authors revised the article for important intellectual content.

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Supplemental Material

STROBE checklist
Tables S1–S4
Figure S1

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