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Relation between baseline LDL-cholesterol and cardiovascular outcomes in high cardiovascular risk hypertensive patients: a post-hoc SPRINT data analysis

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Word count: 1042

Declarations of interest: none.

Abstract (250 words)

Background. Patients at increased cardiovascular (CV) risk, noticeably hypertensive patients, have multiple CV risk factors which may be treatment targets. LDL-cholesterol is one of such targets. Using the SPRINT cohort, studying the cardiovascular outcomes of hypertensive patients at increased CV risk, this post-hoc study aimed to assess the association of LDL-C with CV outcomes.

Methods. Clinical outcomes were those defined in SPRINT: a composite of various CV outcomes, all-cause mortality, and CV mortality. Association between LDL-C and the primary outcome was analysed using survival regression adjusted on confounding factors (age, sex, body-mass index, active smoking status, eGFR-estimated kidney function, history of CV disease, Framingham risk score, SPRINT treatment arm (intensive or control), baseline high-density-lipoprotein-bound cholesterol, and co-treatments by aspirin and statins).

Results. LDL-C was not associated with the primary outcome in the overall cohort (n=9631). Among patients in secondary prevention (i.e. with a previous history of CV disease) (n=1562), LDL-C was marginally associated with the incidence of the primary outcome (adjusted hazard-ratio 1.005 (95% CI=1.002-1.009), p=0.005 (per 1 mg/dl increase)) however, discrimination was poor with a ROC AUC of 0.54, p=0.087. There was no association between LDL-C and the primary outcome in other subgroup analyses (those under statin or not, and those in primary prevention).

Conclusion. This post-hoc analysis of SPRINT indicates that LDL-C levels do not influence cardiovascular events over a period of 3 years in a large cohort of

hypertensive patients at increased risk of cardiovascular events but without previous history of clinical cardiovascular disease other than stroke.

Introduction

Cardiovascular (CV) disease prevention relies in part on decreasing circulating low-density lipoprotein-bound cholesterol (LDL-C). Treatments include statins, anti-PCSK9 antibodies, ezetimibe. Although indications for these treatments are well-defined, no consensus was achieved regarding a target LDL-C level.[1]

This study uses data from the Systolic Blood Pressure Intervention Trial (SPRINT) to assess CV risk associated with target and non-target LDL-C levels at the time of inclusion.[2]

Methods

In the SPRINT trial, 9361 hypertensive patients were randomly allocated to intensive or standard antihypertensive treatment strategies. Clinical outcomes were monitored for up to 6 years after inclusion and included a primary composite endpoint (including myocardial infarction (MI), acute coronary syndrome (ACS) not resulting in MI, stroke, acute decompensated heart failure, and/or death from cardiovascular causes), all-cause mortality and cardiovascular mortality. All patients were at increased risk of CV events defined by one or more of the following: age >75 years, history of CV disease other than stroke (patients with prior stroke were excluded), chronic kidney disease with estimated glomerular filtration rate (eGFR) between 20 and less than 60 ml/min/1.73m^2 or 10-year Framingham risk score > 15%.

Using the same dataset, this study focuses on post-hoc analysis of the association between LDL-C and the incidence of the primary composite endpoint of

SPRINT. Data were obtained after qualifying for the worldwide data-analysis challenge organized by the New England Journal of Medicine.[3]

Data are presented as mean ± standard deviation. Cox proportional-hazards regressions were performed to analyze time-to-endpoints. Confounding variables that were used for adjustment in multivariable analyses included age, sex, body-mass index, active smoking status, eGFR-estimated kidney function, history of CV disease, Framingham risk score, SPRINT treatment arm (intensive or control), baseline high-density-lipoprotein-bound cholesterol (HDL-C), and co-treatments with aspirin and/or statins. Discriminative performance of LDL-C regarding the prognostication of events (primary endpoint, all-cause mortality and CV mortality), i.e. the capacity of LDL to differentiate patients who develop the outcome from those who would not, was assessed by area under curve (AUC) of receiver-operator characteristics (ROC) curves. All analyses were performed using SPSS v23.0 (IBM, Armonk, USA).

Results

Patients' baseline characteristics are presented in the original article.[2] LDL-C at baseline was 112.1 ± 35.8 mg/dl. Patients under statin medication represented 43.3% of the cohort (n=4054). Patients who had a prior history of CV disease represented 16.7% of the cohort (n=1562). There were 38 (0.4%) missing baseline values for LDL-C.

In the overall SPRINT cohort (n=9361), multivariable Cox regression analyses showed no independent association between baseline LDL-C and the primary

outcome. No threshold of LDL-C was associated with a higher risk of CV events

(**Figure 1**). Receiver operating characteristic (ROC) analysis of LDL-C found an area

under curve of 0.47 for the incidence of the primary outcome. Furthermore, analyses

on separate clinical events included in the primary endpoint (i.e. coronary events,

stroke, CV mortality and all-cause mortality) did not reveal independent association

between LDL-C and these events. There was no interaction between LDL-C and

SPRINT treatment arm.

In a multivariable subgroup analysis limited to patients with a previous

history of clinical CV disease other than stroke at the time of inclusion (n=1562, with

7 missing values), there was a statistically significant association between LDL-C and

the primary outcome with an adjusted hazard ratio of 1.005 (95CI=1.002-1.009),

p=0.005 (per 1 mg/dl increase). Baseline LDL-C was lower in this subgroup than in

the overall cohort (94.6 ± 35.4 vs. 112.1 ± 35.8, p<0.00001). However, ROC analysis

did not reach significance with an AUC of 0.54 (p=0.087). The corresponding survival

curves are shown in **Figure 2**.

Other subgroup analyses did not reveal associations between LDL-C and the

primary outcome. Specifically, patients under statin therapy (n=4054) did not show

any association between LDL-C and clinical events and corresponding ROC AUC was

0.47 (p=0.10).

Discussion

There are several limitations to these results: i) SPRINT was a trial in

hypertension and did not intend to test the hypothesis that LDL-C influences clinical

outcomes; ii) a median follow-up duration of 3.26 years may have been too short to allow for a sufficient number of clinical events (i.e. the primary composite endpoint, or its components) to occur and sufficient statistical power to detect a significant association between LDL-C and outcomes, although LDL-C lowering strategies showed positive outcomes even during the first year of implementation,[4] and recent meta-analysis pooling 34 trials and 270,288 patients showed a positive effect with same median follow-up to that of SPRINT (3.9 years).[5] Moreover, ROC analyses were also in favor of a lack of LDL-C threshold more at risk than another, iii) there was no information on statin prescription changes nor duration under statin treatment after inclusion in SPRINT, and v) as with all multivariable analyses, adjustments were only made on variables available at baseline and other confounding variables may have been ignored.

Nevertheless, the most important finding of this analysis is that no LDL-C threshold was associated more than another, with CV events. In the whole cohort, patients with LDL-C $\geq$ 160 mg/dl at the beginning of the study did not experience more CV events than those with LDL-C < 70 mg/dl. This association between LDL-C and CV events, however, existed in patients who had a prior history of CV disease. This supports contemporary recommendations which emphasize secondary prevention with aggressive LDL-C lowering irrespective of baseline levels.[6-8] This is even more relevant since the amplitude of risk reduction is proportional to the absolute LDL-C reduction, while LDL-C reduction is proportional to baseline LDL-C.[5]

In the recent Standard vs. Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy (EMPATHY) randomized trial comparing intensive vs. standard statin therapy, more than half of patients in the intensive group failed

to reach the target value of 70 mg/dl despite 3 years of treatment.[9] While this may partly explain why there was no statistical significance between the two treatment arms (p=0.15), it also emphasizes the impracticability of such a target approach. This comes in addition to previous analyses from real-world databases,[10] and registry highlighting the difficulty of reaching pre-specified targets.[11]

Conclusion

In conclusion, this *post-hoc* analysis of SPRINT indicates that LDL-C levels do not influence cardiovascular events over a period of 3 years in a large cohort of hypertensive patients at increased risk of cardiovascular events but without previous history of clinical cardiovascular disease other than stroke.

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Figure 1. Cumulative survival curves regarding primary outcome in the overall SPRINT cohort (n=9361), depending on baseline LDL-C levels

There was no association between baseline LDL-C levels and primary outcome, after adjusting for confounding factors (see text). There were 38 (0.4%) baseline missing values for LDL-C.
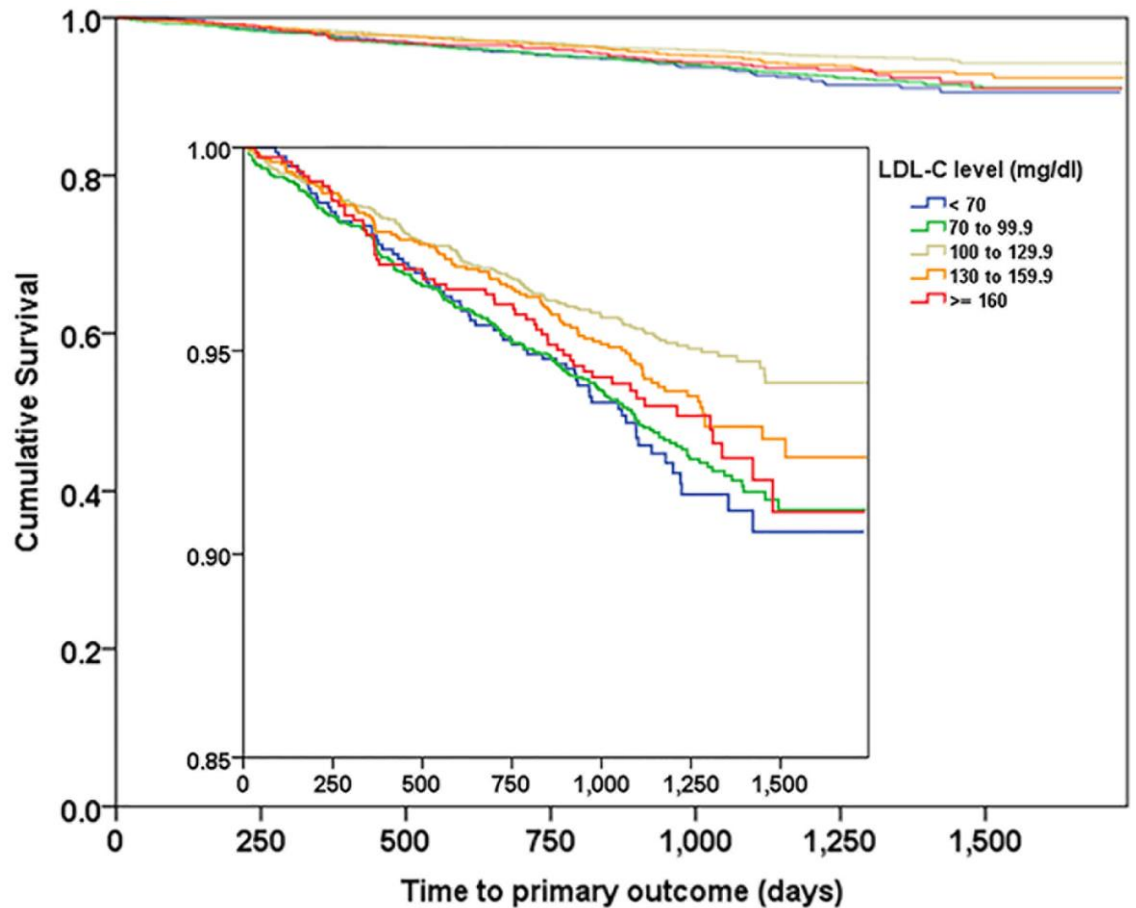
	Baseline	Day 250	Day 500	Day 750	Day 1000	Day 1250	Day 1500
< 70	902	863	836	801	627	317	110
70 to 99.9	2779	2687	2595	2512	2062	1125	361
100 to 129.9	3057	2945	2865	2789	2344	1236	411
130 to 159.9	1732	1665	1611	1558	1333	722	221
>= 160	853	823	797	775	636	346	104

Figure 2. Cumulative survival curves regarding primary outcome in the subgroup of patients in secondary prevention in the SPRINT cohort (n=1562), depending on baseline LDL-C levels.

Multivariable Cox regression analyses showed a significant association between LDL-C and the primary event with an adjusted HR of 1.005 (1.002-1.009), p=0.005. ROC AUC did not reach significance with 0.54, p=0.087. There were 7 (0.4%) missing values for baseline LDL-C.
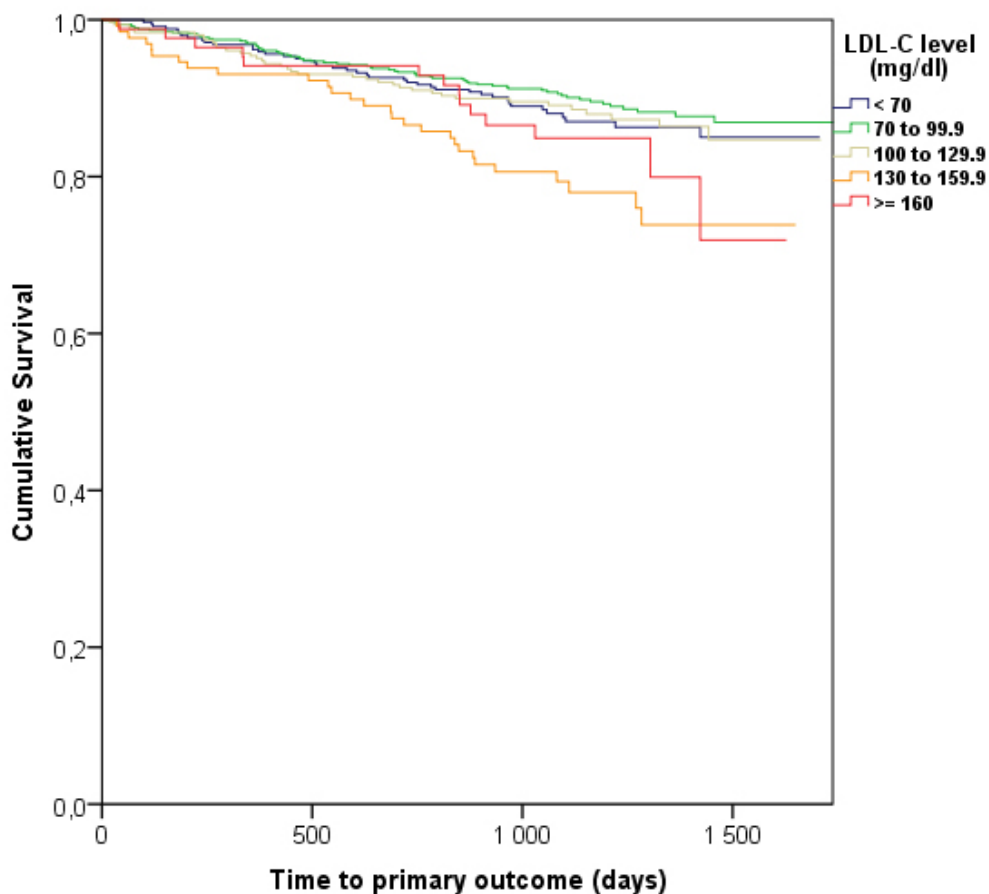
	baseline	Day 250	Day 500	Day 750	Day 1000	Day 1500
< 70	352	334	318	300	213	43
70 to 99.9	669	647	618	601	465	85
100 to 129.9	313	296	276	263	213	35
130 to 159.9	135	120	115	106	79	9
>= 160	86	82	79	76	55	5