Is High Serum LDL/HDL Cholesterol Ratio an Emerging Risk Factor for Sudden Cardiac Death? Findings from the KIHD Study

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Aim: Low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c), which are components of total cholesterol, have each been suggested to be linked to the risk of sudden cardiac death (SCD). However, the relationship between LDL-c/HDL-c ratio and the risk of SCD has not been previously investigated. We aimed to assess the associations of LDL-c, HDL-c, and the ratio of LDL-c/HDL-c with the risk of SCD.

Methods: Serum lipoprotein concentrations were assessed at baseline in the Finnish Kuopio Ischemic Heart Disease prospective cohort study of 2,616 men aged 42–61 years at recruitment. Hazard ratios (HRs) (95% confidence intervals [CI]) were assessed.

Results: During a median follow-up of 23.0 years, a total of 228 SCDs occurred. There was no significant evidence of an association of LDL-c or HDL-c with the risk of SCD. In analyses adjusted for age, examination year, body mass index, systolic blood pressure, smoking, alcohol consumption, physical activity, years of education, diabetes, previous myocardial infarction, family history of coronary heart disease, and serum high sensitivity C-reactive protein, there was approximately a two-fold increase in the risk of SCD (HR 1.94, 95% CI 1.21–3.11; \(p=0.006\)), comparing the top (≥4.22) versus bottom (≤2.30) quintile of serum LDL-c/HDL-c ratio.

Conclusion: In this middle-aged male population, LDL-c or HDL-c was not associated with the risk of SCD. However, a high serum LDL-c/HDL-c ratio was found to be independently associated with an increased risk of SCD. Further research is warranted to understand the mechanistic pathways underlying this association.

Key words: Low-density lipoprotein cholesterol, High-density lipoprotein cholesterol, Sudden cardiac death

Introduction

Sudden cardiac death (SCD), generally defined as a sudden and unexpected death occurring within a short period of time after the onset of symptoms, accounts for 50% of all cardiovascular disease (CVD)-related deaths \(^3\). Given that SCD is a global public health burden \(^2\), preventive strategies which are aimed at modulation of potential risk factors is a desirable approach to decrease the risk of SCD at the population level. Low-density lipoprotein cholesterol (LDL-c) plays a major role in the etiology of atherosclerosis \(^3\). A broad body of evidence shows LDL-c as the primary atherogenic lipoprotein \(^4\) and high-density lipoprotein cholesterol (HDL-c) as the predominant anti-atherosclerotic lipoprotein \(^5\). It is established that HDL-c is an independent protective risk factor for atherosclerotic CVD \(^5, 6\) and serum LDL-c as a causal risk factor for atherosclerotic CVD \(^7, 9\). Levels of these lipoproteins are now routinely measured in clinical practice for the screening of individuals with a high risk of CVD and being used as therapeutic targets for
the primary and secondary prevention of CVD\(^{10, 11}\).
Since approximately 80% of SCDs are attributable to underlying coronary heart disease (CHD)\(^{12}\), it follows
that SCD and CHD share similar risk factors, which include
the traditional cardiovascular risk factors such as hypercholesterolemia, diabetes, smoking, hypertension,
and obesity\(^{13-15}\). HDL-\(c\) and LDL-\(c\) (which are
components of total cholesterol and established factors
for SCD\(^{15}\)) have each been suggested to be linked to
the risk of SCD, but the reports have mostly been
inconsistent\(^{14, 16}\). It has been suggested that an LDL-\(c/\)
HDL-\(c\) ratio is a better risk indicator for CVD than
individual parameters\(^{17-20}\). Thus, we hypothesized that
the LDL-\(c/\)HDL-\(c\) ratio would relate to the risk of
SCD rather than LDL-\(c\) or HDL-\(c\) alone. To the best
of our knowledge, there has been no previous prospective
evaluation of the association of LDL-\(c/\)HDL-\(c\) ratio with the risk of SCD. Our main objective was to
evaluate the nature and magnitude of the prospective
association of LDL-\(c/\)HDL-\(c\) with the risk of SCD in
a population-based cohort of 2,616 apparently healthy
men from eastern Finland. In subsidiary analyses, we
also assessed the individual associations of serum
LDL-\(c\) and HDL-\(c\) levels with the risk of SCD.

**Methods**

This report was conducted according to the
STROBE (STrengthening the Reporting of OBserva-
tional studies in Epidemiology) guidelines for reporting
observational studies in epidemiology\(^{21}\).

**Study Population**
The Kuopio Ischemic Heart Disease (KIHD) risk
factor study, a population-based prospective cohort
study, was designed to investigate traditional and
emerging risk factors for atherosclerotic cardiovascular
outcomes in a population-based sample of men from
eastern Finland. The study population was a representa-
tive sample of men living in the city of Kuopio and
its surrounding rural communities who were 42–60
years of age at baseline examinations performed from
March 1984 through December 1989. A total of 2,682 eligible men participated in this study. The cur-
cent analysis is based on data obtained on 2,616 par-
ticipants who had complete data on serum lipopro-
teins, relevant covariates, and SCD outcomes. The
study was approved by the Research Ethics Commit-
tee of the University of Eastern Finland, and each par-
ticipant provided written informed consent.

**Biochemical Measurements**
Subjects provided blood specimens for lipopro-
tein separation between 8:00 and 10:00 a.m. after hav-
ing abstained from alcohol consumption for 3 days,
from smoking for 12 h, and after an overnight fast.
After the subject had rested in the supine position for
30 min, blood was drawn using Terumo Venoject VT-
100PZ vacuum tubes (Terumo Corp., Tokyo, Japan).
No tourniquet was used. The main serum lipoprotein
fractions consisting of very-low-density lipoprotein,
LDL and HDL were separated within 3 days of blood
sampling by a combination of ultracentrifugation and
precipitation. The cholesterol content (mmol/L) of all
lipoprotein fractions and serum triglycerides (TG)
were determined via enzymatic methods (cholesterol
CHOD-PAP method, Boehringer Mannheim,
Mannheim, Germany\(^{22}\)). Blood glucose was measured
via glucose dehydrogenase method (Merck, Darm-
stadt, Germany) after precipitation of proteins with
trichloric acetic acid. Serum high sensitivity C-reactive
protein (hs-CRP) was measured via the chemilumi-
nescence-immunoassay method using Immulite 2000
analyzer (DPC, Los Angeles, USA).

**Assessment of Risk Markers**
Data on socio-demographics, physical measure-
ments, medical history, and vascular risk factors have
been previously described\(^{23}\). Briefly, resting blood pres-
sure was measured between 8:00 and 10:00 a.m. on
the first examination day by a nurse using a random-
zero mercury sphygmomanometer. The measuring
protocol included, after a supine rest of 5 min, three
measurements in the supine position: one after 1 min
of standing, and two in the sitting position with 5
min intervals. Alcohol consumption was assessed via a
structured quantity-frequency method on drinking
behavior over the previous 12 months. Prevalent CHD
and myocardial infarction (MI) were ascertained via
record linkage from the national computerized hospi-
talization registry, which covers every hospitalization
in Finland. History of diabetes was defined as having
a clinical diagnosis of diabetes and regular treatment
with diet, oral hypoglycemic agents or insulin therapy,
fasting plasma glucose of $\geq 7.0$ mmol/l, or according
to self-reports. A subject was defined as a smoker if he
had ever smoked on a regular basis and had smoked
cigarettes, cigars, or a pipe within the past 30 days.
The assessment of the use of lipid-lowering therapy
over the follow-up period was based on the national
social insurance institution registry.

**Definition of Follow-up Events**
Deaths that occurred by the end of 2010 were
checked against the hospital documents, health centers,
and death certificates. There were no losses to follow-
up. A death was classified as SCD when it occurred
within 24 h of the onset of symptoms, including non-
of covariates were used: Model 1) age and examination year; Model 2) age, examination year, BMI, systolic blood pressure (SBP), smoking, alcohol consumption, physical activity, years of education, diabetes, previous MI, family history of CHD, and hs-CRP. Tests for statistical significance were two-sided, and differences with \( p < 0.05 \) were considered statistically significant.

SPSS software (version 19.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analyses.

### Results

#### Baseline Characteristics

Table 1 describes baseline characteristics of study participants. Men who died suddenly were older, had higher BMIs and SBPs, were more frequently smokers and consumed more alcohol, and were more likely to have had previous MIs and diabetes. They also had higher serum concentrations of LDL-c, hs-CRP, and LDL-c/HDL-c ratio, but lower concentrations of serum HDL-c. Participants in the highest fifth of the ratio of LDL-c/HDL-c (\( > 4.22 \)) compared with those in the lowest fifth (\( \leq 2.30 \)) had higher BMIs, smoked more, but consumed less alcohol, had a higher prevalence of diabetes, and had previous MIs. Serum HDL-c level was lower and LDL-c level was higher for men who died suddenly.

| Table 1. Baseline participant characteristics (N=2616) |
|------------------------------------------------------|
| Without SCD (N=2388) | With SCD (N=228) | \( P \)-value |
|----------------------|------------------|--------------|
| **Demographic characteristics** | | | |
| Age at survey (years) | 52.9 (5.2) | 54.7 (4.0) | <0.001 |
| BMI (kg/m²) | 26.8 (3.5) | 28.1 (4.1) | <0.001 |
| Years of education | 8.7 (3.5) | 8.0 (3.0) | 0.005 |
| Physical activity (kcal/d) | 142.4 (177.1) | 127.0 (146.5) | 0.204 |
| **Medical history** | | | |
| SBP (mmHg) | 134 (17) | 140 (18) | <0.001 |
| Alcohol consumption (g/week) | 74.3 (137.3) | 93.5 (134.0) | 0.044 |
| Smokers | 31 | 45 | <0.001 |
| Smoking (pack-years)* | 7.9 (16.0) | 14.5 (20.9) | <0.001 |
| Diabetics | 5 | 13 | <0.001 |
| Previous MI | 6 | 28 | <0.001 |
| CHD in family | 48 | 56 | 0.033 |
| **Laboratory data** | | | |
| Serum LDL cholesterol (mmol/L) | 4.02 (1.02) | 4.26 (1.01) | 0.001 |
| Serum HDL cholesterol (mmol/L) | 1.30 (0.30) | 1.23 (0.31) | 0.001 |
| Serum LDL-c/HDL-c ratio | 3.29 (1.24) | 3.67 (1.22) | <0.001 |
| Serum hs-CRP (mmol/L) | 2.36 (3.98) | 3.38 (5.59) | <0.001 |

* Pack-years denote the lifelong exposure to smoking, estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination.

BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; SCD, sudden cardiac death.
among those in the highest ratio of LDL-c/HDL-c (Table 2).

**Lipoproteins and the Risk of Sudden Cardiac Death**

During a median (interquartile range) follow-up time of 23.0 (0.02–27.4) years, a total of 228 SCD cases occurred. In analyses adjusted for age and examination year, HRs of SCD comparing the top versus bottom fifths of LDL-c concentrations and LDL-c/HDL-c ratio were 1.59 (95% CI: 1.05–2.42; \( p = 0.030 \)) and 2.67 (95% CI: 1.68–4.23; \( p < 0.001 \)), respectively. Comparing the bottom versus top fifths of HDL-c levels, the corresponding risk was 2.08 (95% CI: 1.35–3.19; \( p = 0.001 \)). In fully adjusted analyses, only LDL-c/HDL-c ratio remained significantly associated with the risk of SCD (1.94, 95% CI: 1.21–3.11; \( p = 0.006 \)) (Table 3). In a subsidiary analysis which was limited to men with relevant information on serum lipoproteins, SCD outcomes, as well as information on lipid-lowering medication, the association remained consistent for LDL-c/HDL-c ratio and SCD risk in analysis that adjusted for several established risk factors and lipid-lowering medication. In separate analyses for CHD and CVD death, LDL-c/HDL-c ratio was significantly associated with each of these outcomes, 1.95 (95% CI: 1.30–2.94; \( p = 0.001 \)) and 1.55 (95% CI: 1.14–2.12; \( p = 0.006 \)), respectively. In a sensitivity analysis, we assessed the association between LDL-c/HDL-c ratio and SCD in subjects without a prevalent history of CHD. HRs comparing the top versus bottom fifths of LDL-c/HDL-c ratio were 2.06 (95% CI: 1.21–3.48; \( p = 0.007 \)) and 1.79 (95% CI: 1.05–3.06; \( p = 0.033 \)), respectively, in analyses adjusted initially for age and examination year and further for established risk factors. To put the strength of the association of LDL-c/HDL-c ratio with SCD risk into context, direct comparisons were made to associations of serum triglycerides, non-HDL-c, TG/LDL-c ratio, and non-HDL-c/LDL-c ratio with SCD risk. There were no statistically significant associations of any of these lipid markers with the risk of SCD (Table 4).

**Discussion**

In this population-based study of middle-aged men, we observed an increased risk of SCD with a high LDL-c/HDL-c ratio. The association remained consistent when the analysis was restricted to men without a prevalent history of CHD. However, there was no significant association of SCD risk with HDL-c.
or LDL-c. Although total cholesterol (which has LDL-c and HDL-c as its components) is a major risk factor for SCD\textsuperscript{13,14}, prospective studies on the associations of its component lipoproteins have been limited and mostly conducted in individuals with pre-existing cardiometabolic disease, and the results have been inconsistent\textsuperscript{14,30}. Consistent with our results, it remains uncertain if LDL-c or HDL-c is independently associated with a future risk of SCD.

It is well established that the oxidative modification of LDL-c plays a key role in the pathogenesis of atherosclerosis\textsuperscript{5}. Oxidized LDL has a low affinity for macrophage scavenger receptors, and, thereby, oxidized LDL enters the blood circulation stimulating adhesion molecules and chemokines. Oxidized LDL can be taken up by macrophages through the scavenger receptors, leading to the formation of foam cells\textsuperscript{31}. This cascade leads to initiation and progression of atherosclerosis in coronary arteries, which is an underlying cause of SCD\textsuperscript{52}. In a postmortem study of SCDs, elevated LDL-c levels were shown to be correlated with the severity of coronary atherosclerosis\textsuperscript{59}. It has also been shown that plasma lipid and lipoprotein levels are significantly elevated in SCD cases\textsuperscript{16}. Among the LDL-c subclasses which differ in physicochemical properties and atherogeneity\textsuperscript{30}, small, dense LDL are regarded as more atherogenic than large LDL particles\textsuperscript{35,36}. Non-HDL-c, which can easily be estimated from routine lipid panels, has been suggested to be a surrogate marker of small, dense LDL-c\textsuperscript{37}. In our study, however, we found no evidence of an association when LDL-c/HDL-c ratio was substituted for non-HDL-c/LDL-c ratio. For HDL-c, there is a growing body of evidence which supports the concept that the functional properties of HDL-c rather than circulating levels, may be more important in determining CHD risk\textsuperscript{38}. Recent studies have shown that elevated HDL-c does not necessarily cause a decrease in the risk of CHD. In the Framingham study, 40% of CHD events occurred in individuals with normal or elevated HDL levels\textsuperscript{39}. Very high levels of HDL-c have also been demonstrated not to be associated with the risk of vascular events\textsuperscript{39}. Indeed, the evidence suggests that enhancing HDL-c function rather than increasing its levels, is associated with clinical benefit\textsuperscript{11}.

Given that this is the first prospective study on the association of LDL-c/HDL-c ratio and the risk of SCD in a general population, it is difficult to compare our findings in the context of previous studies. Based on data from clinical trials\textsuperscript{40-42}, a high LDL-c/HDL-c ratio is associated with coronary plaque progression, whereas a decreased LDL-c/HDL-c ratio achieved by pharmacological interventions, may be associated with coronary plaque regression. Some studies have recommended that individuals with a high ratio of LDL-c/HDL-c should commence treatment because of abnormal cholesterol levels\textsuperscript{43}. A pooled analysis of data from four prospective randomized trials revealed a positive linear correlation between an index of LDL-c/HDL-c ratio and changes in coronary plaque volume\textsuperscript{43}. In addition, an elevated LDL-c/HDL-c ratio has been suggested to be a predictor of coronary

$$\text{LDL cholesterol (mmol/L)}$$

| Quintiles | 1 | 2 | 3 | 4 | 5 | \(p\text{-value}\) |
|-----------|---|---|---|---|---|-----------------|
| No. of cases/No. of participants | 35/525 | 31/518 | 48/524 | 53/526 | 61/523 |
| HR (95% CI) | 0.87 (0.53 - 1.41) | 1.35 (0.87 - 2.08) | 1.42 (0.93 - 2.18) | 1.59 (1.05 - 2.42) | 0.030 |
| HDL cholesterol (mmol/L) | 1.52 | 1.34 | 1.52 | 1.19 | 1.33 | <= 1.04 |
| No. of cases/No. of participants | 32/532 | 28/517 | 54/525 | 54/525 | 60/517 |
| HR (95% CI) | 0.88 (0.53 - 1.47) | 1.73 (1.11 - 2.67) | 1.78 (1.15 - 2.75) | 2.08 (1.35 - 3.19) | 0.001 |
| LDL-c/HDL-c ratio | <= 2.30 | 2.30 | 2.86 | 2.87 | 3.44 | <= 2.86 |
| No. of cases/No. of participants | 25/523 | 36/523 | 35/524 | 65/523 | 67/523 |
| HR (95% CI) | 1.37 (0.82 - 2.28) | 1.32 (0.79 - 2.21) | 2.59 (1.63 - 4.11) | 2.67 (1.68 - 4.23) | <= 0.001 |
| HDL cholesterol (mmol/L) | 1.08 (0.64 - 1.82) | 1.16 (0.69 - 1.95) | 1.96 (1.22 - 3.15) | 1.94 (1.21 - 3.11) | <= 0.006 |

\(^{1}\)Adjusted for age and examination year.\(^{2}\)Adjusted for Model 1 plus BMI, systolic blood pressure, smoking, alcohol consumption, physical activity, years of education, diabetes, previous MI, CHD history in family and serum hs-CRP. BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction.
lipid-rich plaques and plaque vulnerability leading to an elevated SCD risk\textsuperscript{44, 45}. Rupture of high-risk vulnerable plaques is considered to be the major pathway in the development of coronary thrombosis, which eventually leads to acute MI and SCD\textsuperscript{46}. Coronary heart disease is the most common pathology underlying SCD\textsuperscript{47, 48}. However, in our study, the observed association of LDL-c/HDL-c ratio with the risk of SCD persisted when we restricted analysis to men without a history of CHD. Though the findings may partly reflect undiagnosed CHD, other pathways such as chronic inflammation may be involved. Further research is needed to help understand the mechanistic pathways of LDL-c/HDL-c ratio in the pathogenesis of SCD. Our findings demonstrate a clear and independent link between LDL-c/HDL-c ratio and SCD risk, which may have potential clinical implications. Assays for these lipoproteins are already being used in clinical practice to predict CVD risk in patients. Estimation of the ratio may have the potential to be used in the identification of individuals at high risk for SCD. However, further studies are needed to unequivocally establish this potential preventive strategy.

The strengths and limitations of the current study merit consideration. Strengths include its prospective population-based design, complete and long follow-up period, assessment of a comprehensive range of potential confounders, which enabled reliable assessments of the associations. Our representative sample makes it possible to generalize the observed results to male Caucasian populations, which was the primary focus of the study design; however, these results need to be replicated in female populations. The assessment of baseline clinical conditions by self-administered questionnaires is a limitation of the study. Further, we could not correct for regression dilution bias, which may have underestimated the observed associations, as we had only one-time assessment of lipid profiles, which may have changed during follow-up because of the probable changes in health habits or medication of participants over the time. Though many potential confounders were measured and carefully adjusted to ensure the validity of our key findings, there was still a potential for residual confounding owing to unmeasured risk factors.

In conclusion, the evidence suggests that a high LDL-c/HDL-c ratio, but not the individual lipoprotein components, is associated with an increased risk of SCD. Further studies are needed to replicate these associations and assess the mechanistic pathways underlying the relationships.

### Table 4. Hazard ratios for sudden cardiac death by quintiles of serum triglycerides, non-HDL-c, TG/LDL-c ratio, and non-HDL-c/LDL-c ratio

| Quintiles | 1 | 2 | 3 | 4 | 5 | p-value |
|-----------|---|---|---|---|---|---------|
| Triglycerides (mmol/L) | <0.76 | 0.76–0.99 | 1.00–1.26 | 1.27–1.73 | >1.73 |         |
| No. of cases/No. of participants | 37/525 | 45/531 | 31/492 | 52/513 | 63/555 |         |
| HR (95% CI)\textsuperscript{1} | Reference | 1.24 (0.80–1.91) | 0.86 (0.53–1.39) | 1.54 (1.01–2.36) | 2.03 (1.33–3.08) | <0.001 |
| HR (95% CI)\textsuperscript{2} | Reference | 1.09 (0.70–1.69) | 0.73 (0.45–1.18) | 1.15 (0.74–1.78) | 1.15 (0.73–1.80) | 0.503 |
| non-HDL-c (mmol/L) | <1.57 | 1.57–1.73 | 1.74–1.89 | 1.90–2.11 | >2.11 |         |
| No. of cases/No. of participants | 32/527 | 38/541 | 41/510 | 48/516 | 49/522 |         |
| HR (95% CI)\textsuperscript{1} | Reference | 0.70 (0.46–1.06) | 0.80 (0.53–1.20) | 0.95 (0.64–1.42) | 1.00 (0.67–1.48) | 0.555 |
| HR (95% CI)\textsuperscript{2} | Reference | 0.82 (0.54–1.26) | 0.90 (0.59–1.36) | 0.93 (0.62–1.40) | 1.01 (0.67–1.52) | 0.799 |
| TG/LDL-c ratio | <0.19 | 0.19–0.24 | 0.24–0.32 | 0.32–0.44 | >0.44 |         |
| No. of cases/No. of participants | 42/515 | 45/515 | 41/515 | 43/515 | 57/556 |         |
| HR (95% CI)\textsuperscript{1} | Reference | 1.05 (0.69–1.61) | 0.99 (0.64–1.53) | 1.11 (0.72–1.71) | 1.61 (1.06–2.44) | 0.037 |
| HR (95% CI)\textsuperscript{2} | Reference | 0.91 (0.59–1.40) | 0.85 (0.55–1.32) | 0.91 (0.58–1.41) | 0.99 (0.63–1.57) | 0.989 |
| non-HDL-c/LDL-c ratio | <1.07 | 1.07–1.10 | 1.10–1.14 | 1.15–1.20 | >1.20 |         |
| No. of cases/No. of participants | 36/523 | 42/523 | 46/523 | 56/524 | 48/523 |         |
| HR (95% CI)\textsuperscript{1} | Reference | 1.21 (0.77–1.89) | 1.42 (0.91–2.20) | 1.70 (1.10–2.60) | 1.59 (1.02–2.48) | 0.011 |
| HR (95% CI)\textsuperscript{2} | Reference | 1.06 (0.67–1.66) | 1.22 (0.78–1.91) | 1.29 (0.83–1.99) | 1.10 (0.69–1.76) | 0.478 |

\textsuperscript{1} Adjusted for age and examination year.

\textsuperscript{2} Adjusted for Model 1 plus BMI, systolic blood pressure, smoking, alcohol consumption, physical activity, years of education, diabetes, previous MI, CHD history in family and serum hs-CRP.

BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; TG, triglycerides.
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Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

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