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RESEARCH LETTER
Heart failure and cardiomyopathies

High visit-to-visit cholesterol variability predicts heart failure and adverse cardiovascular events: a population-based cohort study

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Dyslipidaemia is associated with elevated cardiovascular risks, with the INTERHEART study observing a tripling of myocardial infarction (MI) risk in patients with dyslipidaemia.[1] Most studies focused on mean levels or point estimates of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), despite well-known visit-to-visit variability.[2] Visit-to-visit cholesterol variability, reflecting fluctuations in cholesterol levels between visits, is prognostic for some adverse cardiovascular outcomes such as cardiac arrhythmias and mortality.[3,4] Nonetheless, associations between cholesterol variability and heart failure (HF) remain unclear. This study therefore investigated the associations between LDL-C and HDL-C variabilities and the risk of new-onset HF and major adverse cardiovascular outcomes.

This retrospective cohort study was performed according to the Declaration of Helsinki and approved by the local institutional review board. Patient consent was not required since deidentified data were used. Underlying data are available upon reasonable request to the corresponding authors. Data were retrieved from Clinical Data Analysis and Reporting System, a city-wide medical database in Hong Kong. Diagnoses are coded by *International Classification of Diseases Ninth revision* codes, which were used for identifying outcomes and comorbidities (see Supplementary material online, *Table S1*). Mortality data were obtained from the Hong Kong Death registry, a governmental registry of all Hong Kong citizens' death records. Both have been used in prior publications.[5]

Adult patients who attended any family medicine clinic in Hong Kong between 1 January 2000–31 December 2003 with more than three sets of fasting lipid profiles were included. Exclusion criteria were known HF, prior MI, using HF medications, pregnancy, known human immunodeficiency virus infection, and less than three sets of lipid profiles. Patients were followed up until 31 December 2019. Primary outcome was new-onset HF. Secondary outcomes were cardiovascular mortality, and MI.

Fasting LDL-C, HDL-C, and total cholesterol during index period were recorded, from which mean, standard deviation (SD), and coefficient of variation (CV) were calculated. As SD is only interpretable together with mean, CV ($\frac{SD}{mean}$) was reported to facilitate interpretation.

Student's *t*-test and Fisher's exact test were used to compare continuous and binary variables between subgroups, respectively. Univariable Cox regression identified covariates ($P < 0.010$;

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Part of this study has been presented as an oral presentation at ESC Asia 2021.

Supplementary material online, *Tables S3–5*) for adjustments in multivariable Cox regression which assessed associations between cholesterol measurements and outcomes. A prespecified subgroup analysis by the use of any lipid-lowering medication(s) at baseline was performed. Marginal effects were calculated by identifying partial derivatives of cholesterol measurements in Cox models for each data unit. All p-values were two-sided, with $P < 0.05$ considered significant. All analyses were performed on Statistical Package for Social Sciences (v25.0), Stata (v13.0), RStudio (v1.1.456), and/or Python (v3.6).

In total, 155 065 patients were identified, of which 5662 were included [2152 (38.0%) males; mean age 63.3 ± 12.4 years; Supplementary material online, *Figure S1* and Supplementary material online, *Table S2*]. Over a mean follow-up of 15.3 ± 4.6 years with 13 ± 9 sets of lipid profile (median of per-patient median between-test duration 0.9 years, interquartile range 0.5–1.1 years), new-onset HF, cardiovascular mortality, and MI occurred in 1196 (21.1%), 548 (9.7%), and 656 (11.6%) patients, respectively. Patients with baseline use of lipid-lowering medication(s) had higher variability of LDL-C, HDL-C, and total cholesterol.

HDL-C measures, but not LDL-C measures, were strongly associated with new-onset HF risk (*Table 1*). Higher HDL-C variability was associated with significantly higher new-onset HF risk [adjusted hazard ratio (aHR) for CV 48.68 (21.37, 110.90), $P < 0.001$, *Figure 1F*]. No significant association was observed between LDL-C variability and new-onset HF risk. Lower mean HDL-C was associated with significantly higher new-onset HF risk [aHR 0.60 (0.50, 0.72), $P < 0.001$; *Figure 1D*], but not mean LDL-C. Meanwhile, cholesterol variability was not significantly associated with cardiovascular mortality, whilst higher mean LDL-C [aHR 1.37 (1.20, 1.55), $P < 0.001$; Supplementary material online, *Figure S2A*] and lower mean HDL-C [aHR 0.54 (0.41, 0.71), $P < 0.001$; Supplementary material online, *Figure S2D*)] were both associated with higher cardiovascular mortality risk. Furthermore, higher variability of LDL-C [aHR for CV 3.64 (1.81, 7.33), $P < 0.001$; Supplementary material online, *Figure S3C*] and HDL-C (aHR for CV 39.87 [13.77, 115.47], $P < 0.001$; Supplementary material online, *Figure S3F*) were associated with higher MI risk. Lower mean HDL-C was associated with higher MI risk [aHR 0.46 (0.36, 0.60), $P < 0.001$; Supplementary material online, *Figure S3D*], but not mean LDL-C. Total cholesterol measures showed congruent results.

Subgroup analysis by use of lipid-lowering medication(s) (see Supplementary material online, *Tables S6*) found that in patients who did not use lipid-lowering medication(s) ($N = 4068$), associations between cholesterol measures and outcomes remained similar. Contrastingly, in patients who used lipid-lowering medication(s) ($N = 1594$), LDL-C and HDL-C variability were not prognostic. While lower mean HDL-C was associated with higher new-onset HF risk [aHR 0.43 (0.31, 0.61), $P < 0.001$], no association was observed for SD of HDL-C [aHR 1.829 (0.659, 5.078), $P = 0.247$], suggesting that the positive correlation between CV of HDL-C and new-onset HF risk was driven by inverse correlation for mean HDL-C. Meanwhile, HDL-C variability was not associated with MI risk, but higher total cholesterol variability remained associated with higher MI risk [aHR for CV 25.89 (3.74, 179.01), $P = 0.001$].

In this population-based study, we showed important but varying associations between visit-to-visit cholesterol variability and long-term risks of new-onset HF and major adverse cardiovascular outcomes, which may be partially negated by lipid-lowering medications. As far as we know, this is the first study demonstrating links between cholesterol variability and new-onset HF risk. Using population-based data with long follow-up, our results are widely applicable. Nonetheless, this study was limited by its retrospective nature, and the type of HF was unknown as echocardiographic data were unavailable. Additionally, many were excluded for having less than three sets of fasting lipid profiles during index period, limiting generalizability and possibly biasing for those indicated for lipid testing. Lastly, there may have been residual confounders, such as response to pharmacotherapy, smoking history, and blood pressure.

Table 1 Results of multivariable Cox regression analysis for the overall study cohort

	Hazard ratio [95% confidence interval], *P* value		
	New-onset heart failure[a]	Cardiovascular mortality[b]	Myocardial infarction[c]
Mean LDL-C	1.00 [0.91, 1.10], $P = 0.946$	1.37 [1.20, 1.55], $P < 0.001$	0.94 [0.83, 1.07], $P = 0.368$
SD of LDL-C	1.03 [0.85, 1.25], $P = 0.745$	0.94 [0.72, 1.24], $P = 0.677$	1.46 [1.15, 1.85], $P = 0.002$
CV of LDL-C	0.63 [0.36, 1.11], $P = 0.109$	0.19 [0.08, 0.42], $P < 0.001$	3.64 [1.81, 7.33], $P < 0.001$
Mean HDL-C	0.60 [0.50, 0.72], $P < 0.001$	0.54 [0.41, 0.71], $P < 0.001$	0.46 [0.36, 0.60], $P < 0.001$
SD of HDL-C	4.40 [2.72, 7.13], $P < 0.001$	1.05 [0.46, 2.39], $P = 0.901$	2.82 [1.42, 5.59], $P = 0.003$
CV of HDL-C	48.68 [21.37, 110.90], $P < 0.001$	1.63 [0.45, 5.97], $P = 0.460$	39.87 [13.77, 115.47], $P < 0.001$
Mean total cholesterol	0.89 [0.82, 0.96], $P = 0.004$	1.21 [1.08, 1.36], $P = 0.001$	0.87 [0.78, 0.98], $P = 0.017$
SD of total cholesterol	1.38 [1.18, 1.62], $P < 0.001$	1.18 [0.93, 1.51], $P = 0.169$	1.69 [1.39, 2.06], $P < 0.001$
CV of total cholesterol	5.49 [2.29, 13.15], $P < 0.001$	0.58 [0.16, 2.11], $P = 0.406$	29.94 [9.83, 91.19], $P < 0.001$

CV, coefficient of variation; SD, standard deviation.
[a]Adjusted for age, hypertension, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, ischaemic heart disease, peripheral vascular disease, stroke or transient ischaemic attack, dementia or Alzheimer's disease, and use of lipid-lowering medication(s).
[b]Adjusted for age, sex, hypertension, diabetes mellitus, atrial fibrillation, ischaemic heart disease, peripheral vascular disease, stroke or transient ischaemic attack, dementia or Alzheimer's disease, and use of lipid-lowering medication(s).
[c]Adjusted for age, sex, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, ischaemic heart disease, peripheral vascular disease, stroke or transient ischaemic attack, and use of lipid-lowering medication(s).

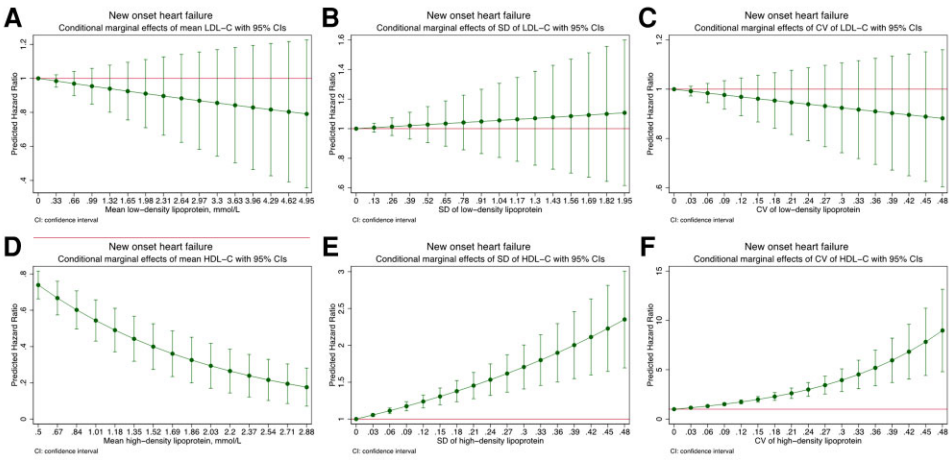

Figure 1 Marginal effects of (A) mean low density lipoprotein cholesterol (LDL-C) level, (B) standarddeviation (SD) of LDL-C level, (C) coefficient of variation (CV) of LDL-C level, (D) mean high-density lipoprotein cholesterol (HDL-C) level, (E) SD of HDL-C level, and (F) CV of HDL-C level on the risk of heart failure.

Nonetheless, we adjusted for numerous cardiovascular risk factors which should account for most pertinent confounders.

Although underlying mechanisms remain unclear, cholesterol variability's links to atherosclerotic progression[6,7] and inflammation[8,9] may be important, as these play important roles in HF.[10] Clinicians should be aware of the importance of controlling cholesterol fluctuations, and further investigations should explore measures which reduce such fluctuations.

Authors' contributions

J.S.K.C., D.I.S., and G.T. contributed to the conception or design of the work. T.T.L.L., O.H.I.C., A.K.C.W., B.M.Y.C., and G.T. contributed to the acquisition of data for the work. T.T.L.L., O.H.I.C., and J.Z. curated the data for the work. J.S.K.C. and J.Z. contributed to formal analysis and visualization for the work. J.S.K.C. and G.T. contributed to project administration. J.S.K.C. and D.I.S. drafted the manuscript. All authors critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Data availability

Underlying data are available upon reasonable request to the corresponding authors.

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