Association of lipoprotein (a) and 1 year prognosis in patients with heart failure with reduced ejection fraction

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Abstract

Aim Current study was to evaluate relationship between baseline serum lipoprotein (a) [Lp(a)] level and prognosis in patients with heart failure with reduced ejection fraction (HFrEF) and to explore whether the relationship would be modified by baseline high-sensitivity C-reactive protein (Hs-CRP) level.

Methods and results This is an observational prospective study. HFrEF patients from outpatient clinic were consecutively recruited (n = 362). Based on Lp(a) cutoff (30 mg/dL), patients were divided into normal and high Lp(a) groups; and based on Hs-CRP cutoff (3 mg/dL), patients were divided into low-degree and high-degree groups. The 1 year rate of HF rehospitalization was similar between these two groups (22.7% vs. 24.1%, P = 0.18), while the 1 year rate of cardiovascular mortality was higher in Lp(a) ≥ 30 mg/dL versus Lp(a) < 30 mg/dL groups (20.3% vs. 13.3%, P = 0.009), as was composite endpoint (44.4% vs. 36.0%, P < 0.001). After adjusting for covariates, elevated Lp(a) level remained associated with a higher risk of cardiovascular mortality [hazard ratio (HR) 1.22 and 95% confidence interval (CI) 1.04–1.64, P = 0.02] and composite endpoint (HR 1.38 and 95% CI 1.16–2.01, P = 0.006). In Hs-CRP ≥ 3 mg/dL group, elevated Lp(a) level was associated with HF rehospitalization, cardiovascular mortality, and composite endpoint, which was not observed in Hs-CRP < 3 mg/dL group. The association was greater for cardiovascular mortality (P-interaction = 0.04) and composite endpoint (P-interaction = 0.02) in Hs-CRP ≥ 3 mg/dL versus Hs-CRP < 3 mg/dL groups.

Conclusion Elevated Lp(a) level is associated with higher risk of cardiovascular mortality in HFrEF patients, which might be due to enhanced systemic inflammation.

Keywords Lipoprotein(a); Prognosis; Heart failure; Systemic inflammation

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Introduction

Heart failure (HF) is associated with substantial cardiovascular morbidity and mortality in China and worldwide. Although progress in medication and device therapy has been made in recent decade, prognosis of HF patients remains poor. Patients with HF with reduced ejection fraction (HFrEF) accounts for approximately 50% of all patients with HF. Ischaemic heart disease is the major cause of HFrEF. Interestingly and importantly, in recent decade, few studies from the western populations suggested that elevated serum lipoprotein (a) [Lp(a)] level was associated with HF development. Some studies reported that elevated serum Lp(a) level at baseline was associated with worse prognosis in HF patients. Nevertheless, the mechanisms are not fully understood yet, which deserves further elucidation. The adverse effects of elevated Lp(a) level on cardiovascular system have been well documented. In general, elevated Lp(a) level is associated with endothelial dysfunction, inflammatory cells migration and infiltration, oxidative stress, and fibrinolysis inhibition. These pathophysiological processes together lead to cardiovascular events. One recent study suggested that in patients with acute coronary syndrome (ACS) undergoing percutaneous coro-
nary intervention (PCI), elevated Lp(a) level was associated with a higher risk of in-hospital cardiovascular event, including incident HF.\textsuperscript{10} However, whether this association would be modified by baseline systemic inflammation was unknown. Importantly, two recent studies indicated that the relationship between elevated Lp(a) level and cardiovascular event in community populations was modified by baseline high-sensitivity C-reactive protein (Hs-CRP) level.\textsuperscript{17,18} Therefore, we herein evaluated the relationship between serum Lp(a) level and 1 year risk of HF rehospitalization and cardiovascular mortality in HFrEF patients. In addition, we evaluated whether the relationship would be modified by baseline systemic inflammation, which may provide information on the mechanisms underlying the association between elevated Lp(a) level and cardiovascular risk in HFrEF populations.

Methods

Study design and participants enrolment

This is an observational prospective cohort study. The current study was approved by the Clinical Research Ethic Committee of Huizhou Municipal Central Hospital and all the procedures were performed according to the Declaration of Helsinki. Written informed consent was obtained before participants’ enrolment. HF patients in our outpatient clinic from January 2019 to June of 2020 were consecutively screened and the inclusion criteria were as follow: (i) left ventricular ejection fraction (LVEF) $< 40\%$ as determined in the prior 1 month or during the index clinic visit; (ii) the aetiology of HF was ischaemic heart disease. The exclusion criteria were as follows: (i) LVEF $\geq 40\%$; (ii) HF due to other aetiology such as valvular heart disease or idiopathic dilated cardiomyopathy; (iii) existent systemic inflammatory disease such as rheumatoid arthritis or infectious disease; (iv) with non-steroid anti-inflammatory drug or glucocorticoid therapy; (v) end stage renal disease requiring haemodialysis; (vi) New York Heart Association (NYHA) class IV; or (vii) life expectancy less than 1 year. Briefly, the definition of HFrEF was based on the following criteria: (i) had prior or present HF symptoms and signs (e.g. exertional dyspnoea, bilateral pulmonary rales, ankle swelling etc.); (ii) pulmonary oedema at chest X-ray; (iii) elevated natriuretic peptide level; and (iv) LVEF $< 40\%$ based on echocardiographic examination. Based on the cutoff of Lp(a) as previously described,\textsuperscript{10} patients were divided into normal and high Lp(a) groups, respectively; and based on the cutoff of Hs-CRP (3 mg/dL) as recommended by the CDC/AHA,\textsuperscript{19} baseline inflammatory status was divided into low- and high-degree groups, respectively.

Data collection

Baseline data were collected using standard questionnaires by three independent investigators. Data, including demographics (age and sex), vital signs (blood pressure and heart rate), risk factor (smoking and obese status), co-morbidities [hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, prior myocardial infarction, prior PCI, prior coronary artery bypass grafting (CABG), and ischaemic stroke/transient ischaemic stroke (TIA)], and current medications used, were collected. Fasting venous blood was drawn to evaluate lipid profiles, fasting plasma glucose (FPG), creatinine, Hs-CRP, N-terminal pro-B type natriuretic peptide (NT-proBNP), and Lp(a). Creatinine was used to calculate estimated glomerular filtration rate (eGFR) and eGFR $< 60$ mL/min/1.73 m$^2$ was defined as chronic kidney disease (CKD). In brief, serum Lp(a) level was measured using latex agglutination immunoassays with a HITACHI 7600 chemistry auto-analyser.

Study endpoint

The study endpoint was HF rehospitalization and cardiovascular mortality. All patients were followed for up to 1 year either with telephone interview or outpatient clinic visit by study investigators. Patients who experienced either study endpoint, physical, and/or electronic medical record was obtained and reviewed by an independent cardiologist who did not participate in the current study. Patients who were loss to follow-up, their relatives were contacted to confirm their vital status. Follow-up duration was determined from the date of baseline visit to the date of occurrence of study endpoint or censoring date, whichever came first.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range; IQR), and categorical variables were presented as number (frequency). Between-group differences were evaluated using Student’s $t$-test or Mann–Whitney–Wilcoxon test for continuous variables, and $\chi^2$ test for categorical variables. Cox proportion regression analysis was performed to evaluate the association between baseline serum Lp(a) level and study endpoint, and the normal Lp(a) group was considered as the reference group. Covariates, including sex, age, blood pressure, heart rate, smoking and obese status, co-morbidities, and medications used, were adjusted for in the model. Kaplan–Meier curve was plotted. Hazard ratio (HR) and 95% confidence interval (CI) were reported. In addition, to evaluate whether baseline systemic inflammation would modify the relationship between serum Lp(a) level and study endpoint, additional analysis according to Hs-CRP level was performed.
Results

Comparisons of baseline characteristics

A total of 362 HFrEF patients were included, and study flow-chart is presented in Figure 1. Among these patients, the mean age was 65.9 years and women accounted for 35.6% (n = 129). The median serum Lp(a) level was 78.4 mg/dL, and patients with Lp(a) ≥ 30 mg/dL were 58.5% (n = 212). The median serum Hs-CRP level was 5.3 mg/dL, and patients with Hs-CRP ≥ 3 mg/dL were 62.6% (n = 227). Baseline characteristics were presented in Table 1. Compared with Lp(a) < 30 mg/dL group, patients in Lp(a) ≥ 30 mg/dL group were older and more likely to be women. They had higher heart rate, and they were more likely to have diabetes, dyslipidaemia, prior myocardial infarction, and ischaemic stroke/TIA. In addition, they had a higher Hs-CRP level and a lower eGFR.

Comparisons of medication therapy

Compared with Lp(a) < 30 mg/dL group (Table 2), patients in Lp(a) ≥ 30 mg/dL group were less likely to receive beta-blocker and mineralocorticoid receptor antagonist (MRA).

Association between serum lipoprotein (a) level and study endpoint

At 1 year follow-up, the rate of HF rehospitalization was similar between these two groups (22.7% vs. 24.1%; Table 3), while the rate of cardiovascular mortality was higher in Lp(a) ≥ 30 mg/dL group versus Lp(a) < 30 mg/dL group (20.3% vs. 13.3%), as was composite endpoint (44.4% vs. 36.0%). After adjusting for covariates (Figure 2A–C), elevated Lp(a) level was still associated with a higher risk of cardiovascular mortality (HR 1.22 and 95% CI 1.04–1.64) and composite endpoint (HR 1.38 and 95% CI 1.16–2.01).

Association between serum lipoprotein (a) level and study endpoint according to baseline high-sensitivity C-reactive protein level

We further evaluated whether baseline Hs-CRP level would modify the relationship between serum Lp(a) level and study endpoint (Table 4). In Hs-CRP < 3 mg/dL group, elevated Lp(a) level was not associated with study endpoint, while in Hs-CRP ≥ 3 mg/dL group, elevated Lp(a) level was associated with HF rehospitalization, cardiovascular mortality and composite endpoint. Magnitude of the association was greater for cardiovascular mortality (P-interaction = 0.04) and composite endpoint (P-interaction = 0.02) in Hs-CRP ≥ 3 mg/dL group versus Hs-CRP < 3 mg/dL group.

In Hs-CRP ≥ 3 mg/dL group, elevated Lp(a) level was associated with NYHA class III (OR 1.21 and 95% CI 1.08–1.37; P = 0.01), and similar findings were observed in Hs-CRP < 3 mg/dL group (OR 1.14 and 95% CI 1.02–1.29; P = 0.03).

Discussion

To the best of our knowledge, current study should be among the first few studies to evaluate the relationship between serum Lp(a) level and study endpoint in ischaemic HFrEF patients as well as assessing whether the relationship would be modified by baseline Hs-CRP level. There are three important findings. First, compared with patients with normal Lp(a) level, patients with elevated Lp(a) level had a higher cardiovascular risk at baseline; second, HFrEF patients with elevated Lp(a) level had a higher risk of cardiovascular mortality than their counterparts with normal Lp(a) level, even after adjusting for multiple covariates including Hs-CRP; third, baseline Hs-CRP level modified the relationship between serum Lp(a) level and study endpoint. Specifically, when Hs-CRP level was above the normal range, elevated Lp(a) level was associated with an increased risk of HF rehospitali-
Table 1 Baseline characteristics comparisons

| Variables | Lp(a) < 30 mg/dL (n = 150) | Lp(a) ≥ 30 mg/dL (n = 212) | P-value |
|-----------|----------------------------|-----------------------------|---------|
| Age (years) | 63.4 ± 10.7 | 67.8 ± 12.6 | 0.04 |
| Women, n (%) | 45 (30.0) | 84 (39.6) | 0.01 |
| NYHA classification | | | 0.78 |
| I–II, n (%) | 121 (80.6) | 169 (79.7) | |
| III, n (%) | 29 (19.4) | 43 (20.3) | |
| Systolic blood pressure (mmHg) | 135.4 ± 13.8 | 136.8 ± 14.6 | 0.37 |
| Diastolic blood pressure (mmHg) | 70.3 ± 10.6 | 72.4 ± 11.8 | 0.15 |
| Heart rate (b.p.m.) | 80.7 ± 16.9 | 83.6 ± 18.1 | 0.03 |
| Current smoker, n (%) | 52 (34.7) | 75 (35.4) | 0.64 |
| Obesity, n (%) | 35 (23.3) | 58 (27.4) | 0.08 |
| Hypertension, n (%) | 82 (54.7) | 120 (56.6) | 0.25 |
| Diabetes mellitus, n (%) | 31 (20.7) | 81 (38.2) | 0.008 |
| Dyslipidaemia, n (%) | 68 (45.3) | 122 (57.5) | 0.002 |
| Atrial fibrillation, n (%) | 22 (14.7) | 33 (15.6) | 0.93 |
| Prior myocardial infarction, n (%) | 88 (58.7) | 136 (64.2) | 0.03 |
| Prior PCI, n (%) | 104 (69.3) | 152 (71.7) | 0.74 |
| Prior CABG, n (%) | 29 (19.3) | 45 (21.2) | 0.50 |
| Ischaemic stroke/TIA, n (%) | 40 (26.7) | 75 (35.4) | 0.04 |
| Chronic kidney disease, n (%) | 52 (34.7) | 78 (36.8) | 0.18 |
| FPG (mmol/L) | 5.7 ± 0.5 | 5.8 ± 0.5 | 0.75 |
| Total cholesterol (mmol/L) | 5.1 ± 0.8 | 5.2 ± 1.0 | 0.37 |
| LDL-C (mmol/L) | 3.1 ± 0.5 | 3.2 ± 0.6 | 0.42 |
| HDL-C (mmol/L) | 1.0 ± 0.6 | 1.0 ± 0.5 | 0.83 |
| Triglyceride (mmol/L) | 1.7 (0.7–3.0) | 1.8 (0.7–3.2) | 0.10 |
| Lipoprotein (a) (mg/dL) | 16.9 (10.2–27.5) | 95.6 (50.7–155.2) | <0.001 |
| Hs-CRP (mg/dL) | 3.7 (1.8–8.2) | 7.1 (3.2–18.4) | 0.06 |
| NT-proBNP (pg/mL) | 389.3 (155.2–794.3) | 402.5 (184.3–790.3) | 0.07 |
| Creatinine (μmol/L) | 83.6 ± 16.7 | 87.2 ± 19.0 | 0.06 |
| eGFR (mL/min/1.73 m²) | 68.4 ± 15.2 | 63.6 ± 14.0 | 0.04 |
| LVEF (%) | 32.5 (26.2–37.7) | 31.8 (25.0–36.5) | 0.19 |
| Ischaemic heart disease | | | 0.24 |
| STEMI, n (%) | 63 (42.0) | 93 (43.9) | |
| NSTEMI, n (%) | 70 (46.6) | 100 (47.1) | |
| MINOCA, n (%) | 17 (11.4) | 19 (9.0) | |
| Duration since MI (years) | 4.5 (2.1–7.3) | 4.1 (1.9–6.4) | 0.09 |
| Number of stenotic vessels | 2.1 ± 1.1 | 2.3 ± 1.2 | 0.06 |

CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; Hs-CRP, high-sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructive coronary arteries; NSTEMI, non-ST-elevation myocardial infarction; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.

Dyslipidaemia has been considered as one of the potential mechanisms. Speciﬁcally, poor control of dyslipidaemia could lead to ischaemic event, aggravating cardiac function. Moreover, dyslipidaemia could enhance systemic inﬂammation, causing endothelia dysfunction and cardiac ﬁbrosis. Lp(a) is one of the circulating lipoproteins and serum Lp(a) level is mainly determined by the LPA genotypes. The pathophysiological function of Lp(a) has been well elucidated previously. In general, elevated Lp(a) level is associated with atherosclerosis progress and thrombosis formation.

In recent three decades, several observational studies have reported the relationship between elevated Lp(a) level and incident HF. For example, leveraging data from two cohort studies of the Danish general population, Kamstrup et al. reported that elevated Lp(a) level was associated with an increased risk of HF development, and the association appeared to be partly mediated by myocardial infarction and aortic valve stenosis. Interestingly, Steffen et al. reported that elevated Lp(a) level was associated with incident HF only in the Whites but not in the Blacks, Hispanics, or Chinese, suggesting the possibility of a racial/ethnic difference in the association between Lp(a) and the HF risk. Some studies have reported the relationship between serum Lp(a) level and prognosis in HF patients. For example, Agarwala et al. reported that in the US community populations, ele-
Table 2 Medications used comparisons

| Medications       | Lp(a) < 30 mg/dL (n = 150) | Lp(a) ≥ 30 mg/dL (n = 212) | P-value |
|-------------------|-----------------------------|-----------------------------|---------|
| Aspirin, n (%)    | 142 (94.7)                  | 202 (95.3)                  | 0.89    |
| Clopidogrel, n (%)| 43 (28.7)                   | 56 (26.4)                   | 0.43    |
| Ticagrelor, n (%) | 20 (13.3)                   | 29 (13.7)                   | 0.15    |
| Statins, n (%)    | 98 (65.3)                   | 147 (69.3)                  | 0.09    |
| ACE/ARB, n (%)    | 105 (70.0)                  | 152 (71.7)                  | 0.21    |
| Beta-blocker, n (%)| 86 (57.3)                   | 103 (48.6)                  | 0.03    |
| ARNI, n (%)       | 13 (8.7)                    | 16 (7.5)                    | 0.56    |
| MRA, n (%)        | 53 (35.3)                   | 43 (20.3)                   | 0.04    |
| Furosemide, n (%) | 62 (41.3)                   | 99 (44.8)                   | 0.07    |
| Insulin, n (%)    | 19 (12.7)                   | 34 (16.0)                   | 0.33    |
| OAD, n (%)        | 35 (23.3)                   | 46 (21.7)                   | 0.29    |

ACE/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; OAD, oral anti-diabetics.

Table 3 Association of Lp(a) and study endpoint

| Cardiovascular events | Lp(a) < 30 mg/dL (n = 150) | Lp(a) ≥ 30 mg/dL (n = 212) | Unadjusted HR (95% CI) | Adjusted HR (95% CI) |
|-----------------------|-----------------------------|-----------------------------|------------------------|----------------------|
| HF rehospitalization, n (%) | 34 (22.7)                   | 51 (24.1)                   | 1.11 (0.94–1.34)       | 1.00 (0.81–1.21)     |
| Cardiovascular mortality, n (%) | 20 (13.3)                   | 43 (20.3)                   | 1.54 (1.18–2.00)       | 1.22 (1.04–1.46)     |
| Composite, n (%)       | 54 (36.0)                   | 94 (44.4)                   | 1.70 (1.35–2.14)       | 1.38 (1.16–2.01)     |

Cl, confidence interval; HF, heart failure; HR, hazard ratio.

Notably, among patients with ischaemic HFrEF, the most important and effective therapy to improve prognosis is to adhere to the guideline-directed medication therapy (GDMT). Secondary prevention for ischaemic event is also important regarding elevated Lp(a) level. Based on the guideline recommendation and current daily clinical practice, we believe that adherence to GDMT plus cardiopulmonary rehabilitation would be essential to improve prognosis for ischaemic HFrEF patients. Unfortunately, in current study, we only obtained baseline data on medication used. In the future, it is needed...
to assess the adherence to GDMT and the use of cardiopulmonary rehabilitation post-discharge so as to better elucidate the impact of these therapies on prognosis for HFrEF patients.

Serum low-density lipoprotein cholesterol (LDL-C) level is commonly used to assess the ASCVD risk. Several medications such as statins have been used to reduce LDL-C and the ASCVD risk. Currently, accumulating evidence has shown that Lp(a) reduction with PCSK9 inhibitor therapy might be associated with a lower risk of cardiovascular event, which was independent of LDL-C reduction.28 In current study, among ischaemic HFrEF patients, there was no difference in baseline LDL-C level between the normal and high Lp(a) groups. In addition, after adjusting for covariates including

Table 4 Association of Lp(a) and study endpoint according to Hs-CRP level

| Lp(a) ≥ 30 mg/dL versus Lp(a) < 30 mg/dL | Adjusted HR (95% CI) | P-value | P-interaction |
|---------------------------------------|----------------------|---------|--------------|
| **HF rehospitalization**              |                      |         |              |
| Hs-CRP < 3 mg/dL                      | 1.02 (0.82–1.64)     | 0.39    | 0.13         |
| Hs-CRP ≥ 3 mg/dL                      | 1.12 (1.01–1.84)     | 0.04    |              |
| **Cardiovascular mortality**          |                      |         |              |
| Hs-CRP < 3 mg/dL                      | 1.10 (0.87–1.52)     | 0.10    | 0.04         |
| Hs-CRP ≥ 3 mg/dL                      | 1.43 (1.08–1.95)     | 0.03    |              |
| **Composite endpoint**                |                      |         |              |
| Hs-CRP < 3 mg/dL                      | 1.16 (0.95–1.52)     | 0.07    | 0.02         |
| Hs-CRP ≥ 3 mg/dL                      | 1.81 (1.30–2.14)     | 0.01    |              |

CI, confidence interval; HF, heart failure; HR, hazard ratio; Hs-CRP, high-sensitive C-reactive protein.

Adjusted for sex, age, hypertension, dyslipidaemia, mellitus diabetes, prior myocardial infarction, left ventricular ejection fraction, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, angiotensin receptor angiotensin receptor-neprilysin inhibitor, and mineralocorticoid receptor antagonist.

Figure 2 Kaplan–Meier curve of study endpoints. (A) Cumulative incidence of heart failure hospitalization. (B) Cumulative incidence of cardiovascular mortality. (C) Cumulative incidence of composite endpoint.

(A) HR 1.00 (95% CI 0.81–1.31; P-value=0.83)

(B) HR 1.22 (95% CI 1.04–1.46; P-value=0.02)

(C) HR 1.38 (95% CI 1.16–1.61; P-value=0.006)
dyslipidaemia, elevated Lp(a) level was still associated with poor prognosis, suggesting that the relationship between serum Lp(a) level and study endpoint might be independent of LDL-C. Indeed, prior study also suggested that elevated Lp(a) level was associated with an increased risk of revascularization in patients undergoing coronary revascularization, which was independent of baseline LDL-C level.30 These findings together indicate that Lp(a) may provide additional value in predicting the ASCVD risk.

Current study has three potential important clinical implications. First, in patients with ischaemic HFrEF, routinely implementing baseline Lp(a) evaluation in daily clinical practice may help better stratify the risk of HF hospitalization and cardiovascular mortality. Second, when assessing the relationship between serum Lp(a) level and prognosis, it is clinically relevant and pertinent to assess baseline systemic inflammatory status such as Hs-CRP level. Third, among ischaemic HFrEF patients with high Lp(a) and Hs-CRP levels, high-intensive statins or PCSK9 inhibitor therapy might be warranted to mitigate the cardiovascular risk.

There are some limitations of current study. First, this is an observational study and findings of current study can only be used for hypothesis generation. Second, this is a single-centre study with a moderate sample size, further multi-centre studies with large sample are needed to corroborate current study with a moderate sample size, further multi-centre studies with large sample are needed to corroborate current findings. Third, only HFrEF patients were included and whether these findings can be extrapolated to patients with HF with preserved ejection fraction is unknown. Fourth, the aetiology of HFrEF was ischaemic heart disease and whether these findings can be extrapolated to HFrEF with other aetiologies was also unclear. Last but not the least, Lp(a) is mainly determined by the genetics, and findings from the Chinese might not be extrapolated to other racial/ethnic groups.

**Conclusion**

Among ischaemic HFrEF patients, elevated Lp(a) level is associated with a higher risk of cardiovascular mortality at 1 year follow-up, which might be due to enhanced systemic inflammation. Closer monitoring Lp(a) and Hs-CRP levels and more aggressive cardiovascular risk management may be warranted for these population groups.

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**Conflict of interest**

None declared.

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