


ORIGINAL RESEARCH

# Association of Serum Lipoprotein (a) With the Requirement for a Peripheral Artery Operation and the Incidence of Major Adverse Cardiovascular Events in People With Peripheral Artery Disease

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**BACKGROUND:** The aim of this study was to assess the relationship between serum lipoprotein (a) (Lp[a]) concentration and the requirement for peripheral artery disease (PAD) operations or incidence of major adverse cardiovascular events.

**METHODS AND RESULTS:** A total of 1472 people with PAD presenting with intermittent claudication (n=355), abdominal aortic aneurysm (n=989) or critical limb ischemia (n=128) were prospectively recruited from 4 outpatient clinics in Australia. Lp(a) was measured in serum samples collected at recruitment using an immunoassay. Participants were followed for a median (interquartile range) of 2.4 (0.1–6.1) years to record requirement for any PAD operation, defined to include any open or endovascular PAD intervention (lower limb peripheral revascularization, abdominal aortic aneurysm repair, other aneurysm repair, or carotid artery revascularization). Myocardial infarctions, strokes, and deaths were also recorded. The association of Lp(a) with events was assessed using Cox proportional hazard analysis adjusting for traditional risk factors. Participants with Lp(a)  $\geq 30$  mg/dL had a greater requirement for any PAD operation (hazard ratio, 1.20, 95% CI, 1.02–1.41) and lower limb peripheral revascularization alone (hazard ratio 1.33, 95% CI, 1.06–1.66) but no increased risk of major adverse cardiovascular events or all-cause mortality. Lp(a)  $\geq 50$  mg/dL and a 40 mg/dL increase in Lp(a) were also associated with an increased risk of lower limb peripheral revascularization alone but not with other outcomes.

**CONCLUSIONS:** In participants with PAD referred for hospital management those with high Lp(a) had greater requirement for lower limb peripheral revascularization but Lp(a) was not consistently associated with other clinical events.

**Key Words:** Peripheral artery disease ■ surgical treatment ■ lipoprotein (a)

**D**iseases of the abdominal aorta and its branches (peripheral artery disease; PAD), are a collection of chronic occlusive and aneurysmal diseases, commonly presenting as intermittent claudication, abdominal aortic aneurysm (AAA) and critical limb ischemia.<sup>1–4</sup> People with these PAD presentations have an incidence of major cardiovascular events (MACE;

myocardial infarction, stroke or cardiovascular death) and requirement for arterial interventions, such as lower limb peripheral revascularization or AAA repair, of  $\approx 20\%$  and  $30\%$ , respectively, during short-term follow-up.<sup>5–10</sup>

Apolipoprotein B-containing lipoproteins, such as low-density lipoprotein-cholesterol (LDL-C), are

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## CLINICAL PERSPECTIVE

### What Is New?

- High serum lipoprotein (a) was associated with a small increased requirement for lower limb revascularization but not consistently associated with other clinical events in people referred for management of peripheral artery disease.

### What Are the Clinical Implications?

- More research is required to test whether lipoprotein (a) lowering therapies are beneficial for people with established arterial disease, such as those with peripheral artery disease.

## Nonstandard Abbreviations and Acronyms

|              |                                      |
|--------------|--------------------------------------|
| <b>Lp(a)</b> | lipoprotein (a)                      |
| <b>PAD</b>   | peripheral artery disease            |
| <b>MACE</b>  | major adverse cardiovascular events  |
| <b>AAA</b>   | abdominal aortic aneurysm            |
| <b>HR</b>    | hazard ratio                         |
| <b>LDL-C</b> | low-density lipoprotein-cholesterol  |
| <b>eGFR</b>  | estimated glomerular filtration rate |
| <b>CHD</b>   | coronary heart disease               |
| <b>IQR</b>   | interquartile range                  |

strongly implicated in cardiovascular disease.<sup>11</sup> There is now a range of effective drugs for lowering LDL-C, such as statins and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, which have been shown to substantially reduce MACE.<sup>8,12</sup> Lipoprotein (a) (Lp [a]) is an LDL-like particle with a highly glycosylated lipoprotein, called apolipoprotein (a), that has potent atherothrombotic and inflammatory properties.<sup>13</sup> Circulating concentrations of Lp (a) are highly heritable and transmitted in families as a co-dominant trait.<sup>13</sup> Population and case-control studies suggest that a high circulating concentration of Lp (a) is an important risk factor for the development of PAD.<sup>14–20</sup> The association of elevated circulating concentrations of Lp (a) with clinical events in people with established PAD has not been well studied. A smaller number of studies have investigated the association of elevation of Lp (a) with MACE<sup>21</sup> and peripheral events<sup>22,23</sup> in people with established PAD. These studies have had a number of limitations, such as small sample sizes,<sup>22,23</sup> studying populations of people presenting with PAD mixed with those presenting with other cardiovascular diseases,<sup>21</sup> not including the full spectrum

of PAD presentations,<sup>21–23</sup> and focusing on imaging outcomes such as patency<sup>22</sup> rather than clinical end points.

Lp (a) is implicated in promoting atherosclerosis progression, thrombosis, and inflammation, which are all pathological processes thought to be critical in stimulating PAD progression and the need for surgical intervention.<sup>24</sup> There is, therefore, a need to clarify the association of elevation in Lp (a) with requirement for peripheral artery operations and the incidence of MACE in a heterogeneous population of people with established PAD. The aims of the current study were to examine the associations of elevation in serum Lp (a) with requirement for peripheral artery operations and the incidence of MACE in a heterogeneous population of people with established PAD.

## METHODS

Requests for access to data, analytic methods, and study materials should be made to the corresponding author.

### Study Design and Participants

This investigation was designed as part of an ongoing prospective cohort study that commenced in 2002 and aimed to identify risk factors associated with the outcomes of people with PAD.<sup>25,26</sup> Participants were recruited from outpatient vascular services in Australia, including The Townsville University Hospital, the Mater Hospital Townsville, Gosford Vascular Services and The Royal Brisbane and Women's Hospital. The current study included participants with intermittent claudication, critical limb ischemia or an AAA diagnosed by a vascular specialist.<sup>27,28</sup> Intermittent claudication was diagnosed in people with a history of leg pain on walking and absence of lower limb pulses, ankle-brachial index  $\leq 0.9$  or imaging evidence of a lower limb artery stenosis of  $\geq 50\%$  or occlusion.<sup>25,26</sup> AAA was diagnosed if the orthogonal maximum outer to outer infra-renal aortic wall diameter was  $\geq 30$  mm measured from ultrasound or computed tomographic angiography.<sup>25,26</sup> Critical limb ischemia was diagnosed in people with symptoms of rest pain, gangrene or arterial ulceration and evidence of limb ischemia.<sup>25,26</sup> Written informed consent was obtained from all participants upon entry into the study. The study was performed in accordance with the Declaration of Helsinki and ethical approval was granted from institutional ethics committees (HREC/13/QTHS/125 and HREC/14/QTHS/203).

### Blood Analyses

At recruitment, participants had a fasting blood test, to measure total cholesterol, triglyceride, LDL-C,

high-density lipoprotein-cholesterol, and C-reactive protein, as previously described.<sup>28,29</sup> Serum was isolated at recruitment and stored at  $-80^{\circ}\text{C}$  until later batch analysis of Lp (a). Lp (a) was measured by an automated latex enhanced immunoassay (Quantia Lp (a) assay, Abbott Laboratories). Briefly, the Quantia Lp (a) assay is a turbidimetric immunoassay for the estimation of Lp (a) in human serum in an Architect autoanalyzer C16000 (Abbott Diagnostics) and is based on the principle of an agglutination reaction.<sup>30,31</sup> The interassay coefficient of variation for samples was  $<7\%$ . Lp (a) measurement using this method has been significantly correlated with an liquid chromatography–mass spectrometry method ( $n=50$ ,  $r=0.972$ ,  $P<0.001$ ). The definition of elevated Lp (a) is controversial with some guidelines considering  $\geq 30$  mg/dL abnormal<sup>32</sup> but others proposing  $\geq 50$  mg/dL.<sup>33</sup> In the

current study  $\geq 30$  mg/dL was selected for the primary analysis since this threshold has been previously associated with increased clinical events in prior studies of other high-risk populations<sup>22,34</sup> and also within meta-analyses.<sup>33</sup> Sensitivity analyses were performed using other thresholds, including  $\geq 50$  mg/dl and a 40 mg/dL (approximate standard deviation in the population) increase. Serum creatinine was measured as previously described<sup>26</sup> and estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.<sup>26</sup>

## Definitions of Risk Factors and Medications Recorded

Smoking history was classified as current, former, or never smokers.<sup>25,35</sup> Hypertension and diabetes

**Table 1. Comparison of Risk Factors in Participants With Different Presenting Problems**

| Risk Factor   | Presenting Peripheral Artery Disease Problem |                  |                                | P Value    |
|---|--|------------------|--------------------------------|------------|
|   | Intermittent Claudication (n=355)            | AAA (n=989)      | Critical Limb Ischemia (n=128) |            |
| Age, y  | 66.4 (59.7–73.3)                             | 74.0 (68.3–79.0) | 68.7 (59.6–76.2)               | $<0.001^*$ |
| Men   | 265 (74.6%)                                  | 808 (81.7%)      | 81 (63.3%)                     | $<0.001^*$ |
| Smoking   |  |                  |                                | $<0.001^*$ |
| Current   | 133 (37.5%)                                  | 286 (28.9%)      | 35 (27.3%)                     |            |
| Previous  | 182 (51.3%)                                  | 574 (58.0%)      | 60 (46.9%)                     |            |
| Never   | 40 (11.3%)                                   | 129 (13.0%)      | 33 (25.8%)                     |            |
| Hypertension  | 264 (74.4%)                                  | 765 (77.4%)      | 95 (74.2%)                     | 0.439      |
| Diabetes mellitus   | 120 (33.8%)                                  | 199 (20.1%)      | 63 (49.2%)                     | $<0.001^*$ |
| Coronary heart disease  | 170 (47.9%)                                  | 507 (51.3%)      | 66 (51.6%)                     | 0.533      |
| Aspirin   | 258 (72.7%)                                  | 589 (59.6%)      | 84 (65.6%)                     | $<0.001^*$ |
| Other anti-platelets  | 67 (18.9%)                                   | 195 (19.7%)      | 19 (14.8%)                     | 0.415      |
| Statin  | 257 (72.4%)                                  | 665 (67.2%)      | 83 (64.8%)                     | 0.138      |
| Fibrates  | 13 (3.7%)                                    | 29 (2.9%)        | 7 (5.5%)                       | 0.297      |
| Calcium channel blocker   | 105 (29.6%)                                  | 263 (26.6%)      | 39 (30.5%)                     | 0.423      |
| Beta-blockers   | 112 (31.5%)                                  | 374 (37.8%)      | 42 (32.8%)                     | 0.081      |
| Angiotensin converting enzyme inhibitor   | 141 (39.7%)                                  | 407 (41.2%)      | 61 (47.7%)                     | 0.286      |
| Angiotensin receptor blocker  | 86 (24.2%)                                   | 223 (22.5%)      | 32 (25.0%)                     | 0.713      |
| Metformin   | 82 (23.1%)                                   | 95 (9.6%)        | 40 (31.3%)                     | $<0.001^*$ |
| Estimated glomerular filtration rate (mL/min per $1.73\text{ m}^2$ ) <sup>†</sup> | 83.0 (64.8–94.0)                             | 68.0 (52.0–83.0) | 75.5 (58.3–92.0)               | $<0.001^*$ |
| Total cholesterol <sup>‡</sup>  | 4.40 (3.60–5.30)                             | 4.30 (3.60–5.10) | 4.00 (3.40–4.75)               | 0.001*     |
| Triglyceride  | 1.60 (1.10–2.30)                             | 1.40 (1.10–2.00) | 1.35 (1.00–2.00)               | 0.086      |
| Low-density lipoprotein <sup>‡</sup>  | 2.30 (1.70–3.10)                             | 2.30 (1.80–3.00) | 1.95 (1.60–2.60)               | $<0.001^*$ |
| High-density lipoprotein <sup>‡</sup>   | 1.20 (1.00–1.48)                             | 1.14 (0.95–1.40) | 1.20 (0.95–1.50)               | 0.126      |
| C-reactive protein (mg/L) <sup>§</sup>  | 3.0 (1.0–5.0)                                | 3.0 (1.9–6.0)    | 5.0 (2.2–10.0)                 | $<0.001^*$ |
| Lipoprotein (a) (mg/dL)   | 18.7 (7.4–52.9)                              | 18.3 (9.4–55.2)  | 15.5 (5.8–40.8)                | 0.067      |
| Lipoprotein (a) levels  |  |                  |                                | 0.261      |
| $<30$ mg/dL   | 221 (62.3%)                                  | 632 (63.9%)      | 90 (70.3%)                     |            |
| $\geq 30$ mg/dL   | 134 (37.7%)                                  | 357 (36.1%)      | 38 (29.7%)                     |            |

Shown are numbers (%) or medians and interquartile ranges. Lipids were reported in mmol/L. AAA indicates abdominal aortic aneurysm.

\* $P<0.01$ . Missing in <sup>†</sup>8, <sup>‡</sup>1, and <sup>§</sup>36.

**Table 2. Comparison of Risk Factors in Participants With Different Serum Lipoprotein (a) Concentrations**

| Risk Factor   | Serum Lipoprotein Concentration (mg/dL) |                  | P Value |
|---|---|------------------|---------|
|   | <30 (n=943)                             | ≥30 (n=529)      |         |
| Age   | 72.0 (66.2–77.4)                        | 71.3 (65.0–78.1) | 0.451   |
| Men   | 737 (78.2%)                             | 417 (78.8%)      | 0.763   |
| Smoking   |   |                  | 0.163   |
| Current   | 275 (29.2%)                             | 179 (33.8%)      |         |
| Previous  | 533 (56.5%)                             | 283 (53.5%)      |         |
| Never   | 135 (14.3%)                             | 67 (12.7%)       |         |
| Hypertension  | 708 (75.1%)                             | 416 (78.6%)      | 0.123   |
| Diabetes mellitus   | 234 (24.8%)                             | 148 (28.0%)      | 0.184   |
| Coronary heart disease  | 464 (49.2%)                             | 279 (52.7%)      | 0.193   |
| Aspirin   | 583 (61.8%)                             | 348 (65.8%)      | 0.130   |
| Other anti-platelets  | 172 (18.2%)                             | 109 (20.6%)      | 0.268   |
| Statin  | 621 (65.9%)                             | 384 (72.6%)      | 0.008*  |
| Fibrates  |   |                  |         |
| Calcium channel blocker   | 248 (26.3%)                             | 159 (30.1%)      | 0.122   |
| Beta-blockers   | 339 (35.9%)                             | 189 (35.7%)      | 0.932   |
| Angiotensin-converting enzyme inhibitor   | 386 (40.9%)                             | 223 (42.2%)      | 0.648   |
| Angiotensin receptor blocker  | 225 (23.9%)                             | 116 (21.9%)      | 0.399   |
| Metformin   | 145 (15.4%)                             | 72 (13.6%)       | 0.359   |
| Estimated glomerular filtration rate (mL/min per 1.73 m <sup>2</sup> ) <sup>†</sup> | 71.0 (56.0–86.0)                        | 73.0 (54.0–88.0) | 0.277   |
| Total cholesterol <sup>‡</sup>  | 4.25 (3.50–5.00)                        | 4.40 (3.70–5.10) | 0.009*  |
| Triglyceride  | 1.50 (1.10–2.10)                        | 1.40 (1.00–2.10) | 0.157   |
| Low-density lipoprotein <sup>†</sup>  | 2.20 (1.70–3.00)                        | 2.40 (1.90–3.10) | 0.004*  |
| High-density lipoprotein <sup>†</sup>   | 1.14 (0.95–1.40)                        | 1.20 (1.00–1.46) | 0.088   |
| C-reactive protein (mg/L) <sup>§</sup>  | 3.0 (1.9–6.0)                           | 3.00 (1.9–6.2)   | 0.938   |

Shown are numbers (%) or medians and interquartile ranges. Lipids were reported in mmol/L.

\* $P < 0.01$ . Missing in <sup>†</sup>8, <sup>‡</sup>1, and <sup>§</sup>36.

mellitus were defined by a past history of diagnosis or treatment for these conditions.<sup>25,35</sup> Coronary heart disease (CHD) was defined as a history of myocardial infarction, angina, or previous treatment for CHD.<sup>35</sup> All prescribed medications including antiplatelet agents, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and metformin were recorded at the time of recruitment.

### Definition and Assessment of Cardiovascular and Peripheral Vascular Outcomes

Participants were followed up as part of normal care. Outpatient follow-up was performed according to local clinical practice. Participants were offered at least annual follow-up. Outcome data were recorded during clinical reviews on prospectively defined case report forms. Hospital charts and electronic records were also reviewed by a vascular specialist. Outcome data were also obtained from linked hospital admission

records as previously described.<sup>25,26,36,37</sup> Linked data were obtained from the Queensland Hospital admitted patient data collection which is regularly audited to minimize inaccuracies.<sup>38</sup> PAD operations recorded included lower limb (open and endovascular) peripheral revascularization, carotid artery revascularization, open and endovascular AAA repair, and other aneurysm repair.<sup>6,10,36</sup> The primary outcome was requirement for any PAD operation, defined as including any of the peripheral artery interventions listed above. Secondary outcomes were MACE, lower limb (open or endovascular) peripheral revascularization, and AAA (open or endovascular) repair. The tertiary outcome was all-cause mortality. MACE was defined as the first occurrence of a major cardiovascular event including myocardial infarction, stroke, or cardiovascular death. Decisions about requirement for operative interventions were at the discretion of the treating consultant surgeon but were in line with current international guidelines,<sup>39,40</sup> including lifestyle limiting intermittent claudication failing to respond to conservative therapy,

symptomatic or large asymptomatic AAA, and critical limb ischemia.<sup>10,41</sup>

## Sample Size

We aimed to have adequate power to test our hypothesis that Lp (a)  $\geq 30$  mg/dL was associated with a greater requirement for any PAD operation. Our prior studies suggest that PAD operations are common in people with established PAD occurring in between 30% and 40% during short-term follow-up.<sup>6,10,36</sup> Monte-Carlo simulations suggest that a multivariable regression model is powered sufficiently when 10 outcome events per degree of freedom of the predictor variables are observed.<sup>42</sup> We estimated that the 2-year requirement for any PAD operation would be  $\approx 30\%$  and planned to adjust for 10 variables, some with multiple degrees of freedom, including age, sex, smoking (current, former or never smokers), presentation (intermittent claudication, AAA, or critical limb ischemia), diabetes mellitus, hypertension, CHD, statin prescription, LDL-C, and estimated glomerular filtration rate in the regression models. Based on these estimates we felt that a sample size of  $>1000$  participants would be well powered to test the main hypothesis.

## Data Analysis

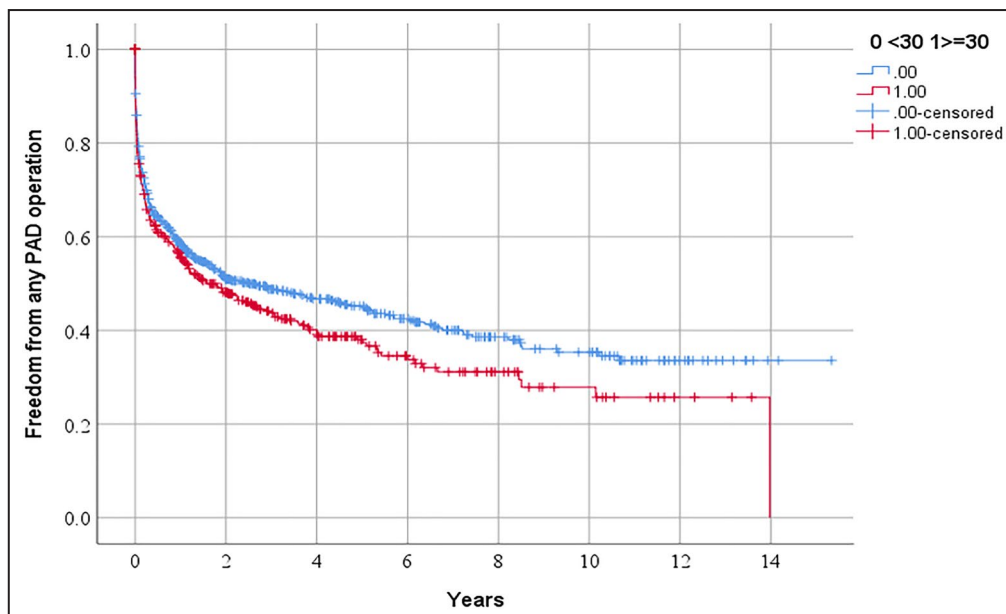
Data were analyzed using the SPSS v 25 (IBM, Armonk, NY) software package. Continuous data that were not normally distributed, as confirmed using the Shapiro–Wilk test, and were presented as median and interquartile range. Between-group comparisons were conducted using the Mann–Whitney *U*

and Kruskal–Wallis tests. Categorical variables were compared using Pearson Chi squared test. Kaplan–Meier analysis was used to calculate the observed incidence of PAD operations and MACE and log-rank test performed to statistically compare incidence rates. For these analyses  $P < 0.05$  were considered significant. Cox proportional hazard analyses assessed the association of serum Lp (a)  $\geq 30$  mg/dL with events adjusted for other risk factors. Analyses were adjusted for age, sex, smoking (current, former, or never smokers), presenting problem (intermittent claudication, AAA, or critical limb ischemia), diabetes mellitus, hypertension, CHD, statin prescription, LDL-C, and estimated glomerular filtration rate. Sensitivity analyses examined the association of events with Lp (a)  $\geq 50$  mg/dL and Lp (a) as a continuous variable using a 40 mg/dL increase (approximate SD in the cohort). For Cox regression analyses, Lp (a) was considered associated with the event concerned when the 95% CI of the hazard ratio did not cross one. The effect of age on the association of Lp (a)  $\geq 30$  mg/dL with events was also examined. For these analyses, participants were divided into those aged  $< 72$  and  $\geq 72$  years (approximate median age of the cohort). The full Cox regression models are available from the corresponding author.

## RESULTS

### Participants and Outcomes

Between March 2002 and March 2018, 1472 people with intermittent claudication ( $n=355$ ), AAA ( $n=989$ )



**Figure 1.** Freedom from requirement for any peripheral artery disease operation in people referred for management of peripheral artery disease in relation to serum lipoprotein (a)  $\geq 30$  mg/dL. PAD indicates peripheral artery disease.



and critical limb ischemia (n=128) were recruited. Participants' age and sex, history of smoking and diabetes mellitus, and prescription of aspirin and metformin varied significantly according to the presenting problem (Table 1). Serum concentrations of total cholesterol, LDL-C, and C-reactive protein, and estimated glomerular filtration rate also varied significantly between participants with different presenting problems (Table 1). Participants were followed for a median (interquartile range) of 2.4 (0.1–6.1) years. During that time participants required a total of 1084 PAD operations, including 672 lower limb peripheral revascularizations, 353 AAA repairs, 31 carotid artery revascularizations, and 28 repairs of other aneurysms. The participants also had a total of 230 myocardial infarctions and 75 strokes. There were a total of 368 deaths of which 242 were attributed to cardiovascular disease.

### Association of High Serum Lp (a) With Risk Factors

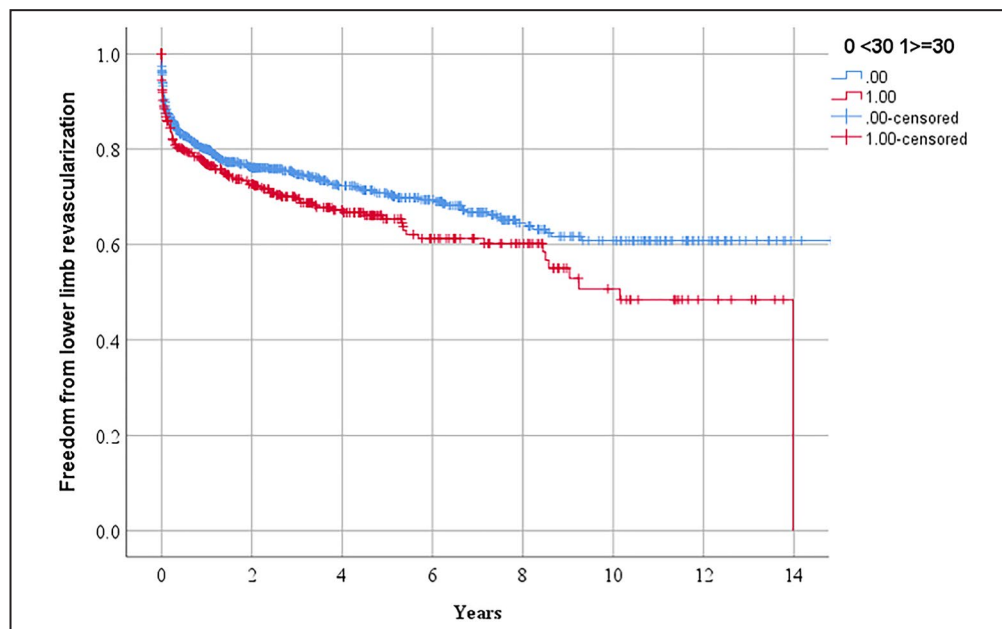
At recruitment, 943 (64.1%) and 529 (35.9%) participants had Lp (a) < and  $\geq 30$  mg/dL, respectively. Three hundred and eighty-nine (26.4%) and 154 (10.5%) participants had Lp (a)  $\geq 50$  and  $\geq 100$  mg/dL, respectively. As previously reported in other cohorts,<sup>43,44</sup> participants with Lp (a)  $\geq 30$  mg/dL were significantly more likely to be prescribed statins than those with lower Lp (a) levels (Table 2). Participants with Lp (a)  $\geq 30$  mg/dL also had significantly higher serum total cholesterol and LDL-C than those with lower Lp (a) levels (Table 2).

### Association of High Serum Lp (a) With First Occurrence of Clinical Events

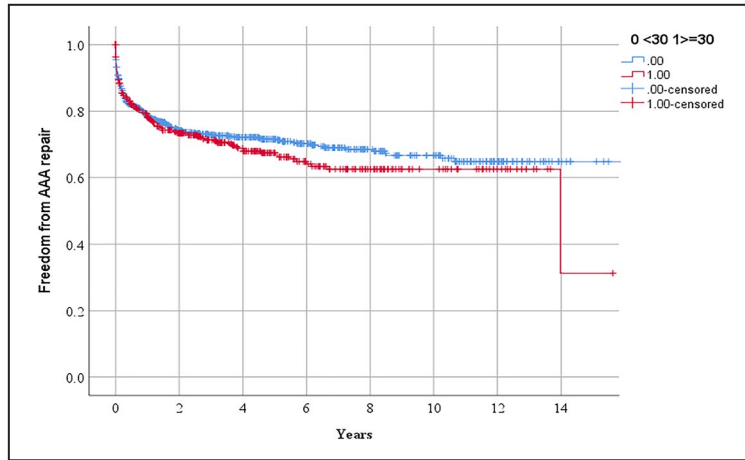
According to Kaplan Meier analyses, the requirements for the following procedures over 3 years were: any PAD operation 51.2% and 56.3% ( $P=0.041$  by log rank test; Figure 1), lower limb peripheral revascularization 25.3% and 30.4% ( $P=0.029$  by log rank test; Figure 2), and AAA repair 27.1% and 28.7% ( $P=0.282$  by log rank test; Figure 3) in participants with Lp (a) < and  $\geq 30$  mg/dL, respectively. The incidences of MACE were 17.7% and 19.7% ( $P=0.250$  by log-rank test; Figure 4) and all-cause mortality were 15.3% and 13.0% ( $P=0.885$  by log-rank test; Figure 5) in participants with Lp (a) < and  $\geq 30$  mg/dL, respectively. After adjustment for other risk factors, Lp (a)  $\geq 30$  mg/dL was associated with greater incidence of any PAD operation and lower limb peripheral revascularization alone but not AAA repair (Table 3 and Table S1). The incidence of MACE and all-cause mortality were not associated with Lp (a)  $\geq 30$  mg/dL (Table 3).

### Association of High Serum Lp (a) With Total Occurrence of Each Clinical Event

Of the 640 participants who had any PAD operation, 422 had 1 operation and 218 had multiple operations (122 participants had 2, 41 had 3, 28 had 4, 11 had 5, 4 had 6, 5 had 7, 3 had 8, 1 had 9, 1 had 10, 1 had 11, and 1 had 15). The total numbers of clinical events in participants with Lp (a) <30 and  $\geq 30$  mg/dL are shown in Table 4.



**Figure 2.** Freedom from requirement for lower limb peripheral revascularization in people referred for management of peripheral artery disease in relationship to serum lipoprotein (a)  $\geq 30$  mg/dL.



**Figure 3.** Freedom from requirement for abdominal aortic aneurysm repair in people referred for management of peripheral artery disease in relationship to serum lipoprotein (a)  $\geq 30$  mg/d. AAA indicates abdominal aortic aneurysm.

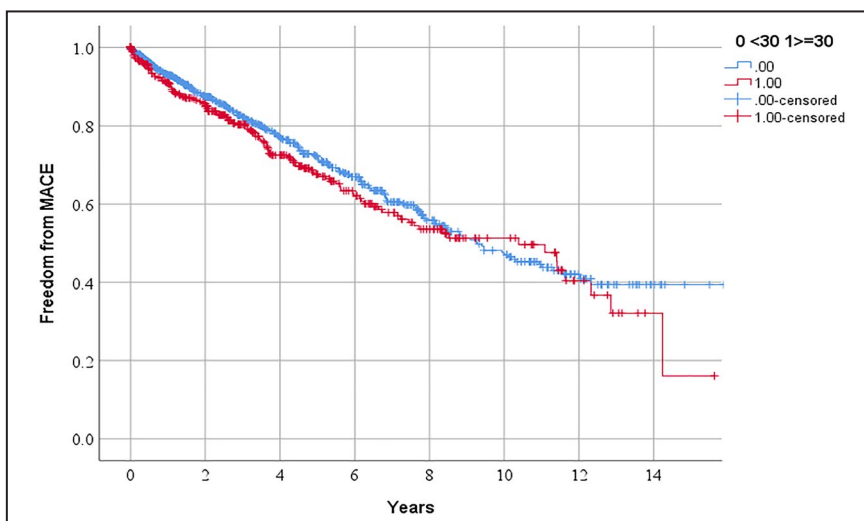
### Sensitivity Analyses

After adjustment for other risk factors, Lp (a)  $\geq 50$  mg/dL or a 40 mg/dL increase in Lp (a) were associated with a greater requirement for lower limb peripheral revascularization but not with other events (Tables 3 and 5). In participants aged  $< 72$  years, Lp (a)  $\geq 30$  mg/dL was associated with a greater requirement for any PAD operation but not with other events (Table 6). In participants aged  $\geq 72$  years, Lp (a)  $\geq 30$  mg/dL was associated with a greater requirement for lower limb peripheral revascularization and all-cause mortality but not with other events (Table 6).

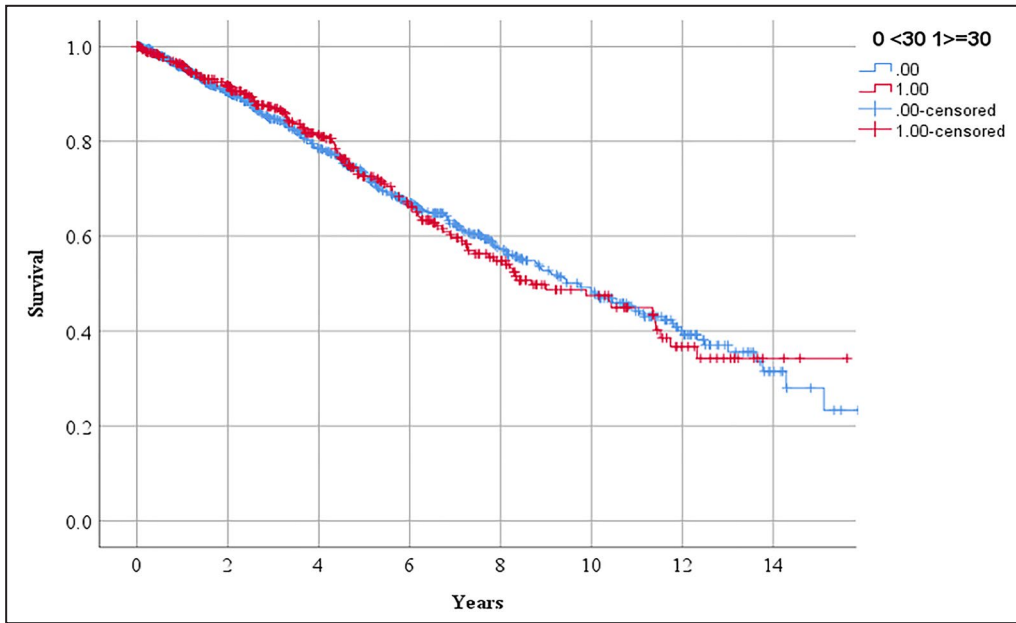
### DISCUSSION

The main finding of this study was that participants with high serum Lp (a) were more likely to require lower limb peripheral revascularization. This finding was consistent in analyses using different definitions of high Lp (a) but not present in a sensitivity analysis limited to younger participants. High Lp (a) was not consistently associated with other clinical events including the incidence of MACE and mortality.

The rate of major cardiovascular events has been reported to be higher in people with PAD than those presenting with other cardiovascular diseases.<sup>8</sup> The cohort



**Figure 4.** Freedom from major adverse cardiovascular events in people referred for management of peripheral artery disease in relationship to serum lipoprotein (a)  $\geq 30$  mg/dL. MACE indicates major cardiovascular event (ie, myocardial infarction, stroke, or cardiovascular death).



**Figure 5.** Survival in people referred for management of peripheral artery disease in relationship to serum lipoprotein (a)  $\geq 30$  mg/dL.

investigated in this study had a high rate of clinically important events. During a median follow-up of  $\approx 2.5$  years, about 40% of participants had at least 1 PAD operation and one quarter died. These event rates are higher than a number of recent reports from randomized trials although these typically include highly selected people.<sup>7,8</sup> The participants included in the current study had a high frequency of cardiovascular risk factors, such as old age, critical limb ischemia, current smoking, diabetes mellitus, and CHD, which likely explains the high incidence of clinical events found. As has been previously reported in other studies, the prescription of best medical management was not optimal in the current cohort.<sup>45</sup> About 30% of participants were not prescribed statins for example. This also likely contributed to the high incidence of events found. More effective methods are needed for

implementation of best medical management in people with PAD.

Lp (a) has been suggested as a target for reducing clinical events using novel treatments to lower its circulating concentration.<sup>46–48</sup> In the current study, high serum Lp (a) was consistently associated with a greater requirement for lower limb peripheral revascularization. Participants with Lp (a)  $\geq 30$  mg/mL, however, only had a 1.2-fold increased rate of lower limb peripheral revascularization. Also, the risk of lower limb peripheral revascularization was only mildly elevated in people with Lp (a)  $\geq 50$  mg/mL (hazard ratio 1.10). Furthermore, high Lp (a) was not associated with other events, such as the incidence of MACE. These findings differ from those reported from other cohorts.<sup>21,49</sup> A study of a mixed cohort of

**Table 3.** Association of Lipoprotein (a)  $\geq 30$  or  $\geq 50$  mg/mL With Clinical Events in People With PAD

| Event Type or Model                     | Serum Lipoprotein Concentration (mg/mL) |                  |                  |                  |
|---|---|------------------|------------------|------------------|
|   | $\geq 30$ mg/mL                         |                  | $\geq 50$ mg/mL  |                  |
| Hazard model                            | Unadjusted                              | Adjusted         | Unadjusted       | Adjusted         |
| Any PAD operation                       | 1.18 (1.01–1.38)                        | 1.20 (1.02–1.41) | 1.08 (0.91–1.29) | 1.10 (0.92–1.31) |
| Lower limb peripheral revascularization | 1.27 (1.02–1.58)                        | 1.33 (1.06–1.66) | 1.17 (0.92–1.47) | 1.29 (1.00–1.65) |
| AAA repair                              | 1.13 (0.91–1.41)                        | 1.14 (0.92–1.43) | 1.15 (0.91–1.45) | 1.06 (0.83–1.34) |
| MACE                                    | 1.14 (0.91–1.41)                        | 1.16 (0.93–1.45) | 1.06 (0.84–1.35) | 1.12 (0.88–1.43) |
| All-cause mortality                     | 1.02 (0.82–1.26)                        | 1.08 (0.87–1.35) | 1.04 (0.82–1.32) | 1.15 (0.90–1.47) |

Shown are hazard ratios and 95% CIs for models that were unadjusted or adjusted for age, sex, smoking history, diabetes mellitus, hypertension, coronary heart disease, presenting problem, statin prescription, low-density lipoprotein-cholesterol, and estimated glomerular filtration rate. Adjusted analyses did not include 16 participants because of missing low-density lipoprotein-cholesterol or estimated glomerular filtration rate results. AAA indicates abdominal aortic aneurysm; MACE, major cardiovascular events; and PAD, peripheral arterial disease.



**Table 4. Total Numbers of Peripheral Artery Disease Operations and Cardiovascular Events in Participants With Different Serum Lipoprotein (a) Concentrations**

| Event or Follow-Up  | Lipoprotein (mg/dL) |               |
|---|---------------------|---------------|
|   | <30 (n=943)         | ≥30 (n=529)   |
| Follow-up, y  | 2.3 (0.1–6.2)       | 2.6 (0.1–5.6) |
| All-cause mortality   | 242 (25.7%)         | 126 (23.8%)   |
| Cardiovascular death  | 156 (16.5%)         | 86 (16.3%)    |
| Total myocardial infarction events  | 137                 | 93            |
| Number of participants who the myocardial infarction events occurred in         | 86 (9.1%)           | 54 (10.2%)    |
| Total stroke events   | 47                  | 28            |
| Number of participants who the stroke events occurred in                        | 39 (4.1%)           | 24 (4.5%)     |
| Total of any peripheral artery disease operations                               | 64                  | 436           |
| Number of participants who the peripheral artery disease operations occurred in | 393 (41.7%)         | 247 (46.7%)   |
| Total of lower limb revascularizations  | 392                 | 280           |
| Number of participants who the lower limb revascularizations occurred in        | 203 (21.5%)         | 137 (25.9%)   |
| Total abdominal aortic aneurysm repairs   | 219                 | 134           |
| Number of participants who abdominal aortic aneurysm repairs occurred in        | 206 (21.8%)         | 130 (24.6%)   |

Shown are median (interquartile range) or numbers (%).

1503 people with coronary, cerebrovascular, or PAD reported that those with Lp (a) ≥50 mg/mL had hazard ratios of 19.5 (95% CI, 10.5–36.1) and 54.5 (95% CI, 25.4–116.7) for myocardial infarction and ischemic stroke, respectively.<sup>21</sup> The disparate findings of the current study could relate to the characteristics of the participants involved, such as their high-risk profile, high incidence of clinical events, and the inclusion of people with unique presentations, such as critical limb ischemia. Further studies are needed in similar PAD populations to clarify the importance of high Lp

(a) as a risk factor for clinical events. Overall, however, the findings of the current study do not make a strong case for novel therapies to lower Lp (a) in people with PAD.

The current study has a number of strengths and weaknesses. A large heterogeneous population of people with PAD was included meaning findings are most relevant to similar populations. Information about a large range of vascular interventions was collected allowing detailed analysis of predictors of PAD operations. Analyses were adjusted for a large

**Table 5. Association of a 40 mg/dL Higher Lipoprotein (a) with Clinical Events in People With PAD**

| Event                                   | Cox Proportional Hazard Model |                  |
|---|-------------------------------|------------------|
|   | Unadjusted                    | Adjusted         |
| Any PAD operation                       | 1.04 (0.98–1.11)              | 1.05 (0.98–1.12) |
| Lower limb peripheral revascularization | 1.09 (1.00–1.18)              | 1.11 (1.02–1.21) |
| AAA repair                              | 1.06 (0.97–1.15)              | 1.04 (0.95–1.15) |
| MACE                                    | 1.00 (0.91–1.09)              | 1.02 (0.93–1.12) |
| All-cause mortality                     | 0.97 (0.88–1.06)              | 1.00 (0.90–1.10) |

Shown are hazard ratios and 95% CIs for models that are unadjusted or adjusted for age, sex, smoking history, diabetes mellitus, hypertension, coronary heart disease, presenting problem, statin prescription, low-density lipoprotein-cholesterol and estimated glomerular filtration rate. Adjusted analyses did not include 16 participants because of missing low-density lipoprotein-cholesterol, or estimated glomerular filtration rate results. AAA indicates abdominal aortic aneurysm; MACE, major cardiovascular events; and PAD, peripheral arterial disease.

**Table 6. Association of Lipoprotein (a) ≥30 mg/mL With Clinical Events in People With PAD Aged <72 or ≥72 Years**

| Event                                   | Age (y)          |                  |
|---|------------------|------------------|
|   | <72              | ≥72              |
| Any PAD operation                       | 1.27 (1.03–1.58) | 1.18 (0.91–1.53) |
| Lower limb peripheral revascularization | 1.19 (0.89–1.58) | 1.71 (1.15–2.55) |
| AAA repair                              | 1.37 (0.99–1.89) | 1.09 (0.79–1.50) |
| MACE                                    | 1.12 (0.80–1.57) | 1.23 (0.90–1.67) |
| All-cause mortality                     | 0.73 (0.50–1.06) | 1.35 (1.01–1.80) |

Shown are hazard ratios and 95% CIs for models that were adjusted for age, sex, smoking history, diabetes mellitus, hypertension, coronary heart disease, presenting problem, statin prescription, low-density lipoprotein-cholesterol and estimated glomerular filtration rate. Adjusted analyses did not include 16 participants because of missing low-density lipoprotein-cholesterol, or estimated glomerular filtration rate results. AAA indicates abdominal aortic aneurysm; MACE, major cardiovascular events; and PAD, peripheral artery disease.

number of potential confounding factors. Sensitivity analyses were also performed. This study also has a number of limitations. It was an observational study and while high Lp (a) was not associated with a number of clinical events, such as MACE, this does not rule out a benefit of Lp (a) lowering. The findings of randomized trials are frequently disparate from those in observational studies. The current study involved a large number of analyses. While these analyses largely tested the same hypothesis (ie, that high serum Lp (a) was associated with an increased risk of clinical events), it needs to be recognized that such multiple testing introduces a risk of false discovery. Furthermore, despite including 1472 participants it is possible the study was underpowered to detect some of the associations that were tested particularly within the subgroups of younger and older participants. The distribution of Lp (a) concentrations did not include sufficiently large number of people with concentrations >100 mg/dL to fully assess the associations of circulating Lp (a) concentrations. Finally, recruitment for the current study occurred over a prolonged period from 2002 to 2018. This has a number of implications. Firstly, medical management has varied substantially during this period, which may have implications for generalizing the results. Secondly, some of the samples were stored for a long period before analysis. Samples were stored at  $-80^{\circ}\text{C}$  and thus we believe this had no impact on the findings, however this remains possible.

In conclusion, this study emphasizes the high incidence of clinical events in people with PAD. High serum Lp (a) was associated with a greater requirement for lower limb peripheral revascularization but not consistently associated with other important clinical events.

## ARTICLE INFORMATION

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### Supplemental Materials

Table S1

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Fully adjusted Cox regression model for association of lipoprotein (a)  $\geq$  30 mg/ml with requirement for any PAD operation.**

| <b>Risk factor</b>                    | <b>Beta coefficient</b> | <b>Standard error</b> | <b>P value</b> | <b>Hazard ratio</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> |
|---------------------------------------|-------------------------|-----------------------|----------------|---------------------|---------------------|---------------------|
| Lipoprotein (a) $\geq$ 30             | 0.179                   | 0.083                 | 0.032          | 1.20                | 1.02                | 1.41                |
| Age (per year)                        | -0.003                  | 0.005                 | 0.553          | 1.00                | 0.99                | 1.01                |
| Female sex                            | -0.152                  | 0.104                 | 0.142          | 0.86                | 0.70                | 1.05                |
| Diabetes                              | -0.101                  | 0.096                 | 0.294          | 0.90                | 0.75                | 1.09                |
| Hypertension                          | 0.043                   | 0.101                 | 0.668          | 1.04                | 0.86                | 1.27                |
| Coronary heart disease                | -0.005                  | 0.085                 | 0.950          | 1.00                | 0.84                | 1.18                |
| Smoking history*                      |                         |                       | 0.123          |                     |                     |                     |
| Former smoking                        | 0.130                   | 0.141                 | 0.355          | 1.14                | 0.87                | 1.50                |
| Current smoking                       | 0.243                   | 0.128                 | 0.059          | 1.28                | 0.99                | 1.64                |
| Presenting problem†                   |                         |                       | <0.001         |                     |                     |                     |
| AAA                                   | 0.140                   | 0.097                 | 0.150          | 1.15                | 0.95                | 1.39                |
| CLI                                   | 0.631                   | 0.140                 | <0.001         | 1.88                | 1.43                | 2.48                |
| LDL-C (per mmol/l)                    | -0.006                  | 0.044                 | 0.893          | 0.99                | 0.91                | 1.08                |
| eGFR (per ml/min/1.73m <sup>2</sup> ) | 0.005                   | 0.002                 | 0.037          | 1.01                | 1.00                | 1.01                |
| Statin prescription                   | -0.031                  | 0.096                 | 0.745          | 0.97                | 0.80                | 1.17                |

AAA= abdominal aortic aneurysm; CLI= critical limb ischemia; LDL-C= low density lipoprotein-cholesterol; eGFR= estimated glomerular filtration rate; CI= confidence interval.