Lipoprotein(a) and the risk of Major Adverse Limb Events in Patients with Stable Atherosclerotic Vascular Disease

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BACKGROUND

• Patients with atherosclerotic vascular disease are at heightened risk of ischemic events, including adverse limb events.
• The pathobiology of adverse limb events ranges from events that are predominantly thrombotic, such as acute limb ischemia (ALI), to those that are due primarily to progressive atherosclerosis, such as worsening functional limitation requiring elective peripheral revascularization and development of critical limb ischemia (CLI).
• Evolving data suggest that lipoprotein(a) (Lp(a)) may be associated with the risk of adverse limb events; however, which type of events are related to Lp(a) has not been well described.

METHODS

• Data from two randomized clinical trials including patients with stable atherosclerotic vascular disease were combined: TRA2P-TIMI 50 (NCT00526474) and FOURIER (NCT01764633).
• We measured Lp(a) (Randox Laboratories) in baseline samples in a central core laboratory. Major adverse cardiovascular events (MACE) (CV death, myocardial infarction (MI), or stroke) were the primary or key secondary outcomes of the trials.
• Peripheral revascularization procedures occurring during follow up were investigated separately. Adverse limb events, including CLI and ALI, were categorized through the review of safety data by two blinded vascular specialists.
• Major adverse limb events (MALE) were defined as the composite of peripheral revascularization, CLI, or ALI. Lp(a) was analyzed as a continuous variable and by cutpoint (<50, 125, and 200 nmol/L). The association of Lp(a) and MALE was assessed and adjusted for randomized therapy in each trial, age, sex, race, region, prior MI, prior stroke, peripheral artery disease, hypertension, diabetes mellitus, smoking status, and statin use.

RESULTS

• A total of 28,892 patients were included in the combined analysis population.
• The median Lp(a) was 36 nmol/L (IQR 12 – 159). A total of 1336 MALE events occurred during follow up, including 1307 peripheral revascularizations (127 elective, 173 urgent), 259 CLI events, and 148 ALI events. Lp(a) was associated with an increased risk of MALE (Adj HR 1.07 per SD, 95% CI 1.02 – 1.13, p=0.007, Figure 1) with the risk of a similar magnitude for that of MACE (Adj HR 1.05 per SD, 95% CI 1.01 – 1.10, p=0.020, Figure 2).
• The association of Lp(a) and MALE was driven by peripheral revascularizations including elective revascularization (Adj HR 1.07, 95% CI 1.02 – 1.13, p=0.010) with a consistent trend for CLI; however, a relationship with ALI was not apparent and in light of a limited number of events (Figure 3).

CONCLUSION

In patients with stable atherosclerotic vascular disease, Lp(a) is associated with the risk of major adverse limb events. The magnitude of risk, after adjustment, is similar to that observed for MACE. The relationship between Lp(a) and MALE was driven by peripheral revascularization procedures (regardless of urgency) but generally consistent for critical limb ischemia. There was no apparent relationship with ALI, however, there were few events. Overall, these findings support the potential pathogenic role of Lp(a) in PAD and in limb outcomes and support investigation of novel mechanisms to reduce Lp(a) in this population and for these outcomes.

DISCLOSURE INFORMATION

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Figure 1 – Lp(a) and Risk of Major Adverse Limb Events

Table 1: Probability of CLI + any peripheral revascularization and 95% CI at 1080 days: Overall Population

<table>
<thead>
<tr>
<th>Lp(a) (nmol/L)</th>
<th>N Events</th>
<th>3 Year KM Rate</th>
<th>Adj HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>1205</td>
<td>707</td>
<td>0.71</td>
</tr>
<tr>
<td>50 – 125</td>
<td>3601</td>
<td>158</td>
<td>1.14 (0.97 – 1.34)</td>
</tr>
<tr>
<td>125 – 200</td>
<td>4855</td>
<td>298</td>
<td>1.16 (0.98 – 1.36)</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>2405</td>
<td>121</td>
<td>1.25 (1.09 – 1.40)</td>
</tr>
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</table>

Figure 4 – Limb outcomes by Lp(a) Cutpoint

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*Stratified by TRIAL

Probability of CLI + any peripheral revascularization and 95% CI at 1080 days: Overall Population

Log-transformed Lp(a) per 1 SD

Outcome | N | Events | 3 Year KM Rate | Adj HR (95% CI) | p-value
----- | ---- | ------ | -------------- | ---------------- | ----
MACE   | 26852 | 1306 | 1.07 (1.02 – 1.13) | 0.007

Any peripheral revascularization | 26852 | 1307 | 1.07 (1.02 – 1.13) | 0.007

Critical limb ischemia | 26852 | 259 | 1.05 (0.84 – 1.31) | 0.41

Acute limb ischemia | 26852 | 148 | 0.88 (0.76 – 1.02) | 0.002

Major adverse limb events – composite of peripheral revascularization, critical limb ischemia, or acute limb ischemia

Adjusted for randomized treatment, age, sex, race, region, prior MI, stroke, PAD, hypertension, diabetes, current smoking, and statin use

P<0.05 for trend across HR