Discussion of the Results of the VISTA-16 Study

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Structural and functional features of sPLA\textsubscript{2}s and Lp-PLA\textsubscript{2}

sPLA\textsubscript{2} enzymes hydrolyze phospholipids from cell membranes and lipoproteins, producing proinflammatory substances. They modify LDL-C particles and promote atherosclerosis.

<table>
<thead>
<tr>
<th>Structural Features</th>
<th>Enzymatic Properties</th>
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<tbody>
<tr>
<td>sPLA\textsubscript{2-IA}</td>
<td>13.9</td>
</tr>
<tr>
<td>sPLA\textsubscript{2-III}</td>
<td>18.3*</td>
</tr>
<tr>
<td>sPLA\textsubscript{2-V}</td>
<td>13.8</td>
</tr>
<tr>
<td>sPLA\textsubscript{2-X}</td>
<td>13.6</td>
</tr>
<tr>
<td>Lp-PLA\textsubscript{2}</td>
<td>45</td>
</tr>
</tbody>
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PE: phosphatidylethanolamine. PC: phosphatidylcholine

Mallat Z et al. *Circulation* 2010
Supporting evidence for a role of sPLA₂ in human CAD

✓ Localization in atherosclerotic lesions, in proximity of lipid deposits

✓ Epidemiological evidence of association between circulating plasma levels of sPLA₂-IIA and CV risk after ACS, in stable CAD and in high-risk patients

✓ Impact of mice knockout or overexpression of sPLA₂-IIA on experimental atherosclerosis

✓ Varespladib blocks sPLA₂-IIA but also has lesser inhibitory effects on isoforms X and V.

✓ But...
Mendelian randomization study of sPLA2-IIA and CVD outcomes

Meta-analysis pooled estimates of the association between PLA2G2A rs11573156 and major vascular events in the general population and in ACS patients

VISTA-16: the trialist’s view

✓ A clear negative response, with a harmful effect of V.

✓ Premature discontinuation was justified

? An ambitious (underpowered/undersized) trial?

? Harm may be overestimated (premature discontinuation)

☐ Delayed access to data from sponsor and incomplete ascertainment of 6-month outcomes are problematic
Biological interpretation uncertain

✔ Was sPLA2 a reasonable target? Yes!

? Was the intervention strong/specific enough?

? What is the mechanism for the increased risk of MI: adverse effect of Varespladib unrelated to sPLA₂ or side effect of sPLA₂ inhibition?

? Does this have implications for Lp-PLA2 inhibition trials with Darapladib

✗ Does this rule out the « inflammation hypothesis »? No!
Thank you!