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APAC treatment limits collar-induced carotid atherosclerotic plaque development in apoE^{-/-} miceDoctor Bot I¹, Miss Delfos L¹, Miss Hemme E¹, Professor Kovanen PT², Doctor Jouppila A³, Professor Lassila R⁴

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Introduction and aim: Mimics of mast cell-derived heparin proteoglycans (HEP-PG) can be tailored to molecules carrying both antiplatelet and anticoagulant properties. These dual antiplatelet and anticoagulant (APAC) constructs can also shield adhesion molecules such as P-selectin and VCAM-1 expressed by endothelial cells upon atherosclerosis development. We hypothesize that via this way, APAC prevents macrophage accumulation and lesion development. In this study, we therefore determined the efficacy of APAC in inhibiting atherosclerosis.

Methods: Male western-type diet fed apoE^{-/-} mice were equipped with perivascular carotid artery collars to induce atherosclerosis. In this collar model, mRNA expression of adhesion molecules such as ICAM-1, VCAM-1, P-Selectin but also of Platelet Factor 4 (PF4) are significantly upregulated upon lesion development (all $P < 0.05$ at 2 weeks after collar placement compared with control arteries). From lesion initiation, mice were treated with 0.2 mg/kg APAC or vehicle control (i.v., 3x per week, $n = 12-14$ per group) for 2.5 weeks. At 5 weeks after collar placement, mice were sacrificed.

Results: APAC treatment did not affect body weight or plasma total cholesterol levels of the mice during the experiment. Interestingly, carotid artery plaque size was reduced by over 50% upon APAC treatment (APAC: $50 \pm 10 \times 10^3$ versus controls: $102 \pm 13 \times 10^3$ square μm ; $P < 0.01$). This observation was aligned with reduced plaque macrophage area (APAC: $20 \pm 5 \times 10^3$ versus controls: $33 \pm 5 \times 10^3$ square μm) and collagen content (APAC: $13 \pm 4 \times 10^3$ versus controls: $28 \pm 6 \times 10^3$ square μm ; $P < 0.05$).

Conclusion: We here show that APAC effectively inhibits atherosclerotic lesion development when administered during lesion initiation and may have potential as therapeutic agent to prevent atherosclerosis.