The omega-3 fatty acid derivative icosabutate improves lipid metabolism and reduces severity of atherogenesis in mice

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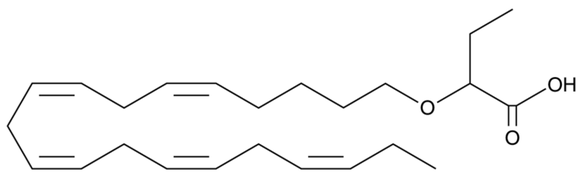
Background

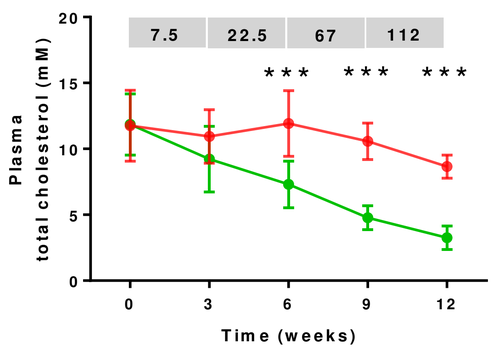
Icosabutate is a synthetic ether from eicosapentaenoic alcohol and 2-bromo butyric acid which decreases plasma triglycerides (TG) and (very-)low-density lipoprotein cholesterol (VLDL-C and LDL-C) in hyperlipidemic patients. Here we examined the mechanism by which icosabutate decreases plasma lipids and affects atherosclerotic lesion formation.

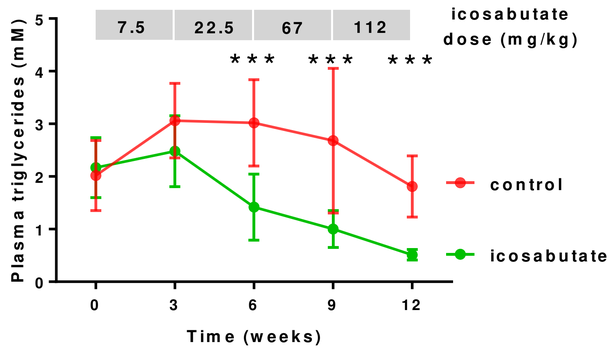


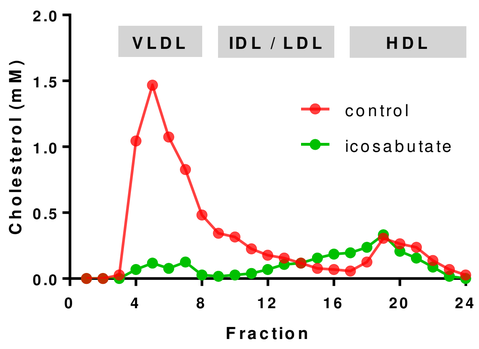
Methods

Male APOE*3Leiden.CETP mice received a semi-synthetic Western-type diet (WTD) supplemented with icosabutate, Omacor® or vehicle for up to 6 weeks. Plasma total cholesterol (TC), TG and lipoprotein profiles were determined in time. VLDL production, VLDL clearance and tissue uptake were measured. To examine progression of atherosclerosis, female APOE*3Leiden.CETP received a WTD for 17 weeks with icosabutate or vehicle supplementation. A low cholesterol WTD group that gave equal cholesterol levels as in the icosabutate group was included as control for potential pleiotropic effects. Plaque formation and severity were scored by image analysis and histopathological scoring.

Icosabutate decreases (V)LDL-C and TG



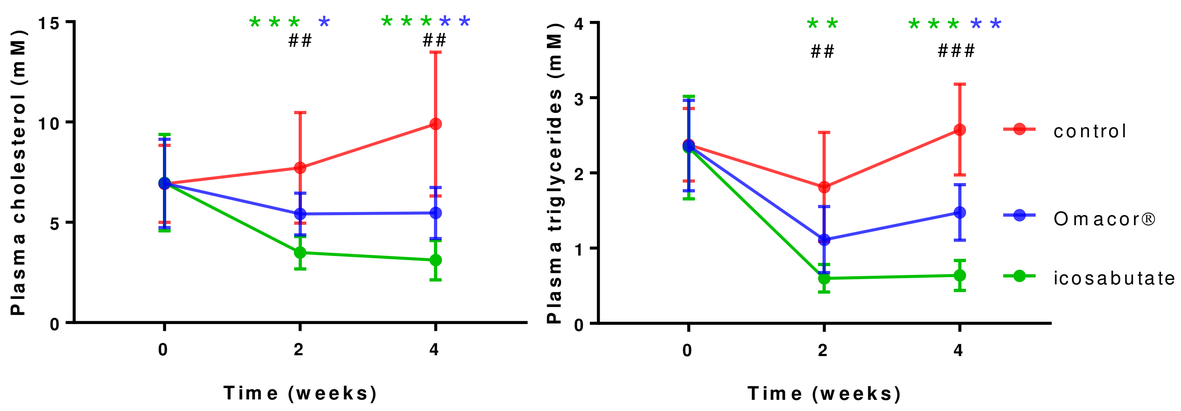




above: Mice were treated with increasing doses of icosabutate (grey boxes). Data are presented as mean ± SD; ***P≤0.001

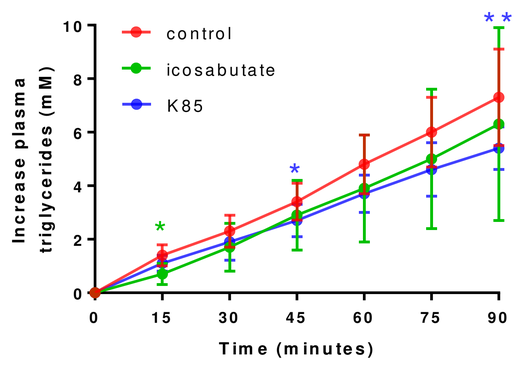
right: Lipoprotein profile

Icosabutate has improved lipid-lowering capacity compared to Omacor®

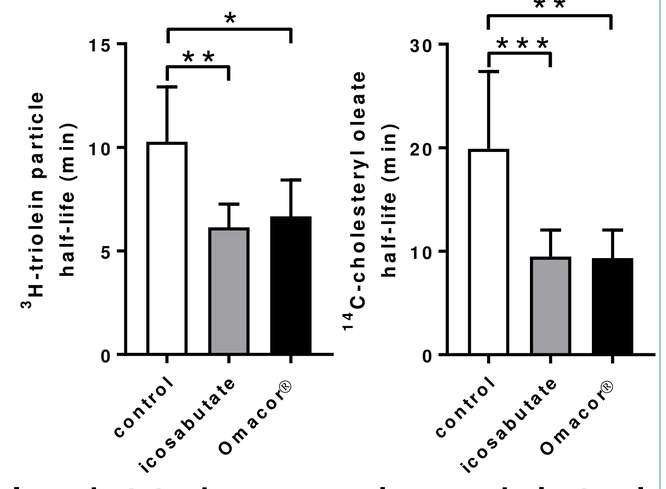


Mice were fed a WTD and received vehicle, 112 mg / kg icosabutate or 862 mg / kg Omacor for 4 weeks. Data are presented as mean ± SD, control vs icosabutate / Omacor **P≤0.01, ***P≤0.001; icosabutate vs Omacor, ##P≤0.01, ###P≤0.001.

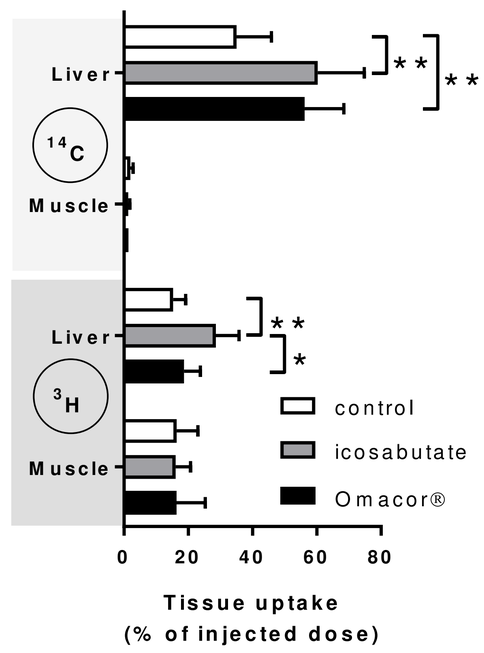
Icosabutate increases cholesterol and TG clearance by the liver



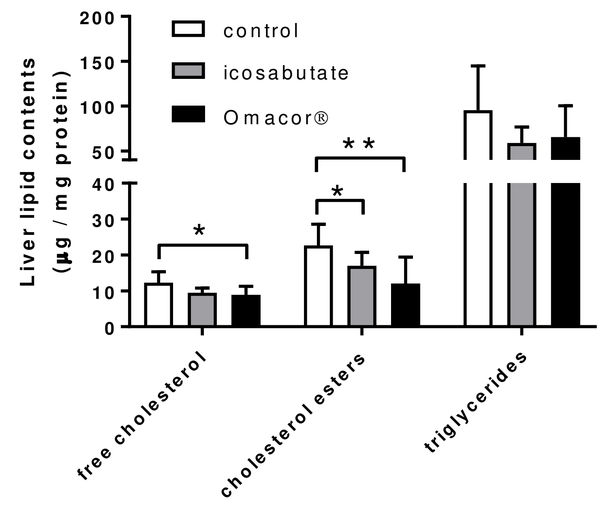
No effect of icosabutate on VLDL production. Determined as plasma triglyceride increase at indicated times after inhibition of lipolysis.



Icosabutate increases plasma cholesterol and TG clearance determined as plasma half-life of ^{3}H-triolein and ^{14}C-labeled cholesteryl oleate after injection of VLDL-like particles. Data are presented as mean±SD *P≤0.05, **P≤0.01, ***P≤0.001.

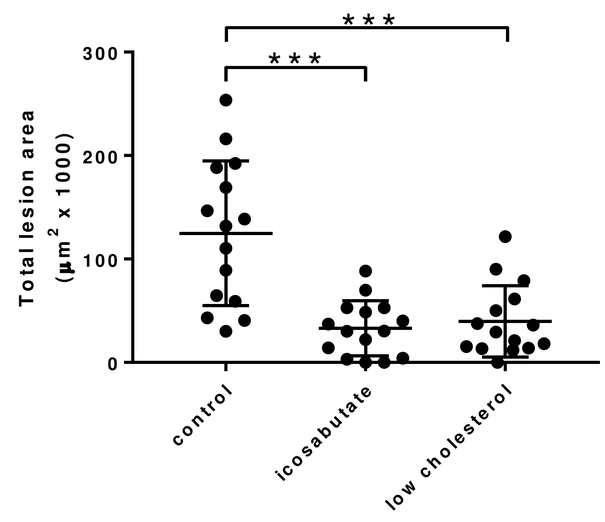


Tissue uptake of ^{14}C-cholesteryl oleate and ^{3}H-triolein. Data are presented as mean ± SD, *P≤0.05, **P≤0.01

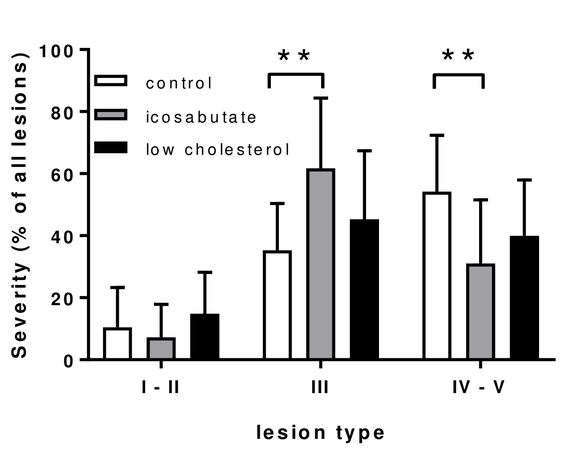


Icosabutate decreases liver cholesterol ester contents. Data are presented as mean ± SD, *P≤0.05, **P≤0.01

Icosabutate reduces formation of atherosclerotic lesions in line with plasma cholesterol-lowering



Total lesion area determined by digital image analysis of histological stains. Data are presented individually and as mean ± SD; ***P≤0.001.



Histopathological scoring of lesion severity. Type I – II: initial lesion / fatty streak, type III: intermediate lesion, type IV – V: (fibro)atheroma lesion. Data are presented as mean ± SD; **P≤0.01.

Conclusion

Treatment with the structurally engineered fatty acid icosabutate has improved lipid-lowering capacity compared to Omacor®, an omega-3 fatty acid ethyl ester. Icosabutate promotes hepatic clearance of VLDL and effectively reduces progression of atherosclerotic lesion development in a translational mouse model.

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