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Effect of EPA, DOACs and their combination on platelet activation

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Declaration of Conflict Of Interest



I have no potential conflict of interest to report

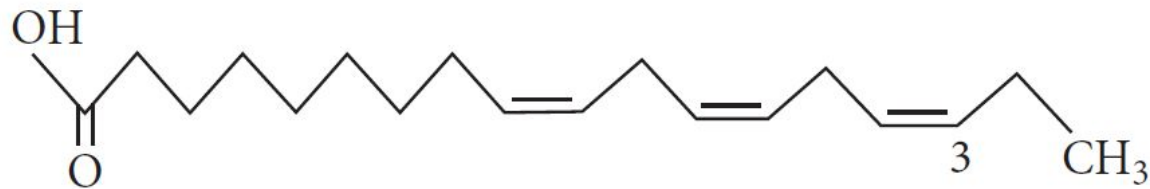
I have the following potential conflict(s) of interest to report



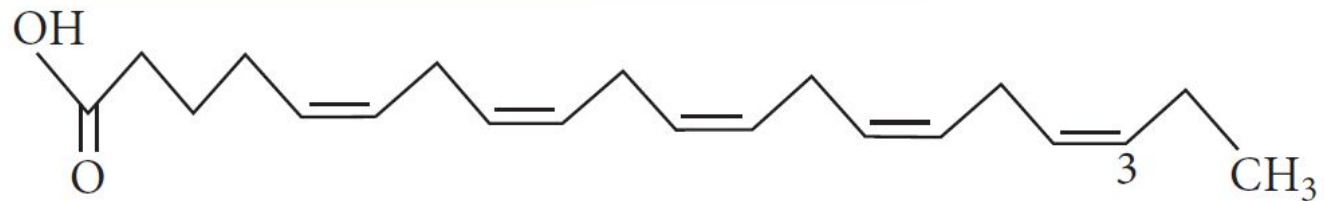
Omega-3 Fatty Acids

Essential Fatty Acids

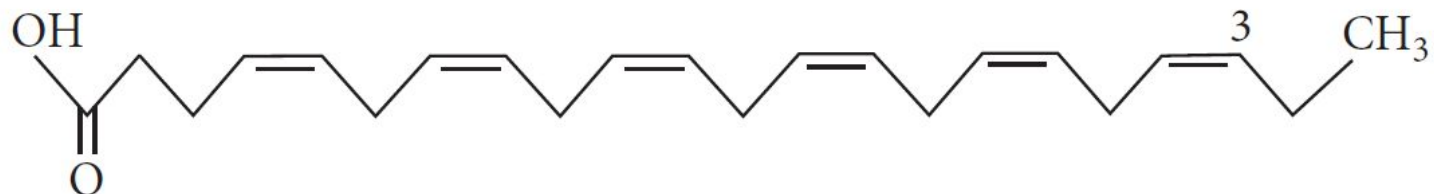
Alpha-linolenic acid (ALA, C18:3, omega-3)



Eicosapentaenoic acid (EPA, C20:5, omega-3)



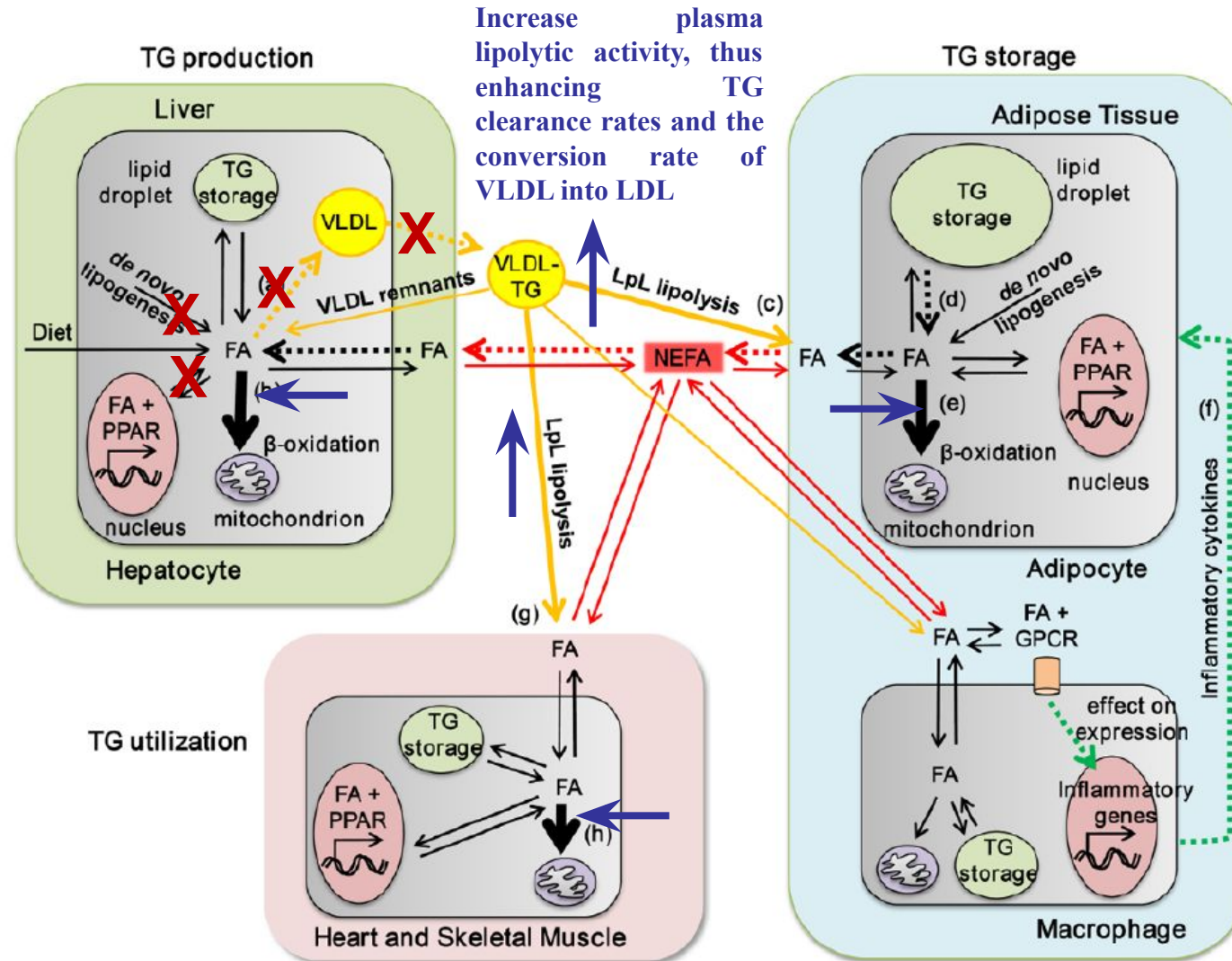
Docosahexaenoic acid (DHA, C22:6, omega-3)



TG-lowering mechanisms of EPA

Pharmacological doses 2-4 g/day

Direct inhibition of hepatic TG and VLDL-ApoB synthesis and reduction of VLDL assembly and secretion



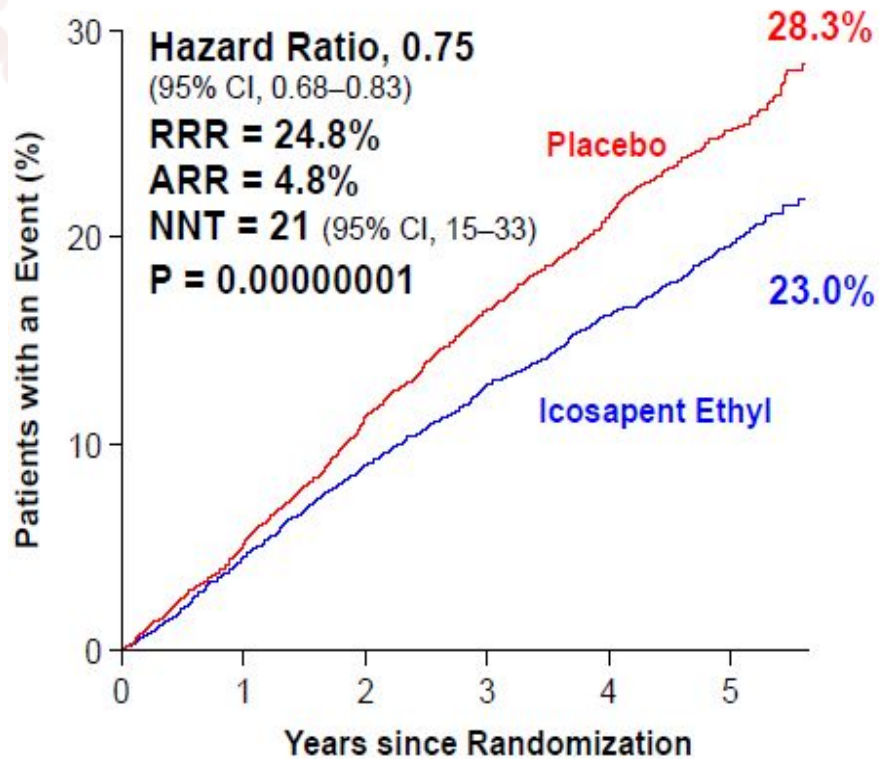
Stimulation of FA oxidation, resulting in less FAs available for TG synthesis

REDUCE-IT trial

Primary and Key Secondary Composite Endpoints

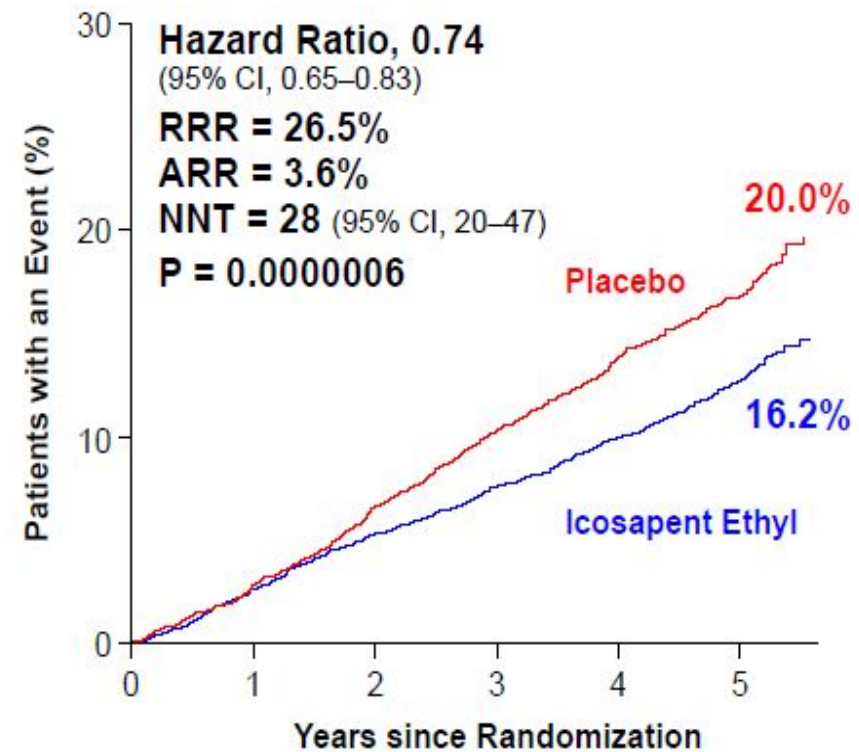
Primary Composite Endpoint:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Key Secondary Composite Endpoint:

CV Death, MI, Stroke



Deepak L. Bhatt, et al. N Engl J Med 2019;380:11-22

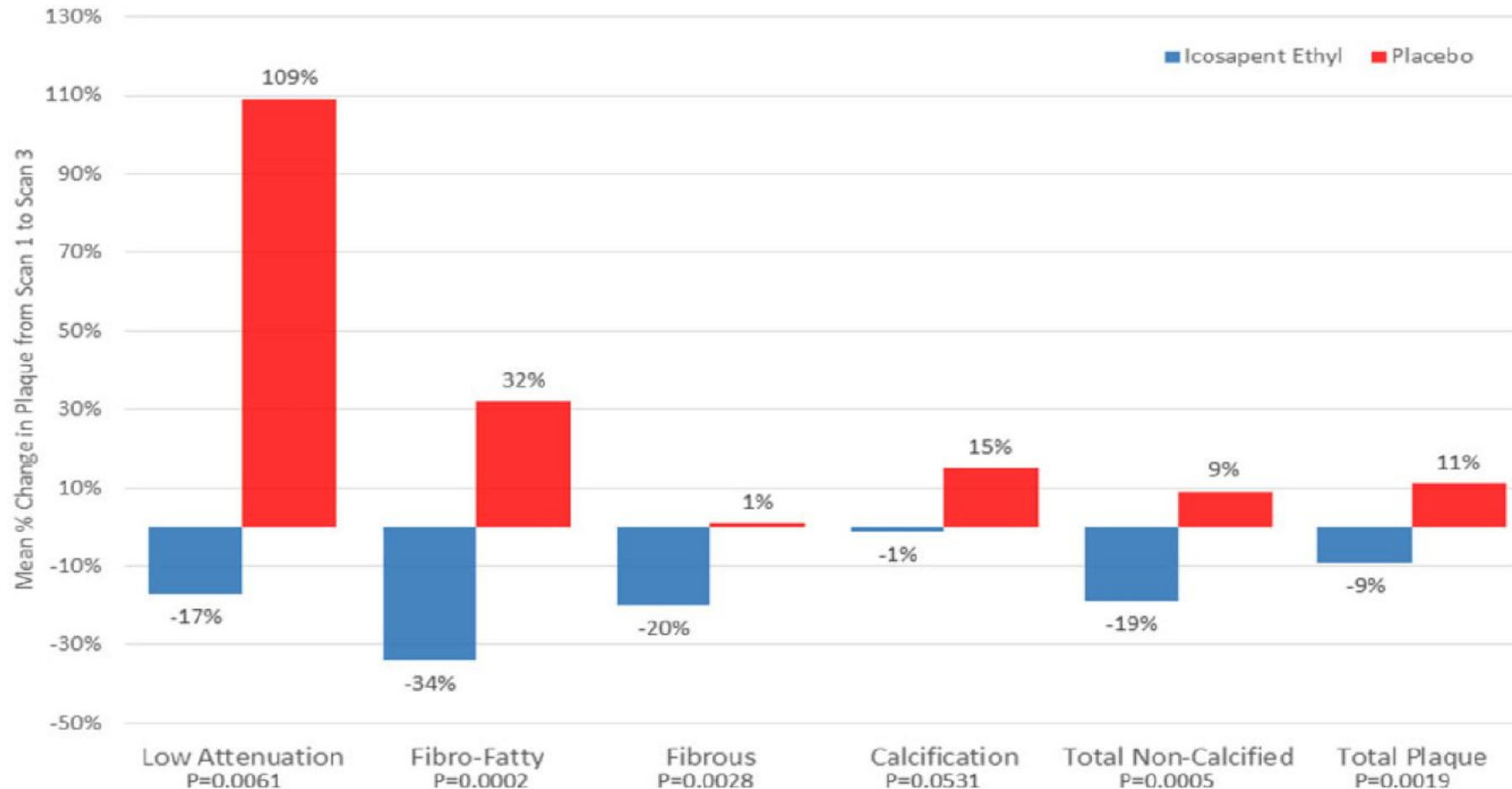
ESC/EAS 2019 Guidelines

Recommendations for drug treatment of patients with Hypertriglyceridemia

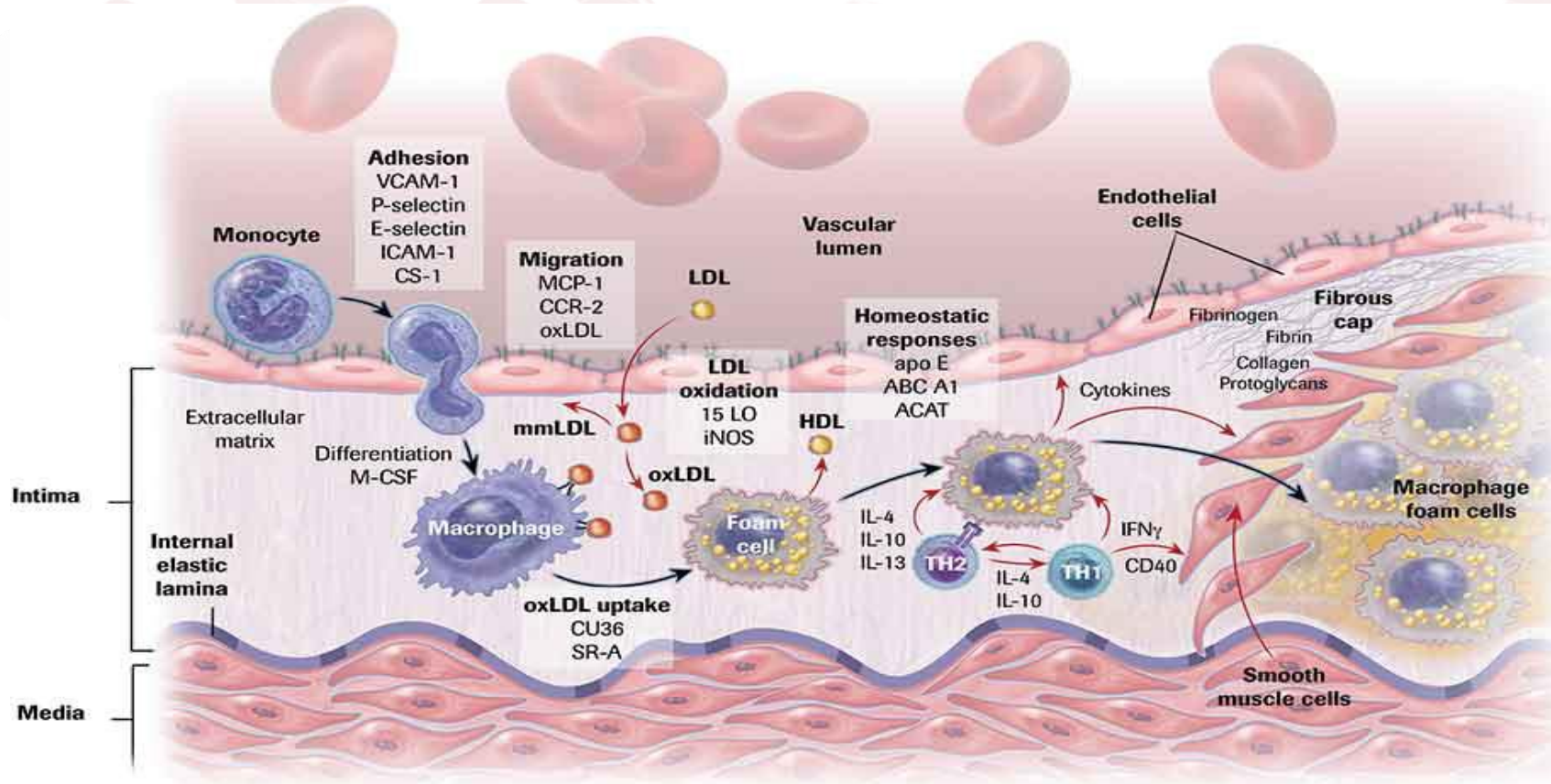
Recommendations	Class ^a	Level ^b
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)]. ³⁵⁵	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, <u>n-3 PUFAs (icosapent ethyl 2×2 g/day)</u> should be considered in combination with a statin. ¹⁹⁴	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins. ^{305–307,356}	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins. ^{305–307,356}	IIb	C

EVAPORATE trial

IPE plus statin were associated with slowed coronary plaque progression, and indeed regression, compared with statin plus placebo over 18 months



Antiatherothrombotic effects of EPA



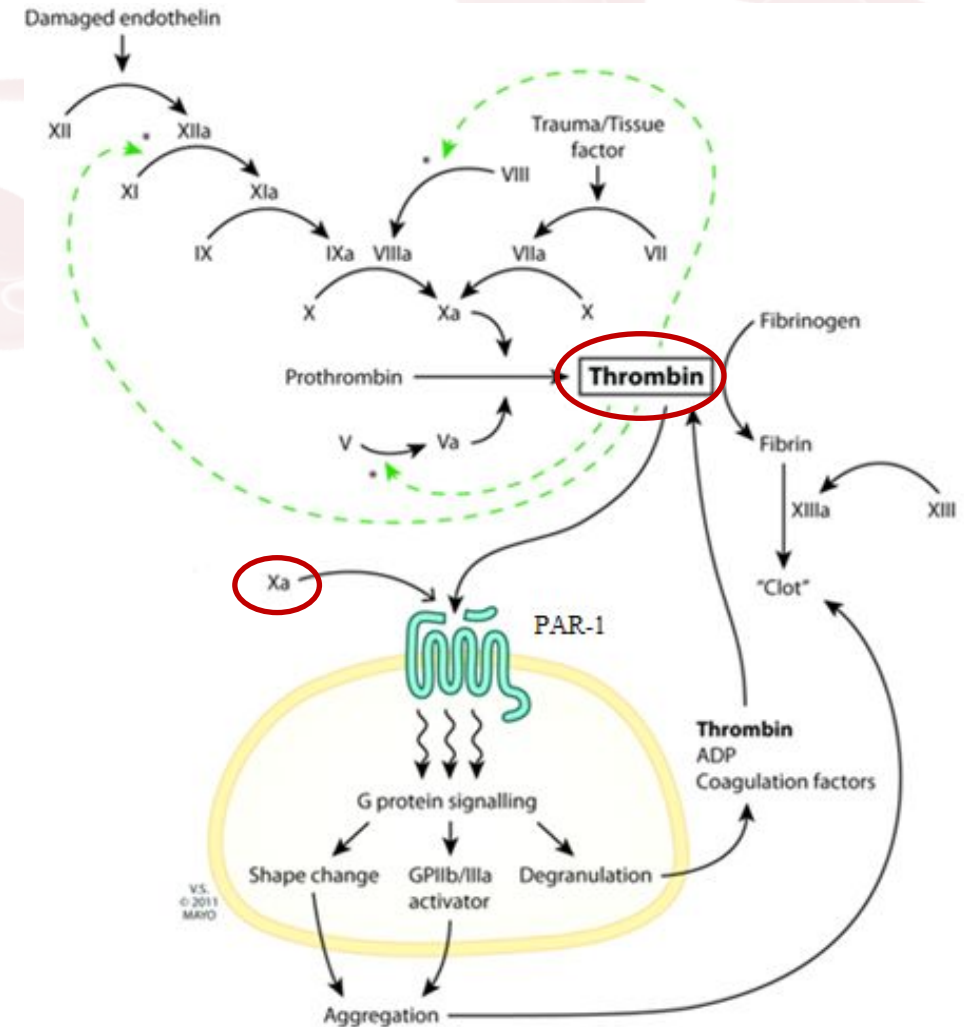
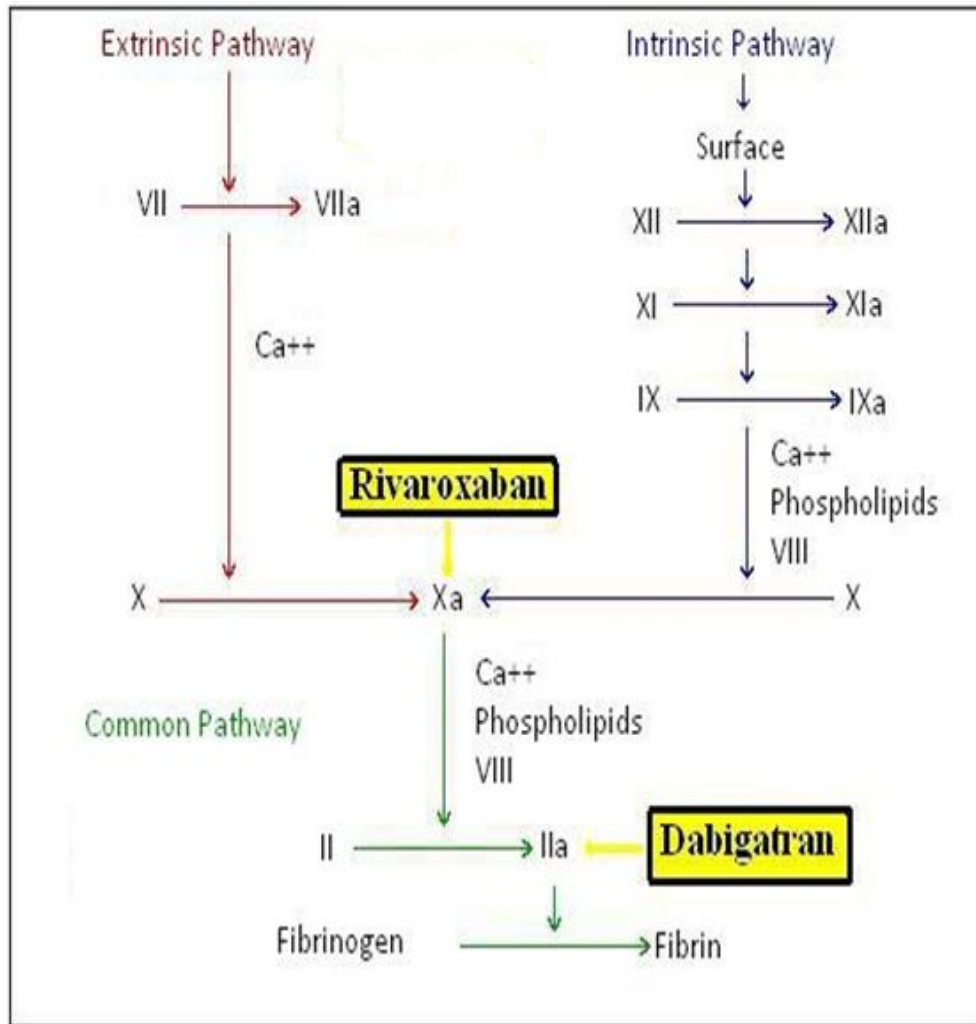
EPA Effects

- Antioxidant effects
- Improved endothelial function
- EPA/AA ratio
- Fibrous cap thickness
- IL-10
- Lumen diameter
- Plaque stability

- Cholesterol crystalline domains
- Ox-LDL
- RLP-C
- Adhesion of monocytes
- Macrophages
- Foam cells
- IL-6
- ICAM-1
- hsCRP
- Lp-PLA2
- Inflammation
- MMPs
- Plaque volume
- Arterial stiffness
- Plaque vulnerability
- Thrombosis
- Platelet response

Nelson JR, et al. *Postgrad Med.* 2021;133(6):651-664

DOACs - Mechanism of action



Gómez-Moreno G, et al. *J Clin Exp Dent.* 2010;2(1):e1-5

Comin J, et al. *AJNR Am J Neuroradiol.* 2012;33(3):426-428



Aim

- Several patients treated with a DOAC may also have elevated TGs and should additionally receive EPA
- The aim of the present study was to investigate the effect of EPA, Rivaroxaban, Dabigatran (its active metabolite), as well as the effect of EPA/DOAC combinations on platelet activation, induced by the PAR-1 receptor agonist, TRAP-6, *in vitro*

Methods

Platelet Rich Plasma (PRP) was prepared from citrated blood of healthy volunteers and adjusted to 250.000 platelets/ μ l.

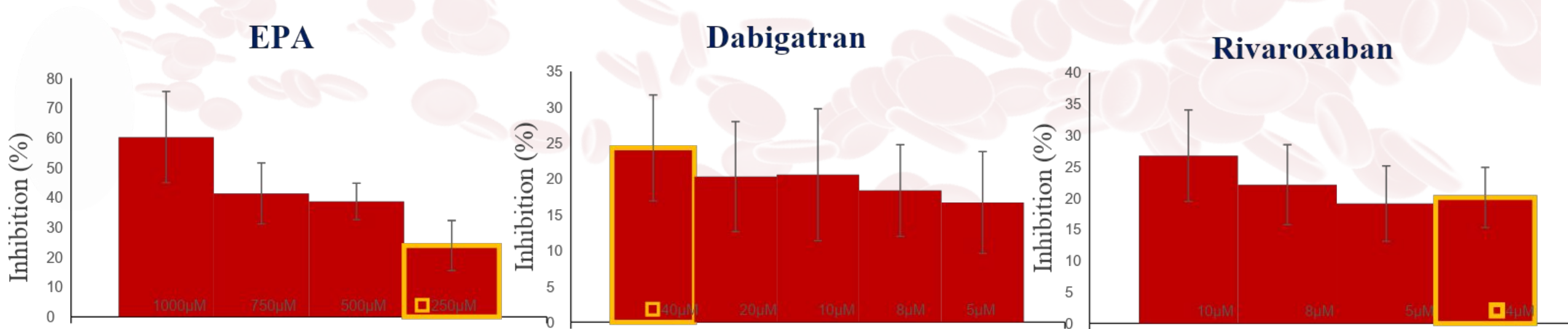
PRP was pre-incubated at 37°C for 10min with EPA, Rivaroxaban, Dabigatran, or the EPA/DOAC combinations in various concentrations.

The inhibitory activity was determined by Light Transmittance Aggregometry.

Platelets were activated by TRAP-6 (10 μ M)

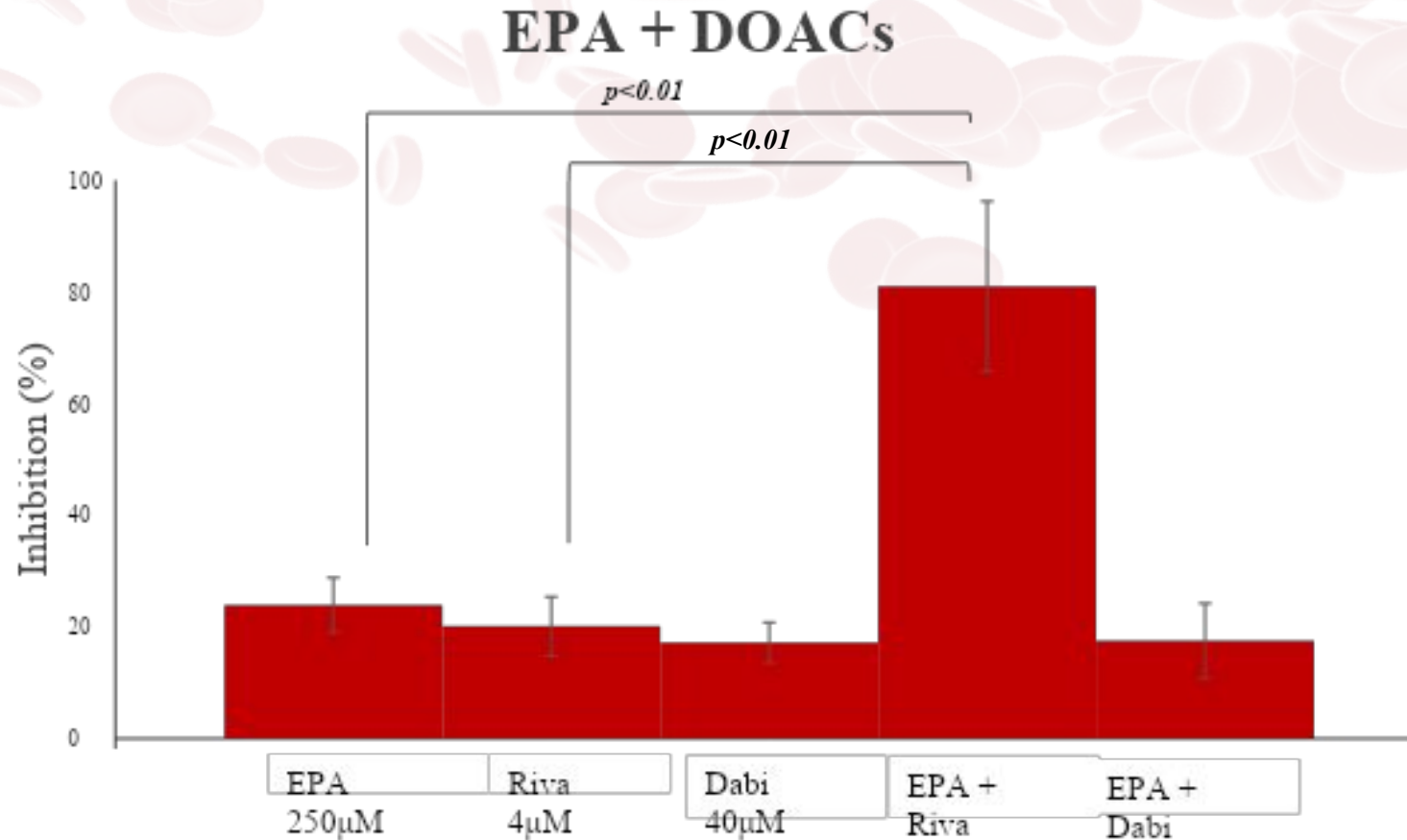
Results

The inhibitory effect of EPA, Rivaroxaban and Dabigatran on TRAP-6 induced platelet aggregation



Results

The inhibitory effect of EPA, Rivaroxaban, Dabigatran, EPA/Rivaroxaban and EPA/Dabigatran on TRAP-6 induced platelet activation



Conclusions

- The combination of EPA and Rivaroxaban exhibited a synergistic antiplatelet effect towards platelet activation induced by TRAP-6
- In contrast, the inhibitory effect of the combination of EPA with Dabigatran was not differentiated from that observed in the presence of each individual compound
- These results may be clinically important in patients receiving both EPA and a DOAC

Acknowledgements

This study was partially supported by grants from LIBYTEC Pharmaceutical S.A. (Greece), which also provided the highly purified EPA.



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Thank you for your attention

