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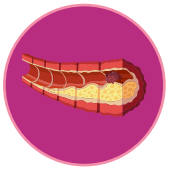
Understanding the Role of Eicosanoids in Atherosclerosis, with a Focus on Icosapent Ethyl as a Therapeutic Option for Cardiovascular Disease

Insights on inflammatory responses in arterial plaque development, precursors of eicosanoids, and key clinical trials

Cardiovascular disease (CVD)



CVD refers to an array of health disorders affecting the cardiovascular system[1,2]

Mortality rates of CVD in 2021[3]

- 20.5 million deaths
- Approximately one-third of all global deaths

Important risk factors of CVD[2]

- Hypercholesterolaemia
- Hypertension
- Diabetes
- Tobacco use/smoking
- Unhealthy diet and obesity
- Physical inactivity
- Excessive consumption of alcohol
- Air pollution

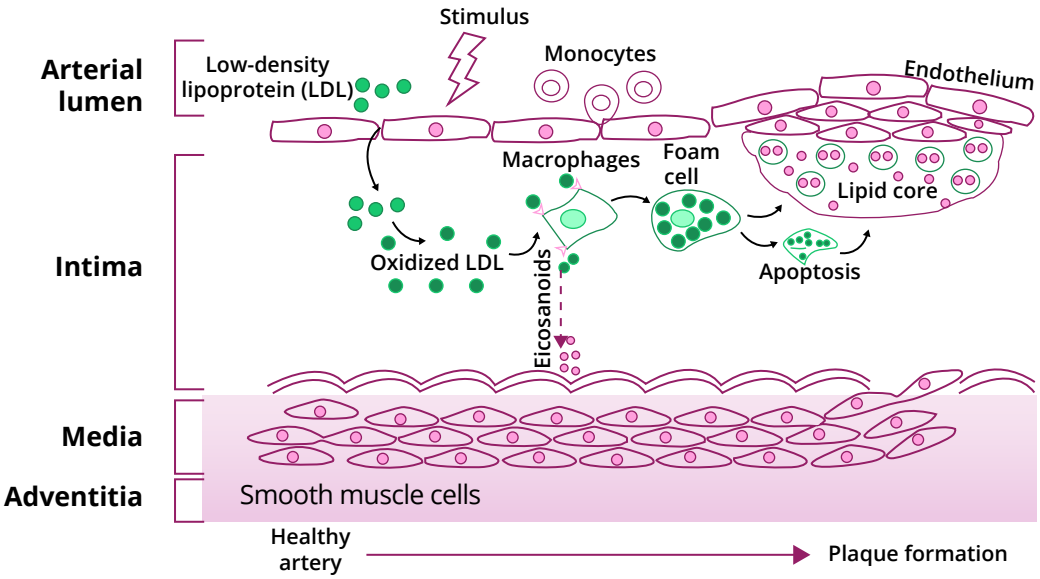
Atherosclerosis[4,5]

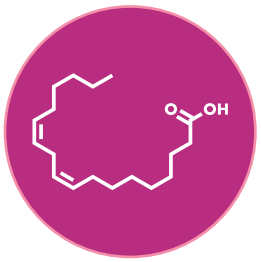
- It involves the build-up of plaques inside arteries
- Plaques, primarily composed of lipids, induce an inflammatory reaction

- Atherosclerotic lesions commonly occur in regions with low wall shear stress and flow separation
- Atherosclerotic CVD (ASCVD) eventually leads to life-threatening complications

Role of inflammation in atherosclerosis[4,6,7]

Events occurring during an inflammatory response to foreign bodies or to clear dead cells





Oxylipins and eicosanoids derived from the oxidation of polyunsaturated fatty acids (PUFAs) regulate inflammation in the tissues

Imbalance in PUFA-derived metabolite levels along with a simultaneous increase in inflammatory stimuli can lead to chronic inflammation in the arteries, resulting in the development of plaques and ASCVD

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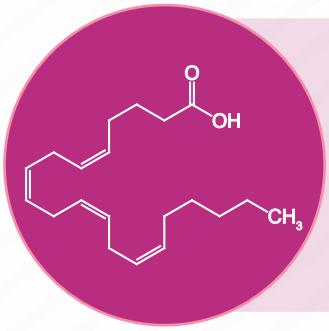
Production of eicosanoids from ω-3 and ω-6 PUFAs[7]



- Eicosanoids, lipid mediators derived from eicosapolyenoic acid, have critical roles in ASCVD
- Polyunsaturated, long fatty acid chains derived from ω-3 (n-3) and ω-6 (n-6) fatty acids are precursors to eicosanoids

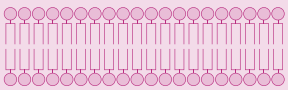
Omega-6
Linoleic acid
↓
Arachidonic acid (AA)
↓
Pro-inflammatory Eicosanoids, prostaglandins (PGEs), leukotrienes (LTs), and thromboxanes

Desaturases
Elongases

Desaturases
Elongases

Cyclooxygenases
Lipoxygenases

Omega-3
α-Linolenic acid
↓
Eicosapentaenoic acid (EPA)
↓
Docosahexaenoic acid (DHA)
↓
Minimally inflammatory Eicosanoids
Inflammation resolving
Resolvins and protectins



The mean EPA/AA ratio was reported as 0.456 ± 0.321 (mean ± standard deviation) in patients with acute coronary syndrome[6]

Main pathways involved in the production of eicosanoids[7]

Cyclooxygenase (COX) pathway
- Mediated by COX-1 and COX-2 enzymes within different cells
- Produces PGEs, prostanoids, and thromboxanes

Lipoxygenase (LOX) pathway
- Mediated by 5-LOX, 12-LOX, or 15-LOX enzymes within leukocytes
- Produces LTs, lipoxins (LXs), and several hydroxyeicosatetraenoic acids (HETEs)

Cytochrome P450 (cyP450) pathway
- Mediated by cyP450 enzyme
- Produces 20-HETE and epoxyeicosatrienoic acids

Eicosanoids involved in the development of atherosclerosis[6]

Eicosanoids derived from EPA and AA play key roles at different stages of the vascular inflammatory processes

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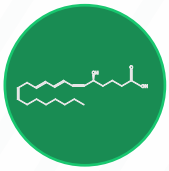
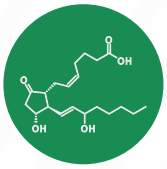
Eicosanoids derived from AA in pro-inflammatory response

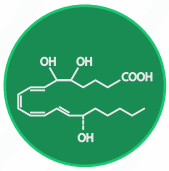


LTB4 induces the recruitment of polymorphonuclear neutrophils (PMNs) to the atherosclerotic lesions

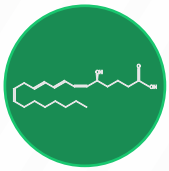


PGE2 facilitates PMN recruitment via vasodilatory effects

PMNs play a key role in the clearance of debris



Subsequently, PGE2 triggers the production of LXA4 from PMNs



LTB4 production is lowered and the clearance of debris by macrophages is stimulated

Oxylipins derived from EPA, DHA, and docosapentaenoic acid are involved in anti-inflammatory processes

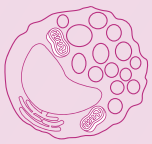
Anti-atherosclerotic properties of oxylipins derived from EPA and DHA

Resolvin D1, derived from DHA via 15-LOX, decreased LTB4 levels in lesions, necrotic core size, and oxidative stress in Ldlr$^{-/-}$ mice[8]

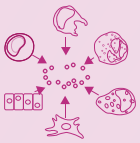
Resolvin E1, derived from EPA in PMNs, reduced lesion size and inflammatory biomarker levels in multiple animal models; it has completed phase 1 trials for healthy volunteers[9]

Role of EPA in lowering CVD risk and atherosclerosis[6]

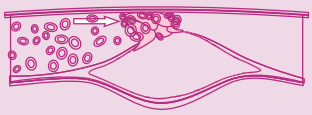
Processes potentially affected by EPA



Endothelial function, oxidative stress, and foam cell formation



Inflammation and cytokine production



Plaque formation/progression, platelet aggregation, thrombus formation, and plaque rupture

Impact of icosapent ethyl (IPE), a highly purified ethyl ester of EPA, on coronary plaque imaging endpoints[10]

Study	Country	Follow-up (months)	Main outcome (mean ± standard error)
CHERRY, 2017	Japan	7.9	11.7% reduction in total plaque volume (−11.7 ± 1.6)
EVAPORATE, 2020	U.S.	18	9% reduction in total plaque volume (−9.0 ± 2.3)
LINK-IT, 2020	Japan	12	23.4% reduction in lipid volume (−23.4 ± 4.6)
Niki *et al*., 2016	Japan	6	1.4% reduction in total plaque volume (−1.4 ± 1.2)
Kita *et al*., 2020	Japan	8	17.4% reduction in lipid volume (−17.4 ± 6.2)
Nishio *et al*., 2014	Japan	9	55.4% reduction in lipid volume (−55.4 ± 9.8)

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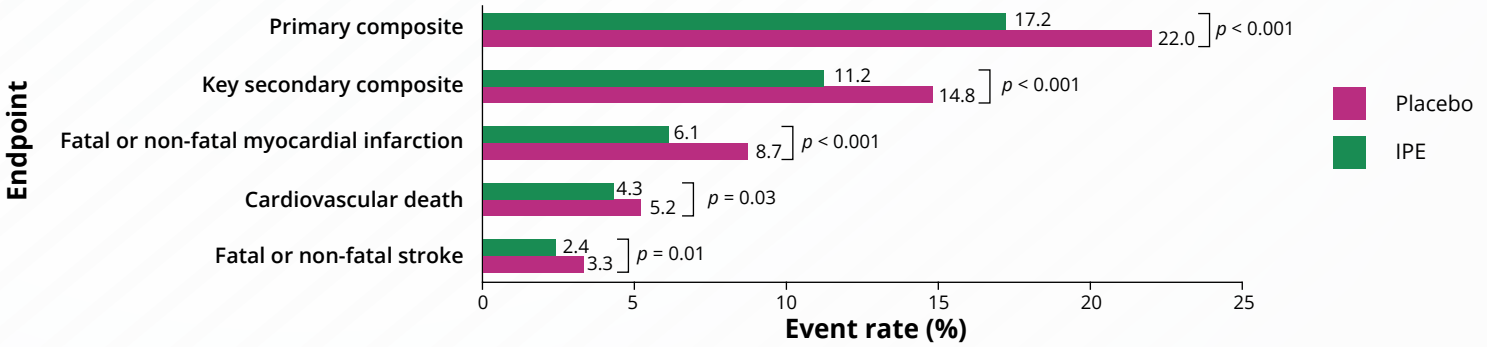
Clinical trials supporting the cardiovascular benefits of IPE

Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)[11]

Study participants (N = 8,179):
patients with CVD or with diabetes and other risk factors, receiving statins

Therapeutic intervention:
IPE at 4 gm per day for 4,089 patients



Post hoc analysis of REDUCE-IT data revealed that the administration of IPE lowered the incidence of major adverse cardiovascular events (MACE) in patients with high levels of lipoprotein(a) as well as showed significant benefits in those with normal lipoprotein(a) levels[12]

Role of IPE treatment

- Lowered the risk of MACE in patients with ASCVD and elevated triglyceride levels[13]
- Reduced fatal and non-fatal ischaemic events across the broad range of baseline estimated glomerular filtration rate categories[15]
- Modulated the vascular regenerative cell content[16]
- In high-risk patients treated with statins with acute coronary syndrome, IPE reduced the risk of ischaemic events[17]
- Consistent benefits of IPE were observed in the endpoints across background statin agent and category[18]

Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid (RESPECT-EPA)[6]

Study participants (N = 2,506):
patients with coronary artery disease with a low EPA/AA ratio

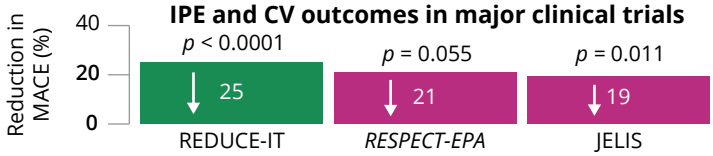
Therapeutic intervention
IPE at 1.8 gm per day

- IPE treatment resulted in a numerically lower risk of cardiovascular events in patients with chronic coronary artery disease, a low EPA/AA ratio, and statin treatment[14]

Japan EPA lipid intervention study (JELIS) trial[19]

Study participants (N = 18,645):
patients with hypercholesterolaemia

Therapeutic intervention
EPA at 1.8 gm per day



- Significant increase in both EPA levels and the EPA/AA ratio
- EPA was shown to be effective for the secondary prevention of coronary artery disease[20]

Key messages

- Atherosclerosis is the result of an acute inflammatory immune response
- Eicosanoids are lipid-based mediators of inflammatory response and play key roles in the development of ASCVD
- The ratio of EPA/AA is a well-established marker of ASCVD risk
- IPE is an important therapeutic option to counter the risks of ASCVD

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