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How Does Vascepa Work?
Potential Mechanisms of Action for Vascepa

NASDAQ: **AMRN**

Pure EPA
Vascepa®
(icosapent ethyl)

Important Information About Mechanism of Action Studies

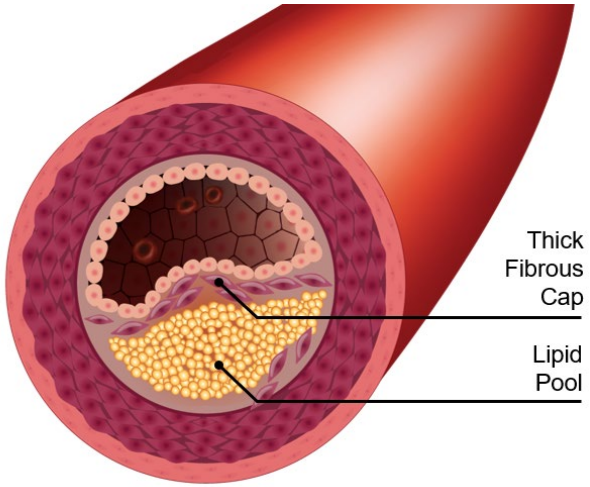
- Studies designed to help understand how a drug may have demonstrated an effect shown in clinical research, so called mechanism of action studies, can lead to more informed understanding of disease and more discoveries to improve public health.
- Mechanism of action studies have different degrees of reliability and often involve evolving methods and analyses that can be difficult to independently verify.
- Due to the complexity of cardiovascular disease, mechanism of action studies and theories on the biological plausibility of mechanistic effects on the reduction of cardiovascular risk have not been reliably predictive of clinical effects (e.g., the generally recognized failure of HDL-raising drugs).
- The degree to which, if any, the mechanistic effects featured herein may have contributed to the risk reduction effects of Vascepa demonstrated in the REDUCE-IT™ cardiovascular outcomes study is not fully understood and may, in certain cases, require additional research.

Vascepa's Mechanisms of Action Are Multifactorial

Plaque reduction, regression and stabilization as contributing mechanisms of action (MoA) of Vascepa

- Coronary heart disease is caused by the buildup of coronary plaque [1]
- Atherosclerosis (coronary plaque in arteries) reduces blood flow, contributing to cardiovascular (CV) events [2]
- Regression: EPA therapy added to high dose statin therapy doubled the incidence of coronary plaque regression compared to statin therapy alone in the Japanese clinical study, CHERRY [3]
- Stabilization: EPA increased fibrous cap thickness in Japanese patients with a recent coronary event, reducing the likelihood that plaque will dislodge and travel down the blood stream, block blood flow, and cause a cardiovascular event [4]

Stable Plaque



Lipid pool=Lipid rich plaque

Vascepa's Mechanisms of Action Are Multifactorial (cont'd)

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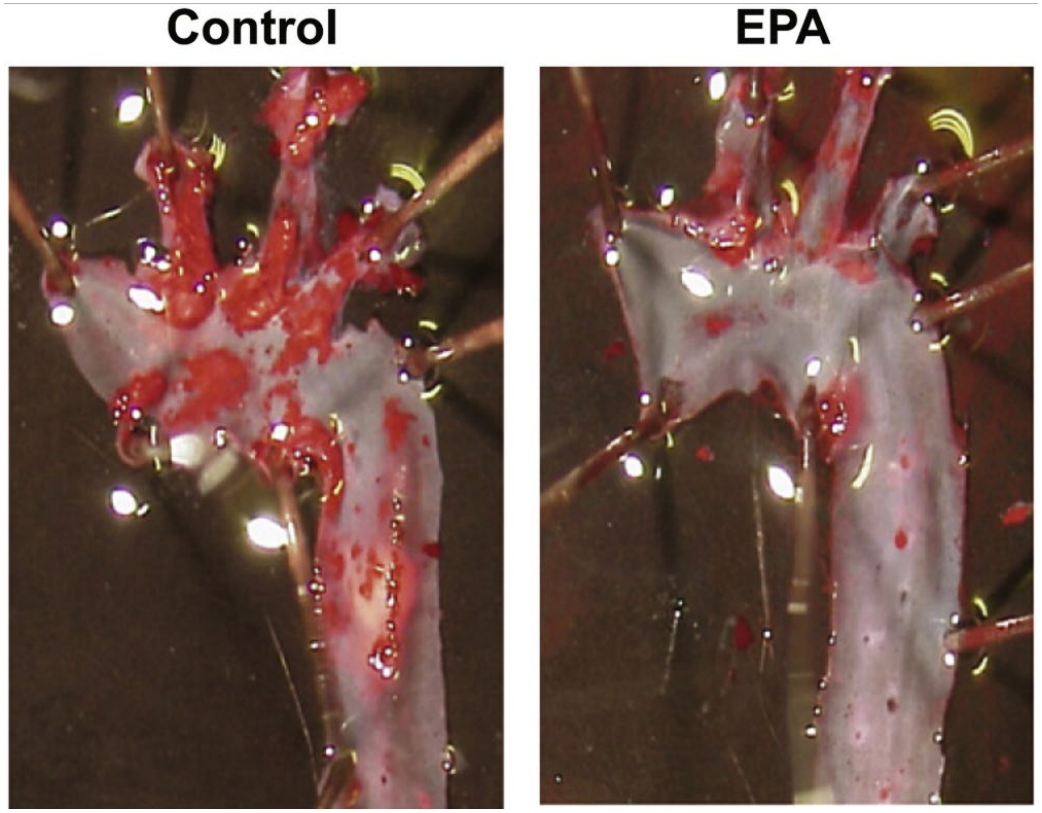
The effects of EPA in conjunction with statins on atherosclerotic plaques have also been evaluated in animal models [5]

Benefits shown in mice include a decrease in coronary plaque lesions [5]



Reprinted from *Atherosclerosis* 197(2), Matsumoto M, et al. Orally administered eicosapentaenoic acid reduces and stabilizes atherosclerotic lesions in ApoE-deficient mice. Copyright 2008, with permission from Elsevier.

Vascepa's Mechanisms of Action Are Multifactorial (cont'd)

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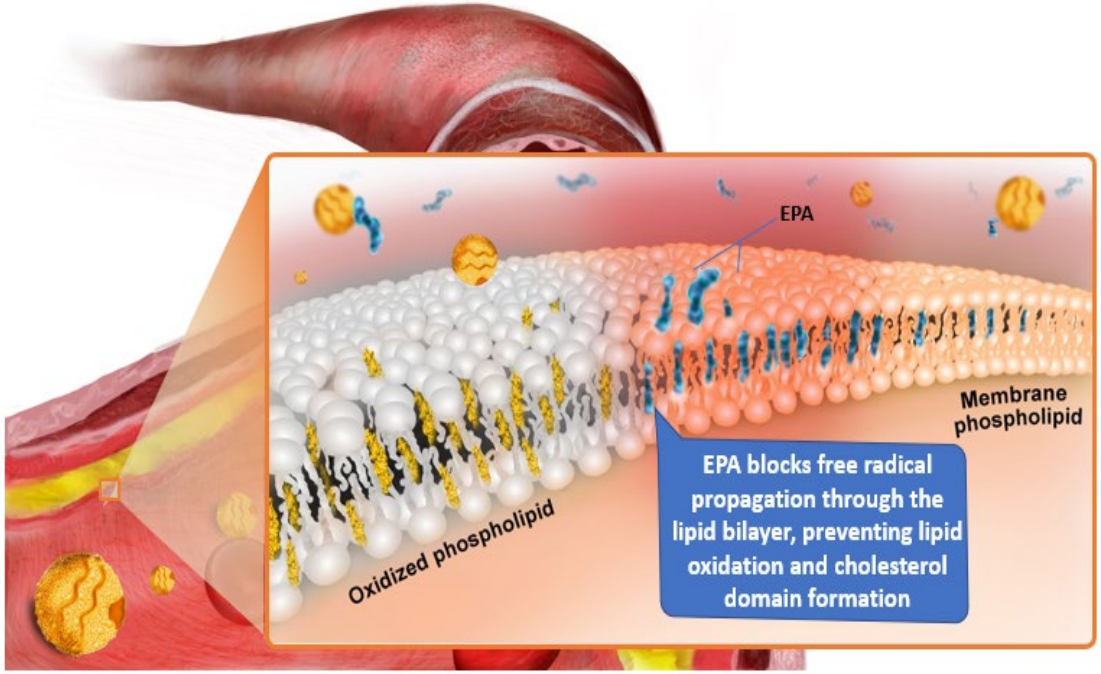
Inflammation and oxidative stress

- Inflammation and oxidative stress can contribute to cardiovascular disease [6]
- Clinical Data: Vascepa has anti-inflammatory effects, both systemic as well as localized. [7] This includes significant reduction of inflammation and oxidation biomarkers such as hsCRP, Lp-PLA2, and oxLDL [8-12]
- Preclinical Data: Oxidative stress leads to cholesterol domain formation [13]

EPA Inhibits Lipid Oxidation and Cholesterol Domain Formation [13]



Vascepa's Mechanisms of Action Are Multifactorial (cont'd)

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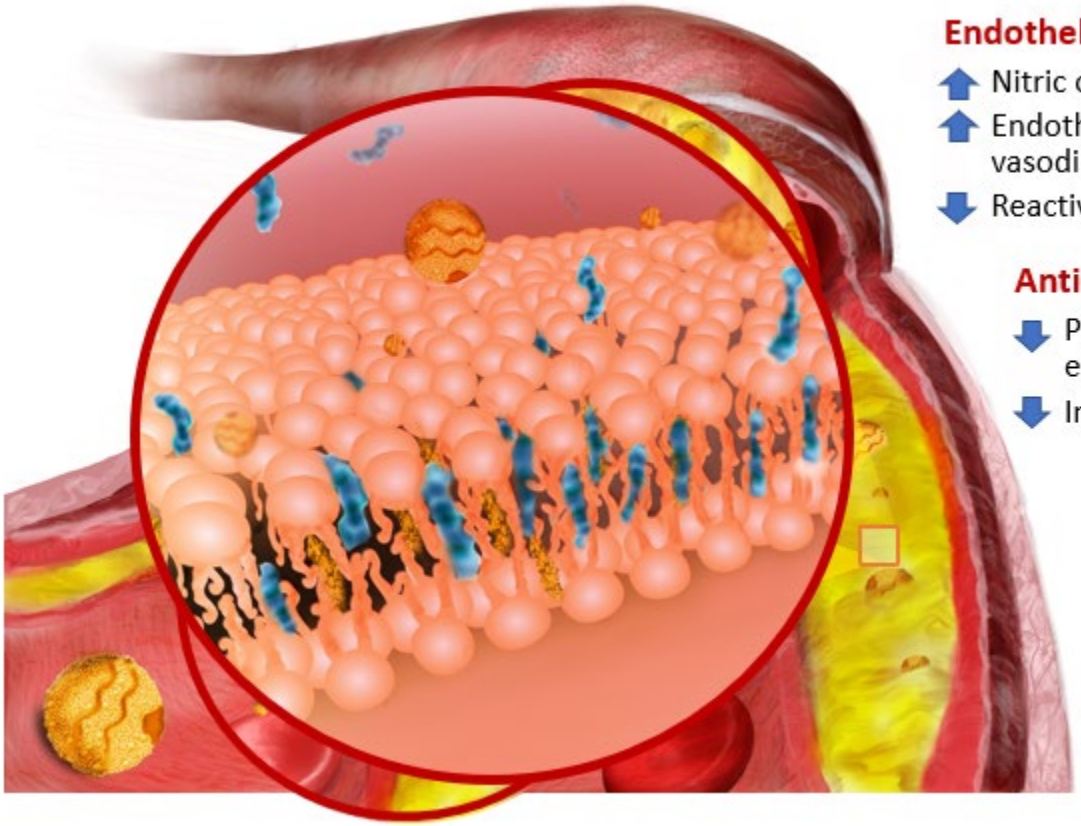
EPA May Have Beneficial Effects on Multiple Atherosclerotic Processes [14-16]



Endothelial function

- ↑ Nitric oxide production
- ↑ Endothelium-dependent vasodilation
- ↓ Reactive oxygen species

Anti-inflammatory effects

- ↓ Proinflammatory eicosanoids and cytokines
- ↓ Inflammatory cell recruitment

Plaque stability

- ↓ Plaque formation, progression, and rupture
- ↓ Thrombosis
- ↓ Platelet activation
- ↑ Fibrous cap thickness

The extent to which these so-called pleiotropic effects of EPA (eicosapentaenoic acid in stable and pure form) may have contributed to the success of Vascepa in the REDUCE-IT study [17, 18] relative to other effects of EPA (e.g. transcriptional gene regulation, membrane stabilization) is under evaluation

Vascepa's Mechanisms of Action are Multifactorial (cont'd)

Cellular transcriptional and membrane stabilizing effects

- EPA regulates genes involved in lipid metabolism and plaque stabilization [19]
- EPA alters membrane function and stabilization [20]

High triglyceride levels and an atherogenic lipid profile

- Vascepa, in multiple clinical studies (MARINE, ANCHOR and REDUCE-IT), has demonstrated that it lowers triglyceride (TG) levels (a type of blood fat) and improves various other markers of lipids and lipoproteins [7, 17, 21]
- Multiple epidemiological, genetic and clinical studies link elevated TG levels to increased cardiovascular (CV) risk https://amarincorp.gcs-web.com/static-files/28493518-0506-43f9-91e2-a88ab47e271b
- However, lowering TG levels alone does not fully explain the CV risk reduction demonstrated by Vascepa
  - Studies of other agents that lower TG levels (Niacin, Fibrates) did not demonstrate cardiovascular risk reduction [22, 23]
  - In REDUCE-IT, Vascepa reduced CV risk rates more than it lowered TG levels (relative risk reduction of 25% in first occurrence of MACE and 30% reduction in first and recurrent MACE, with TG lowering of 20% vs. placebo) [17, 18]
  - JELIS (large outcomes study in Japan that used eicosapentaenoic acid, EPA, the active ingredient in Vascepa) demonstrated a 19% risk reduction in patients with essentially normal TG levels and only 5% lower TG, suggesting the effects of EPA go beyond TG lowering [24]

Vascepa's Mechanisms of Action Background Information

Amarin has invested in extensive research regarding Vascepa's mechanism of action (MoA)

- This document includes dozens of publication references regarding EPA's MoA; many funded by Amarin
- These references highlight Amarin's commitment to researching the science of Vascepa

Complete understanding of Vascepa's MoA is not required for FDA approval

- Many drugs are approved for use and broadly used without MoA's being fully understood

  Examples include:
  - Statins [25]
  - Acetaminophen (active ingredient in Tylenol®) [26]
  - Aspirin [27]
  - Calcium Channel Blockers [28]
  - General anesthesia [29]
  - Lithium [26]
  - Modafinil [26]

Evidence of drug efficacy and safety from a well-controlled, well-conducted clinical development program is the most important element of a supplemental new drug application (sNDA)

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Summary of Publications Regarding Potential Mechanisms of Action of Vascepa's Active Ingredient

Multiple (2 or more) Mechanisms of Action

- Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. *Atherosclerosis*. 2015 Sep;242(1):357-66. https://www.atherosclerosis-journal.com/article/S0021-9150(15)30055-1/pdf
- Preston Mason R. New Insights into Mechanisms of Action for Omega-3 Fatty Acids in Atherothrombotic Cardiovascular Disease. *Curr Atheroscler Rep.* 2019 Jan 12;21(1):2. https://link.springer.com/content/pdf/10.1007%2Fs11883-019-0762-1.pdf
- Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs*. 2013 Feb;13(1):37-46. https://link.springer.com/content/pdf/10.1007%2Fs40256-012-0002-3.pdf
- Video: Animation of potential mechanisms of action
- Video: Biologic Basis of EPA to Reduce Atherosclerosis Burden

Triglyceride Reduction

- See separate summary of multiple publications https://amarincorp.gcs-web.com/static-files/28493518-0506-43f9-91e2-a88ab47e271b

Endothelial Function

- Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. *Atherosclerosis*. 2015 Sep;242(1):357-66. https://www.atherosclerosis-journal.com/article/S0021-9150(15)30055-1/pdf
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Note:

- ***Links may lead to content for which Amarin is not responsible***
- ***The degree to which, if any, the mechanistic effects featured herein may have contributed to the risk reduction effects of Vascepa demonstrated in the REDUCE-IT™ cardiovascular outcomes study requires additional research.***

Summary of Publications Regarding Potential Mechanisms of Action of Vascepa's Active Ingredient (cont'd)

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Anti-oxidant Effects

- Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs*. 2013 Feb;13(1):37-46. https://link.springer.com/content/pdf/10.1007%2Fs40256-012-0002-3.pdf
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Foam Cell Formation

- Cawood AL, Ding R, Napper FL, Young RH, Williams JA, Ward MJ, Gudmundsen O, Vige R, Payne SP, Ye S, Shearman CP, Gallagher PJ, Grimble RF, Calder PC. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. *Atherosclerosis*. 2010 Sep;212(1):252-9. https://www.atherosclerosis-journal.com/article/S0021-9150(10)00400-4/fulltext
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Inflammation

- Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs*. 2013 Feb;13(1):37-46. https://link.springer.com/content/pdf/10.1007%2Fs40256-012-0002-3.pdf
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Plaque Formation/progression

- Watanabe T, Ando K, Daidoji H, Otaki Y, Sugawara S, Matsui M, Ikeno E, Hirono O, Miyawaki H, Yashiro Y, Nishiyama S, Arimoto T, Takahashi H, Shishido T, Miyashita T, Miyamoto T, Kubota I; CHERRY study investigators. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. *J Cardiol.* 2017 Dec;70(6):537-544. https://www.journal-of-cardiology.com/article/S0914-5087(17)30200-9/pdf
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Summary of Publications Regarding Potential Mechanisms of Action of Vascepa's Active Ingredient (cont'd)

Platelet Aggregation

- Terano T, Hirai A, Hamazaki T, Kobayashi S, Fujita T, Tamura Y, Kumagai A. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. *Atherosclerosis*. 1983 Mar;46(3):321-31. https://www.atherosclerosis-journal.com/article/0021-9150(83)90181-8/pdf
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Thrombus Formation

- Krämer HJ, Stevens J, Grimminger F, Seeger W. Fish oil fatty acids and human platelets: dose-dependent decrease in dienoic and increase in trienoic thromboxane generation. *Biochem Pharmacol*. 1996 Oct 25;52(8):1211-7. https://www.sciencedirect.com/science/article/abs/pii/000629529600473X?via%3Dihub
- Terano T, Hirai A, Hamazaki T, Kobayashi S, Fujita T, Tamura Y, Kumagai A. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. *Atherosclerosis*. 1983 Mar;46(3):321-31. https://www.atherosclerosis-journal.com/article/0021-9150(83)90181-8/pdf

Note:

- ***Links may lead to content for which Amarin is not responsible***
- ***The degree to which, if any, the mechanistic effects featured herein may have contributed to the risk reduction effects of Vascepa demonstrated in the REDUCE-IT™ cardiovascular outcomes study requires additional research.***

Summary of Publications Regarding Potential Mechanisms of Action of Vascepa's Active Ingredient (cont'd)

Plaque Stabilization

- Nishio R, Shinke T, Otake H, Nakagawa M, Nagoshi R, Inoue T, Kozuki A, Hariki H, Osue T, Taniguchi Y, Iwasaki M, Hiranuma N, Konishi A, Kinutani H, Shite J, Hirata K. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. *Atherosclerosis*. 2014 May;234(1):114-9. https://www.atherosclerosis-journal.com/article/S0021-9150(14)00123-3/fulltext
- Yamano T, Kubo T, Shiono Y, Shimamura K, Orii M, Tanimoto T, Matsuo Y, Ino Y, Kitabata H, Yamaguchi T, Hirata K, Tanaka A, Imanishi T, Akasaka T. Impact of eicosapentaenoic acid treatment on the fibrous cap thickness in patients with coronary atherosclerotic plaque: an optical coherence tomography study. *J Atheroscler Thromb*. 2015;22(1):52-61. https://www.jstage.jst.go.jp/article/jat/22/1/22_25593/_pdf/-char/en
- Niki T, Wakatsuki T, Yamaguchi K, Taketani Y, Oeduka H, Kusunose K, Ise T, Iwase T, Yamada H, Soeki T, Sata M. Effects of the Addition of Eicosapentaenoic Acid to Strong Statin Therapy on Inflammatory Cytokines and Coronary Plaque Components Assessed by Integrated Backscatter Intravascular Ultrasound. *Circ J.* 2016;80(2):450-60. https://www.jstage.jst.go.jp/article/circj/80/2/80_CJ-15-0813/_pdf/-char/en

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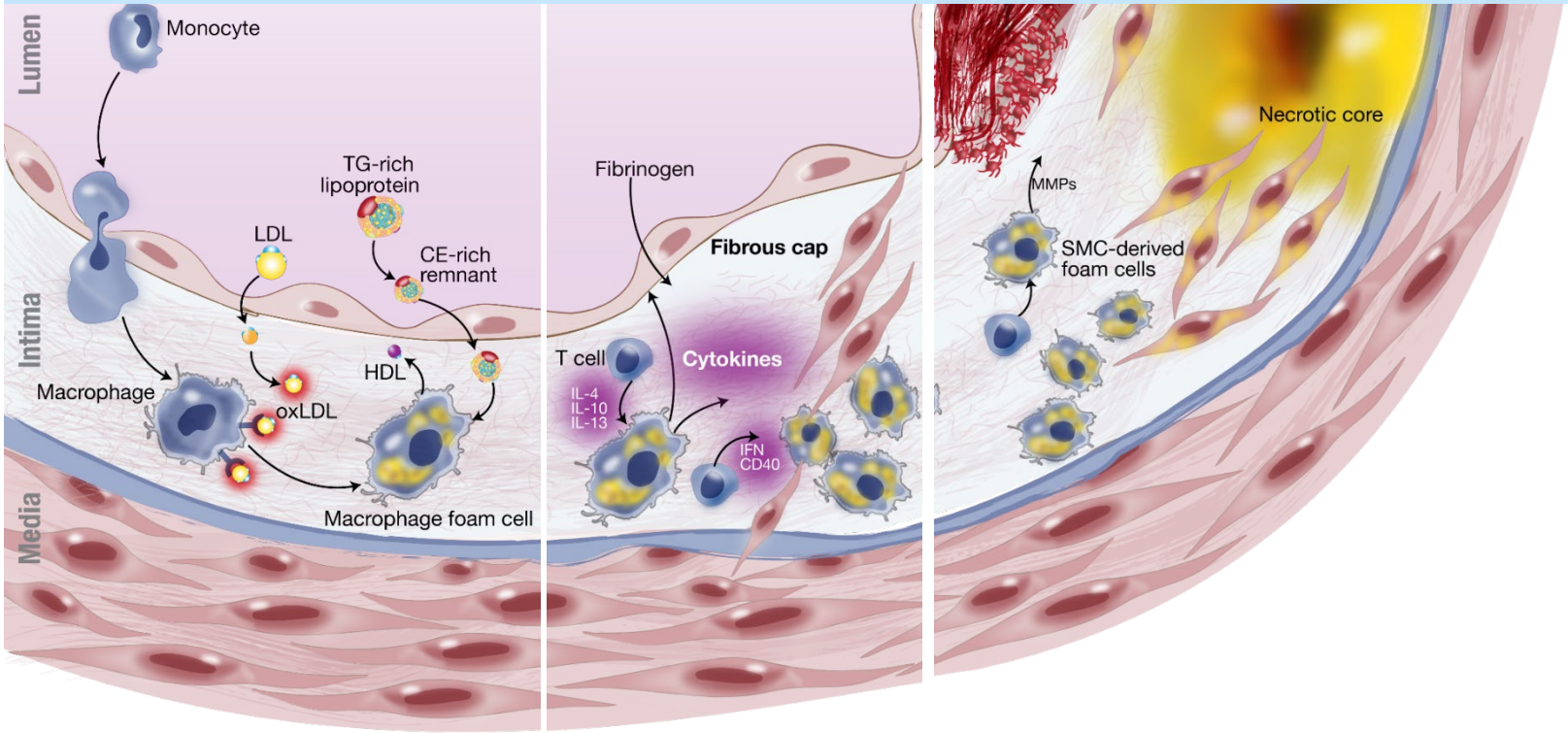
Recap of Potential Mechanistic Effects of Vascepa's Active Ingredient on Multiple Atherosclerotic Processes

Multiple Plaque Formation/Progression Processes Potentially Affected by EPA[16]

- Endothelial function
- Atherogenic lipids/lipoproteins
- Oxidative stress
- Foam cell formation
- Inflammation/cytokines
- Platelet aggregation
- Thrombus formation
- Plaque rupture



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