VibrantWellness

Cardiac Health Panel

Interpretive Guide

Revised 3/19/2024

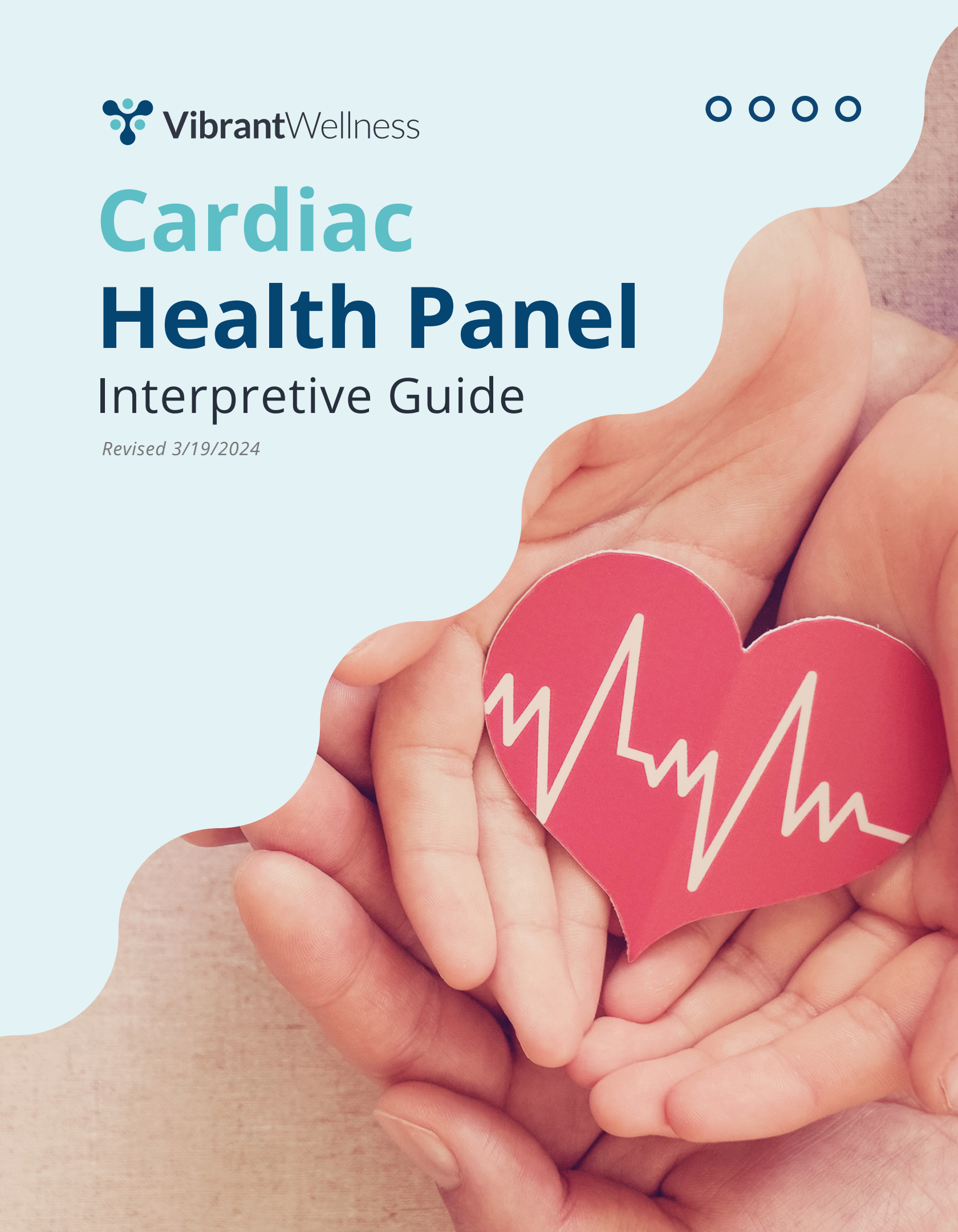
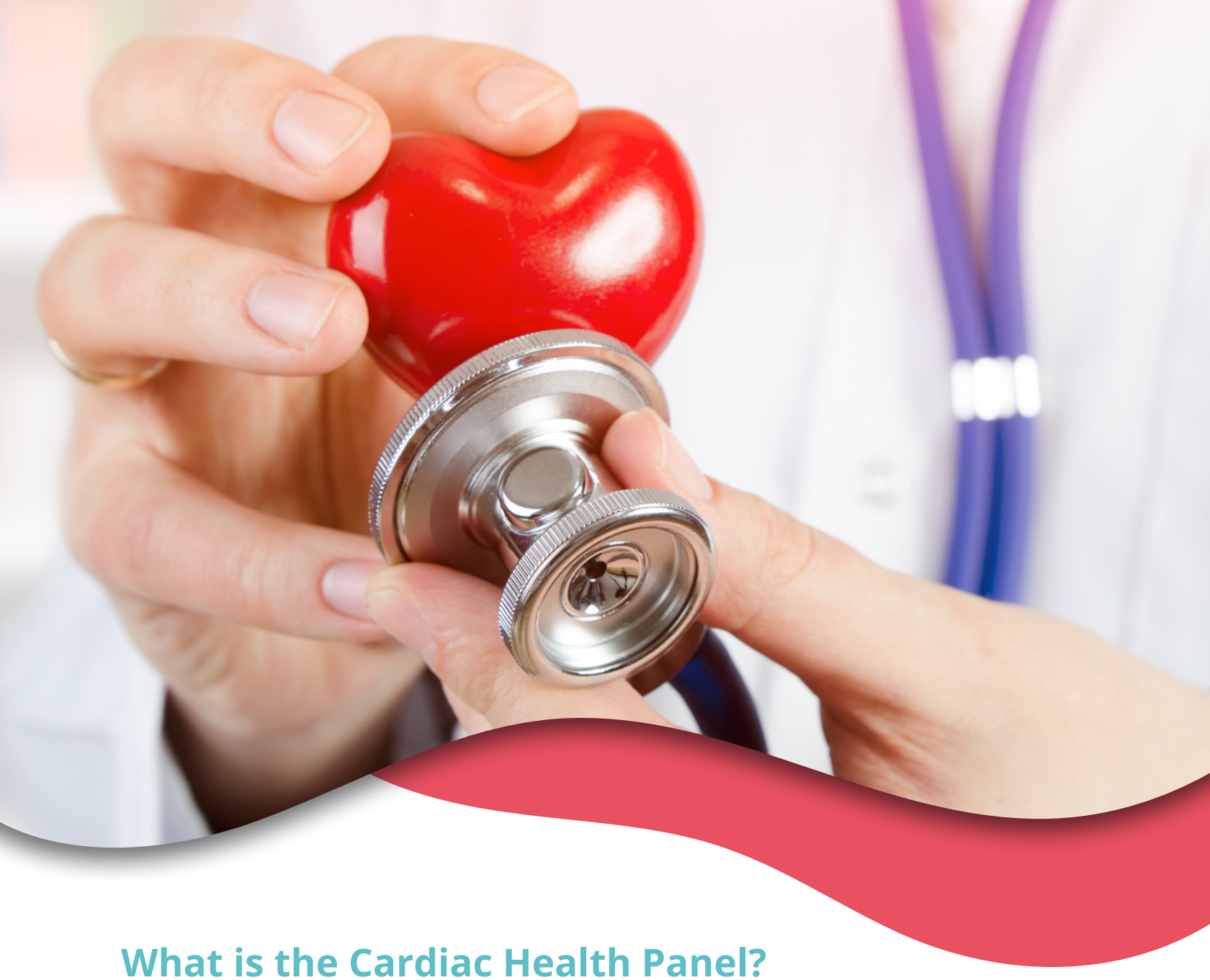


Table of Contents



What is the Cardiac Health Panel?

The Cardiac Health Panel is a blood test that measures serum lipids, apolipoproteins, and cardiovascular-associated markers of inflammation.

Why Run the Cardiac Health Panel?

Cardiovascular disease is a leading cause of death in America. Yet, cardiovascular disease is preventable and modifiable. Vibrant's Cardiac Health Panel helps identify the root causes of inflammation driving heart disease progression to guide therapeutic lifestyle changes that help reduce the potential acuity of cardiovascular disease.

How Should Results Be Interpreted?

Understanding and identifying a patient's lipids, inflammation, and genetic predispositions to cardiovascular disease will help quantify their risk and can be used to probe the formation of chronic disease.

Lipids

Lipids can be categorized into different types, including triglycerides, cholesterol, and phospholipids. Measuring basic lipids, including total cholesterol, LDL calculation, HDL direct, cholesterol to HDL ratio, and triglycerides, is fundamental for assessing cardiovascular health and overall well-being. This interpretive guide provides an overview of the functions of these lipid components, the causes of high and low levels, and steps to maintain healthy lipid levels.

Functions of Basic Lipids

Triglycerides serve a significant dual role in the body. They function as carriers for fatty acids and act as a valuable energy source. Triglycerides undergo breakdown into fatty acids and glycerol, and both of these components can be utilized as substrates for energy production and various metabolic pathways. They provide a source of energy, insulate and protect organs, and help transport fat-soluble vitamins.

Cholesterol is vital for cell membrane structure and serves as a precursor for various hormones, such as the estrogens, progestogens, androgens and mineralocorticoids. It's also essential for the synthesis of vitamin D and bile acids, which aid in fat digestion.

LDL (Low-Density Lipoprotein) serves as the main transporter of cholesterol in the bloodstream, primarily responsible for delivering cholesterol to both peripheral and liver cells. The progression of atherosclerosis occurs when oxidized LDL cholesterol is internalized by macrophages and subsequently accumulates within atheromatous plaques, leading to the development of atherosclerotic lesions.

HDL (High-Density Lipoprotein) facilitates cholesterol scavenging from the bloodstream, escorting it to the liver for elimination. Subsequently, the liver orchestrates the removal of excess cholesterol from the body. Elevated HDL cholesterol levels contribute to a reduced susceptibility to heart disease and stroke.

Measurements

HDL Direct: HDL Direct refers to HDL cholesterol measured directly in a blood sample. It uses a specific test to isolate and quantify HDL cholesterol particles and is considered more accurate than the indirect or calculated method.

LDL Direct: LDL Direct refers to the direct measurement of LDL cholesterol in a blood sample. LDL Direct measurement specifically quantifies the concentration of LDL cholesterol in the blood and is considered more accurate than the indirect or calculated method.

Calculations & Ratios

Cholesterol to HDL Ratio: This ratio is calculated by dividing the total cholesterol by the HDL level. An ideal ratio is 5:1, with an even more favorable ratio at 3.5:1. A lower ratio is generally associated with better cardiovascular health.[1] Given the variability of total cholesterol levels, multiple blood tests may be necessary to ensure an accurate assessment.

LDL Calculation: An LDL calculation, often referred to as the estimated LDL cholesterol (e-LDL), calculates the level of low-density lipoprotein (LDL) cholesterol in your blood based on the results of a standard lipid panel, which typically includes measurements of total cholesterol, HDL cholesterol, and triglycerides. The calculation is based on a formula and is typically used when a direct measurement of LDL cholesterol is not available or deemed unnecessary; however Vibrant provides both types of LDL measurements for accuracy and thoroughness.

The formula most commonly used for calculating LDL cholesterol is the Friedewald equation, which is as follows:

LDL Cholesterol = Total Cholesterol – (HDL Cholesterol + Triglycerides/5)

It's important to note that the Friedewald equation may not be accurate or reliable in certain situations, such as when triglyceride levels are very high (greater than 400 mg/dL) or when a person has fasting triglycerides that are not within the normal range. In such cases, a direct measurement of LDL cholesterol, such as through ultracentrifugation or other methods, may be necessary for a more accurate assessment of LDL cholesterol levels.

Apolipoproteins

Apolipoproteins are proteins that are primarily associated with lipoproteins, complexes of proteins and lipids (fats) that transport lipids through the bloodstream. These proteins play a crucial role in lipid metabolism and are involved in various aspects of lipid transport, including the absorption, distribution, and utilization in the body. There are several different apolipoproteins, each with specific functions. Some of the most well-known apolipoproteins include:

Apo A-1 is the major protein component of HDL particles. HDL helps transport excess cholesterol from peripheral tissues back to the liver for excretion. ApoA-1 plays a crucial role in the structure and function of HDL and is primarily involved in the reverse cholesterol transport pathway, where it promotes the removal of excess cholesterol from the body's tissues.

Apo B is a key structural protein associated with various lipoprotein particles, primarily LDL and very low-density lipoprotein (VLDL). Apo B plays a critical role in the transport of lipids (fats) in the bloodstream and is often associated with the concept of "bad cholesterol" because it's involved in the delivery of cholesterol to peripheral tissues, including the arteries.

Apo B: Apo A-1 Ratio

The Apo B: Apo A-1 ratio is a valuable marker in assessing cardiovascular risk, as it provides insights into the balance of HDL and LDL cholesterol in the body.

Clinical significance of the Apo B: Apo A-1 ratio in cardiovascular risk assessment:

- Atherosclerosis Risk: A high Apo B: Apo A-1 ratio is associated with an increased risk of atherosclerosis, a condition characterized by the buildup of fatty deposits (plaques) in the arteries. Elevated levels of Apo B, and thus LDL cholesterol, are linked to a higher risk of atherosclerosis, while higher levels of Apo A-1 and HDL cholesterol are associated with a reduced risk.[2]
- Cardiovascular Disease Risk: A high Apo B: Apo A-1 ratio is considered a stronger predictor of cardiovascular disease risk than traditional measures of cholesterol, such as total cholesterol, LDL cholesterol, or HDL cholesterol levels.[3] This is because it considers the balance between atherogenic (promoting atherosclerosis) and anti-atherogenic (protecting against atherosclerosis) lipoproteins.
- Treatment Monitoring: The Apo B: Apo A-1 ratio can be useful for assessing the effectiveness of interventions, such as lifestyle changes and medications, aimed at reducing cardiovascular risk. Lowering the Apo B: Apo A-1 ratio by reducing Apo B levels or increasing Apo A-1 levels through various interventions can help improve cardiovascular health.[4]
- Personalized Risk Assessment: Measuring the Apo B: Apo A-1 ratio provides a more personalized approach to assessing cardiovascular risk, as it considers the individual's unique balance of lipoproteins, rather than relying solely on population-based cholesterol targets.

Lipoprotein Markers

sdLDL, or small dense low-density lipoprotein, is a subclass of LDL cholesterol. It refers to LDL particles that are smaller and denser than the typical LDL particles found in the bloodstream. These small, dense LDL particles are often associated with an increased risk of cardiovascular disease.[5]

Some key points about sdLDL:

- ***Size and Density:*** sdLDL particles are characterized by their smaller size and higher density compared to larger, buoyant LDL particles. These smaller particles are more likely to penetrate the arterial wall, making them potentially more atherogenic.[6]

- ***Atherogenicity:*** sdLDL particles are believed to be more atherogenic than larger LDL particles. Atherosclerosis is a condition in which fatty deposits, including cholesterol, accumulate in the arterial walls. The small size of sdLDL particles allows them to more easily infiltrate the arterial wall, which can contribute to the formation of plaques and increase the risk of heart disease.

- ***Increased Cardiovascular Risk:*** Elevated levels of sdLDL are associated with an increased risk of coronary artery disease and cardiovascular events, such as heart attacks and strokes.[7] Some studies suggest that measuring sdLDL, in addition to traditional LDL cholesterol levels, may provide a more comprehensive assessment of cardiovascular risk.

- ***Causes:*** There are a combination of lifestyle and genetic factors such as insulin resistance, metabolic syndrome, a diet high in saturated fats and refined carbohydrates, physical inactivity, and smoking that can lead to an increase in sdLDL levels.[8]

Lp(a) is a lipoprotein particle that consists of an LDL cholesterol particle attached to a unique protein called apolipoprotein(a). Lp(a) is sometimes referred to as "Lp little-a."

Some key points about Lp(a):

- **Structure:** Lp(a) has a structure similar to LDL cholesterol but with an additional protein component, apolipoprotein(a). This unique protein structure sets Lp(a) apart from other lipoproteins.
- **Atherogenicity:** Elevated levels of Lp(a) are associated with an increased risk of cardiovascular disease, including atherosclerosis, heart attacks, and strokes. Lp(a) is considered an independent risk factor for heart disease, meaning that even if other cholesterol levels are well-controlled, high Lp(a) can still contribute to cardiovascular risk.[9]
- **Genetic Component:** Because Lp(a) is primarily genetically determined, some individuals may have elevated Lp(a) levels without significant lifestyle factors contributing to it. If you have a family history of high Lp(a) levels, you may be at increased risk for elevated Lp(a).[10]
- **Atherosclerosis:** Lp(a) has a strong affinity for accumulating in arterial walls, similar to LDL cholesterol. When Lp(a) particles infiltrate the arterial wall, they can contribute to the development of atherosclerotic plaques.[11]
- **Management:** The management of elevated Lp(a) levels can be challenging, as lifestyle modifications and common cholesterol-lowering medications like statins may not significantly impact Lp(a) levels.

Cardiac Stress Marker

NT-proBNP, or N-terminal pro B-type natriuretic peptide, is a biomarker used to assess and diagnose heart-related conditions, particularly heart failure. It is a prohormone of B-type natriuretic peptide (BNP), which is a hormone produced by the heart ventricles in response to increased pressure and volume. BNP and its N-terminal fragment, NT-proBNP, are released into the bloodstream when the heart is under stress or when there is a strain on the heart, such as in heart failure.

Elevated levels of NT-proBNP are indicative of cardiac stress and can help with the following considerations:

- Elevated levels can be indicative of the presence and severity of heart failure. NT-proBNP levels are often higher in individuals with heart failure; the concentration of NT-proBNP in the blood can be used to estimate the severity of heart failure. Higher levels are generally associated with more severe heart failure.

- NT-proBNP levels can be monitored over time to evaluate the effectiveness of treatment in heart failure patients. A decrease in NT-proBNP levels may indicate that the treatment is working.

- NT-proBNP levels can also be elevated in other heart-related conditions, such as acute coronary syndrome, and can be used to aid in diagnosis.

It's important to note that NT-proBNP levels can also be influenced by other factors such as age, kidney function, and some non-cardiac medical conditions. Therefore, healthcare providers typically consider a combination of clinical assessment, other diagnostic tests, and the NT-proBNP level to make an accurate diagnosis and treatment decisions related to heart conditions.

Inflammation Markers

PLAC is an abbreviation for lipoprotein-associated phospholipase A2. It's an enzyme associated with low-density lipoprotein (LDL) and, to a lesser extent, with HDL particles. PLAC is also sometimes referred to as Lp-PLA2 or simply PLA2.

The main role of PLAC is to breakdown the phospholipids found in LDL and HDL. This enzymatic activity can lead to the formation of proinflammatory and proatherogenic products. Elevated levels of PLAC have been associated with an increased risk of atherosclerosis, heart disease, and stroke, as the enzyme's activity can contribute to inflammation and the formation of atherosclerotic plaques in blood vessels.[12]

Homocysteine is a naturally occurring amino acid that is produced in the body as a byproduct of the metabolism of another amino acid called methionine. Elevated homocysteine levels are often considered a risk factor for atherosclerosis, blood clots, and coronary artery disease. [13]

There are several causes of high homocysteine levels including genetic, dietary, and lifestyle factors. Some of the primary causes of elevated homocysteine levels include:

- **Nutritional Deficiencies:** A deficiency in vitamin B6, vitamin B12, and folate (vitamin B9), can lead to high homocysteine levels. These vitamins are necessary for the breakdown of homocysteine in the body.

- **Diet:** Dietary factors can contribute to elevated homocysteine levels. A diet low in foods that provide these B vitamins, such as leafy green vegetables, legumes, fortified cereals, and animal products (for vitamin B12), may increase the risk of high homocysteine. Conversely, a diet rich in these nutrients can help lower homocysteine levels.

- **Genetics:** Some individuals may have genetic variations that predispose them to higher homocysteine levels. These genetic factors can affect enzymes involved in homocysteine metabolism. While genetic factors play a role, lifestyle and dietary choices can still influence homocysteine levels.

- **Other factors** include increasing age and male sex, cigarette smoking, excessive alcohol consumption, kidney disease, hypothyroidism, medications (anticonvulsants and methotrexate), inflammatory conditions, and oxidative stress.[14]

hs-CRP refers to high-sensitivity C-reactive protein. C-reactive protein (CRP) is a marker of inflammation and can be measured in the blood to assess the level of systemic inflammation.

The "high-sensitivity" version of the CRP test, or hs-CRP, is a more sensitive and specific assay used to detect low levels of CRP in the blood. It is used to assess low-grade or chronic inflammation, which may not be detected by a standard CRP test.

Here are some key points about hs-CRP:

- hs-CRP is used as a marker of inflammation in the body. It can help healthcare professionals identify and monitor inflammation associated with various conditions, including infections, autoimmune diseases, and cardiovascular disease.

- Elevated hs-CRP levels are associated with an increased risk of heart disease, particularly atherosclerosis.[15] It can provide information about the level of inflammation in the blood vessels, which is a risk factor for the development of heart attacks and strokes.

- hs-CRP can also be used to monitor and assess the severity of acute and chronic infections, as well as various inflammatory conditions.

Ox-LDL refers to oxidized LDL. It's a modified form of LDL cholesterol that has undergone oxidative damage. Ox-LDL is often associated with atherosclerosis and is considered a risk factor for cardiovascular disease.[16]

Here are some key points about Ox-LDL:

- Ox-LDL is formed when LDL particles (normal carriers of cholesterol in the bloodstream) are exposed to oxidative stress. Oxidative stress can be caused by various factors, including smoking, high blood pressure, diabetes, and the presence of reactive oxygen species (free radicals).[17]

- Ox-LDL is more atherogenic than native, unoxidized LDL.[18] When ox-LDL accumulates in the arterial walls, it can trigger an inflammatory response and lead to the formation of atherosclerotic plaques.[19]

- Elevated levels of ox-LDL are associated with an increased risk of heart disease, including heart attacks and strokes. As a result, ox-LDL is considered a potential risk factor for cardiovascular disease.[20]

MPO refers to myeloperoxidase, which is an enzyme found in white blood cells, particularly neutrophils and monocytes. Myeloperoxidase plays a crucial role in the body's immune response and inflammation.

Here are some key points about MPO in relation to cardiovascular health.

- MPO is an enzyme involved in the body's innate immune response as part of the body's defense mechanisms against infections and foreign invaders. MPO is used by white blood cells to generate reactive oxygen species and chlorine molecules, which are toxic to pathogens like bacteria and viruses.

- While MPO is essential for the body's defense against infection, it can also contribute to inflammation and tissue damage if it is overly activated or if it is present in excess. In some cases, excessive MPO activity has been linked to inflammatory conditions and tissue injury.

- Elevated levels of MPO have been associated with an increased risk of cardiovascular disease, including atherosclerosis, heart attacks, and strokes. MPO can promote oxidative stress and inflammation in blood vessels, which are key factors in the development of atherosclerosis.

Causes of High Lipid Levels

1. **Diet:** Consuming a diet high in saturated and trans fats can elevate triglyceride and LDL cholesterol levels.[21]
2. **Physical Inactivity:** A sedentary lifestyle can lead to higher triglycerides and lower HDL cholesterol levels.
3. **Genetics:** Some individuals may have a genetic predisposition to high cholesterol levels.
4. **Obesity:** Excess body weight often results in elevated triglycerides and LDL cholesterol levels.
5. **Medical Conditions:** Conditions like diabetes, hypothyroidism, and metabolic syndrome can increase lipid levels.

Causes of Low Lipid Levels

1. **Malnutrition:** An inadequate intake of essential fatty acids and fat-soluble vitamins can lead to low lipid levels.
2. **Hyperthyroidism:** Overactive thyroid function may lower lipid levels.
3. **Malabsorption Disorders:** Conditions that hinder the absorption of dietary fats, such as celiac disease or Crohn's disease, can cause low lipid levels.

Steps to Maintain Healthy Lipid Levels:

1. **Diet:** Consume a balanced diet rich in fruits, vegetables, whole grains, and lean proteins. Limit refined sugars and simple carbohydrates and consider limiting saturated and trans fats.
2. **Physical Activity:** Engage in regular exercise to raise HDL cholesterol and lower triglycerides.
3. **Weight Management:** Maintain a healthy weight through a combination of diet and exercise.
4. **Medication:** In some cases, medication may be prescribed by a healthcare provider to manage lipid levels, especially if genetics or underlying health conditions are significant factors.
5. **Nutritional therapies:** Plant sterols, soluble fiber, omega-3 fatty acids, garlic, vitamin B3, green tea, red yeast rice, and berberine all have a positive effect on lowering lipid levels.
6. **Regular Monitoring:** Periodic lipid profile assessments are crucial to track progress and make necessary adjustments.

Measuring lipids, apolipoproteins and inflammatory markers provide a broad, yet detailed look into cardiovascular risk assessment. Understanding the functions of these various markers, the causes of high and low levels, and the steps to maintain healthy levels allows individuals to take control of their health and make informed decisions to reduce their risk of heart disease and related conditions.

Cardiovascular Care

The following are general recommendations for supporting healthy lipid levels:

Cholesterol, general lowering:

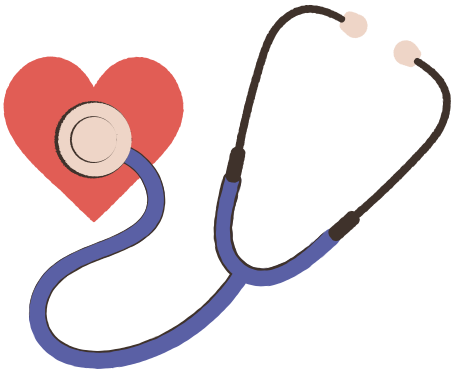
- Dietary fiber: 5-10 grams soluble (oatmeal, legumes, vegetables, fruits) daily[22]
- Omega-3 fatty acids: 1-3 grams daily[23]
- Plant Sterols and Stanols: 3 grams daily[24]
- Red Yeast Rice: Standardized to 10 monacolin K daily[25]
- Coenzyme Q10: 100-200 mg daily[26]
- Berberine: 500 mg three times daily[28]
- Exercise: 30-60 minutes daily[27]
- Policosanol: 10 mg twice daily[13]

HDL Cholesterol & Apolipoprotein A-1 (Increase)

- Regular (daily) exercise of 30 minutes or more
- Increase intake of omega-3 fats through diet (salmon, herring, sardines, walnuts and flaxseed) and supplementation 1-3 grams daily
- Niacin (vitamin B3): 500-2000 mg daily[29]
- Policosanol: 10 mg twice daily[30]

LDL Cholesterol, sdLDL, Apolipoprotein B

- Dietary fiber: 5-10 grams soluble (oatmeal, legumes, vegetables, fruits) daily[22]
- Omega-3 fatty acids: 1-3 grams daily[23]
- Plant Sterols and Stanols: 3 grams daily[24]
- Red Yeast Rice: Standardized to 10 monacolin K daily[25]
- Berberine: 500 mg three times daily[28]
- Green tea (epigallocatechin gallate (EGCG): 300-400 mg daily[31] [32]
- Policosanol: 10 mg twice daily[30]



ox-LDL

- Omega-3 fatty acids: 1-3 grams daily[23]
- Curcumin: 500 mg twice daily[33]
- Coenzyme Q10: 100-200 mg daily[26]
- Berberine: 500 mg three times daily[28]
- Garlic: 3-6 grams daily (approximately 1 large clove)[34]
- Policosanol: 10 mg twice daily[30]

Triglycerides

- Dietary changes: Minimize simple carbohydrates, increase fiber, limit alcohol
- Exercise: Regular exercise for a minimum of 150 minutes per week
- Niacin (vitamin B3): 500-2000 mg daily[29]
- Omega-3 fatty acids: 1-3 grams daily[23]
- Fenugreek (Trigonella foenum-graceum): 5-10 grams daily[35]
- Policosanol: 10 mg twice daily[30]

PLAC, MPO and hs-CRP

- Omega-3 fatty acids: 1-3 grams daily[23]
- Exercise: Regular exercise for a minimum of 150 minutes per week
- Curcumin: 500 mg twice daily[33]

Homocysteine

- B Complex containing the methylated forms of vitamin B12, vitamin B6 and folate[36]

Lp(a)

- Coenzyme Q10: 100 mg twice daily[37]
- L-Carnitine 1 gram twice daily[38]
- Liposomal Vitamin C

NT-proBNP

- Because this marker is associated with cardiovascular stress, the primary focus should be on managing and treating the underlying heart condition.

References

1. Millán J, Pintó X, Muñoz A, Zúñiga M, Rubiés-Prat J, Pallardo LF, Masana L, Mangas A, Hernández-Mijares A, González-Santos P, Ascaso JF, Pedro-Botet J. Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag.* 2009;5:757-65. Epub 2009 Sep 18. PMID: 19774217; PMCID: PMC2747394.
2. Walldius G, de Faire U, Alfredsson L, Leander K, Westerholm P, Malmström H, Ivert T, Hammar N. Long-term risk of a major cardiovascular event by apoB, apoA-1, and the apoB/apoA-1 ratio-Experience from the Swedish AMORIS cohort: A cohort study. PLoS Med. 2021 Dec 1;18(12):e1003853. doi: 10.1371/journal.pmed.1003853. PMID: 34851955; PMCID: PMC8635349.
3. Behbodikhah J, Ahmed S, Elyasi A, Kasselman LJ, De Leon J, Glass AD, Reiss AB. Apolipoprotein B and Cardiovascular Disease: Biomarker and Potential Therapeutic Target. *Metabolites.* 2021 Oct 8;11(10):690. doi: 10.3390/metabo11100690. PMID: 34677405; PMCID: PMC8540246.
4. Lu M, Lu Q, Zhang Y, Tian G. ApoB/apoA1 is an effective predictor of coronary heart disease risk in overweight and obesity. J Biomed Res. 2011 Jul;25(4):266-73. doi: 10.1016/S1674-8301(11)60036-5. PMID: 23554700; PMCID: PMC3597070.
5. Gao S, Zhao D, Qi Y, Wang W, Wang M, Sun J, Liu J, Li Y, Liu J. Circulating Oxidized Low-Density Lipoprotein Levels Independently Predict 10-Year Progression of Subclinical Carotid Atherosclerosis: A Community-Based Cohort Study. J Atheroscler Thromb. 2018 Oct 1;25(10):1032-1043. doi: 10.5551/jat.43299. Epub 2018 Mar 7. PMID: 29515051; PMCID: PMC6193183.
6. Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases. *Oxid Med Cell Longev.* 2017;2017:1273042. doi: 10.1155/2017/1273042. Epub 2017 May 7. PMID: 28572872; PMCID: PMC5441126.
7. Stanciulescu LA, Scafa-Udriste A, Dorobantu M. Exploring the Association between Low-Density Lipoprotein Subfractions and Major Adverse Cardiovascular Outcomes-A Comprehensive Review. *Int J Mol Sci.* 2023 Apr 3;24(7):6669. doi: 10.3390/ijms24076669. PMID: 37047642; PMCID: PMC10095470.
8. Kwon SW, Yoon SJ, Kang TS, Kwon HM, Kim JH, Rhee J, Lee SJ, Park JK, Lim JY, Yoon YW, Hong BK. Significance of small dense low-density lipoprotein as a risk factor for coronary artery disease and acute coronary syndrome. Yonsei Med J. 2006 Jun 30;47(3):405-14. doi: 10.3349/ymj.2006.47.3.405. PMID: 16807992; PMCID: PMC2688162.
9. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, Ginsberg H, Amarenco P, Catapano A, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Reiner Z, Taskinen MR, Tokgözoglu L, Tybjærg-Hansen A; European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J.* 2010 Dec;31(23):2844-53. doi: 10.1093/eurheartj/ehq386. Epub 2010 Oct 21. PMID: 20965889; PMCID: PMC3295201.
10. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, Lloyd-Jones DM, Marcovina SM, Yeang C, Koschinsky ML; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; and Council on Peripheral Vascular Disease. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2022 Jan;42(1):e48-e60. doi: 10.1161/ATV.0000000000000147. Epub 2021 Oct 14. PMID: 34647487; PMCID: PMC9989949.
11. Lu Y, Cui X, Zhang L, Wang X, Xu Y, Qin Z, Liu G, Wang Q, Tian K, Lim KS, Charles CJ, Zhang J, Tang J. The Functional Role of Lipoproteins in Atherosclerosis: Novel Directions for Diagnosis and Targeting Therapy. *Aging Dis.* 2022 Apr 1;13(2):491-520. doi: 10.14336/AD.2021.0929. PMID: 35371605; PMCID: PMC8947823.
12. Cojocaru M, Cojocaru IM, Silosi I. Lipoprotein-associated phospholipase A2 as a predictive biomarker of sub-clinical inflammation in cardiovascular diseases. *Maedica (Bucur).* 2010 Jan;5(1):51-5. PMID: 21977119; PMCID: PMC3150075.
13. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. *Nutr J.* 2015 Jan 10;14:6. doi: 10.1186/1475-2891-14-6. PMID: 25577237; PMCID: PMC4326479.
14. Hankey GJ. B vitamins for stroke prevention. *Stroke Vasc Neurol.* 2018 Jun 6;3(2):51-58. doi: 10.1136/svn-2018-000156. PMID: 30022794; PMCID: PMC6047336.
15. Cederström, S., Lundman, P., Alfredsson, J. et al. Association between high-sensitivity C-reactive protein and coronary atherosclerosis in a general middle-aged population. Sci Rep 13, 12171 (2023). https://doi.org/10.1038/s41598-023-39051-3
16. Hong CG, Florida E, Li H, Parel PM, Mehta NN, Sorokin AV. Oxidized low-density lipoprotein associates with cardiovascular disease by a vicious cycle of atherosclerosis and inflammation: A systematic review and meta-analysis. *Front Cardiovasc Med.* 2023 Jan 16;9:1023651. doi: 10.3389/fcvm.2022.1023651. PMID: 36727024; PMCID: PMC9885196.
17. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative Stress: Harms and Benefits for Human Health. *Oxid Med Cell Longev.* 2017;2017:8416763. doi: 10.1155/2017/8416763. Epub 2017 Jul 27. PMID: 28819546; PMCID: PMC5551541.
18. Levitan I, Volkov S, Subbaiah PV. Oxidized LDL: diversity, patterns of recognition, and pathophysiology. *Antioxid Redox Signal.* 2010 Jul 1;13(1):39-75. doi: 10.1089/ars.2009.2733. PMID: 19888833; PMCID: PMC2877120.
19. Rhoads JP, Major AS. How Oxidized Low-Density Lipoprotein Activates Inflammatory Responses. *Crit Rev Immunol.* 2018;38(4):333-342. doi: 10.1615/CritRevImmunol.2018026483. PMID: 30806246; PMCID: PMC6527110.
20. Gao S, Liu J. Association between circulating oxidized low-density lipoprotein and atherosclerotic cardiovascular disease. *Chronic Dis Transl Med.* 2017 May 25;3(2):89-94. doi: 10.1016/j.cdtm.2017.02.008. PMID: 29063061; PMCID: PMC5627698.
21. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fatty acids and risk of coronary heart disease: modulation by replacement nutrients. *Curr Atheroscler Rep.* 2010 Nov;12(6):384-90. doi: 10.1007/s11883-010-0131-6. PMID: 20711693; PMCID: PMC2943062.
22. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr.* 1999 Jan;69(1):30-42. doi: 10.1093/ajcn/69.1.30. PMID: 9925120.
23. Bradberry JC, Hilleman DE. Overview of omega-3 Fatty Acid therapies. *P T.* 2013 Nov;38(11):681-91. PMID: 24391388; PMCID: PMC3875260.
24. Ras RT, Geleijnse JM, Trautwein EA. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. *Br J Nutr.* 2014 Jul 28;112(2):214-9. doi: 10.1017/S0007114514000750. Epub 2014 Apr 29. PMID: 24780090; PMCID: PMC4071994.

25. Cicero AFG, Fogacci F, Banach M. Red Yeast Rice for Hypercholesterolemia. *Methodist Debakey Cardiovasc J.* 2019 Jul-Sep;15(3):192-199. doi: 10.14797/mdcj-15-3-192. PMID: 31687098; PMCID: PMC6822657.
26. Jorat MV, Tabrizi R, Mirhosseini N, Lankarani KB, Akbari M, Heydari ST, Mottaghi R, Asemi Z. The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis. 2018 Oct 9;17(1):230. doi: 10.1186/s12944-018-0876-4. PMID: 30296936; PMCID: PMC6176512.
27. Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. *Lipids Health Dis.* 2017 Jul 5;16(1):132. doi: 10.1186/s12944-017-0515-5. PMID: 28679436; PMCID: PMC5498979.
28.Koppen LM, Whitaker A, Rosene A, Beckett RD. Efficacy of Berberine Alone and in Combination for the Treatment of Hyperlipidemia: A Systematic Review. *J Evid Based Complementary Altern Med.* 2017 Oct;22(4):956-968. doi: 10.1177/2156587216687695. Epub 2017 Jan 16. PMID: 29228784; PMCID: PMC5871262.
29. Mani P, Rohatgi A. Niacin Therapy, HDL Cholesterol, and Cardiovascular Disease: Is the HDL Hypothesis Defunct? *Curr Atheroscler Rep.* 2015 Aug;17(8):43. doi: 10.1007/s11883-015-0521-x. PMID: 26048725; PMCID: PMC4829575.
30. Castaño G, Mas R, Fernández L, Illnait J, Gámez R, Alvarez E. Effects of policosanol 20 versus 40 mg/day in the treatment of patients with type II hypercholesterolemia: a 6-month double-blind study. *Int J Clin Pharmacol Res.* 2001;21(1):43-57. PMID: 11708574.
31. Xu R, Yang K, Li S, Dai M, Chen G. Effect of green tea consumption on blood lipids: a systematic review and meta-analysis of randomized controlled trials. Nutr J. 2020 May 20;19(1):48. doi: 10.1186/s12937-020-00557-5. PMID: 32434539; PMCID: PMC7240975.
32. Samavat H, Newman AR, Wang R, Yuan JM, Wu AH, Kurzer MS. Effects of green tea catechin extract on serum lipids in postmenopausal women: a randomized, placebo-controlled clinical trial. *Am J Clin Nutr.* 2016 Dec;104(6):1671-1682. doi: 10.3945/ajcn.116.137075. Epub 2016 Nov 2. PMID: 27806972; PMCID: PMC5118731.
33. Cox FF, Misiou A, Vierkant A, Ale-Agha N, Grandoch M, Haendeler J, Altschmied J. Protective Effects of Curcumin in Cardiovascular Diseases-Impact on Oxidative Stress and Mitochondria. *Cells.* 2022 Jan 20;11(3):342. doi: 10.3390/cells11030342. PMID: 35159155; PMCID: PMC8833931.
34. Ried K, Toben C, Fakler P. Effect of garlic on serum lipids: an updated meta-analysis. *Nutr Rev.* 2013 May;71(5):282-99. doi: 10.1111/nure.12012. Epub 2013 Mar 7. PMID: 23590705.
35. Heshmat-Ghahdarijani K, Mashayekhiasl N, Amerizadeh A, Teimouri Jervekani Z, Sadeghi M. Effect of fenugreek consumption on serum lipid profile: A systematic review and meta-analysis. *Phytother Res.* 2020 Sep;34(9):2230-2245. doi: 10.1002/ptr.6690. Epub 2020 May 8. PMID: 32385866.
36. Strain JJ, Dowey L, Ward M, Pentieva K, McNulty H. B-vitamins, homocysteine metabolism and CVD. *Proc Nutr Soc.* 2004 Nov;63(4):597-603. doi: 10.1079/pns2004390. PMID: 15831132.
37. Sahebkar A, Simental-Mendía LE, Stefanutti C, Pirro M. Supplementation with coenzyme Q10 reduces plasma lipoprotein(a) concentrations but not other lipid indices: A systematic review and meta-analysis. *Pharmacol Res.* 2016 Mar;105:198-209. doi: 10.1016/j.phrs.2016.01.030. Epub 2016 Feb 2. PMID: 26836888.
38. Sirtori CR, Calabresi L, Ferrara S, Pazzucconi F, Bondioli A, Baldassarre D, Birreci A, Koverech A. L-carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a). *Nutr Metab Cardiovasc Dis.* 2000 Oct;10(5):247-51. PMID: 11213533.