FOUNDATIONAL VASCULAR HEALTH PROTOCOL

OVATIONLAB

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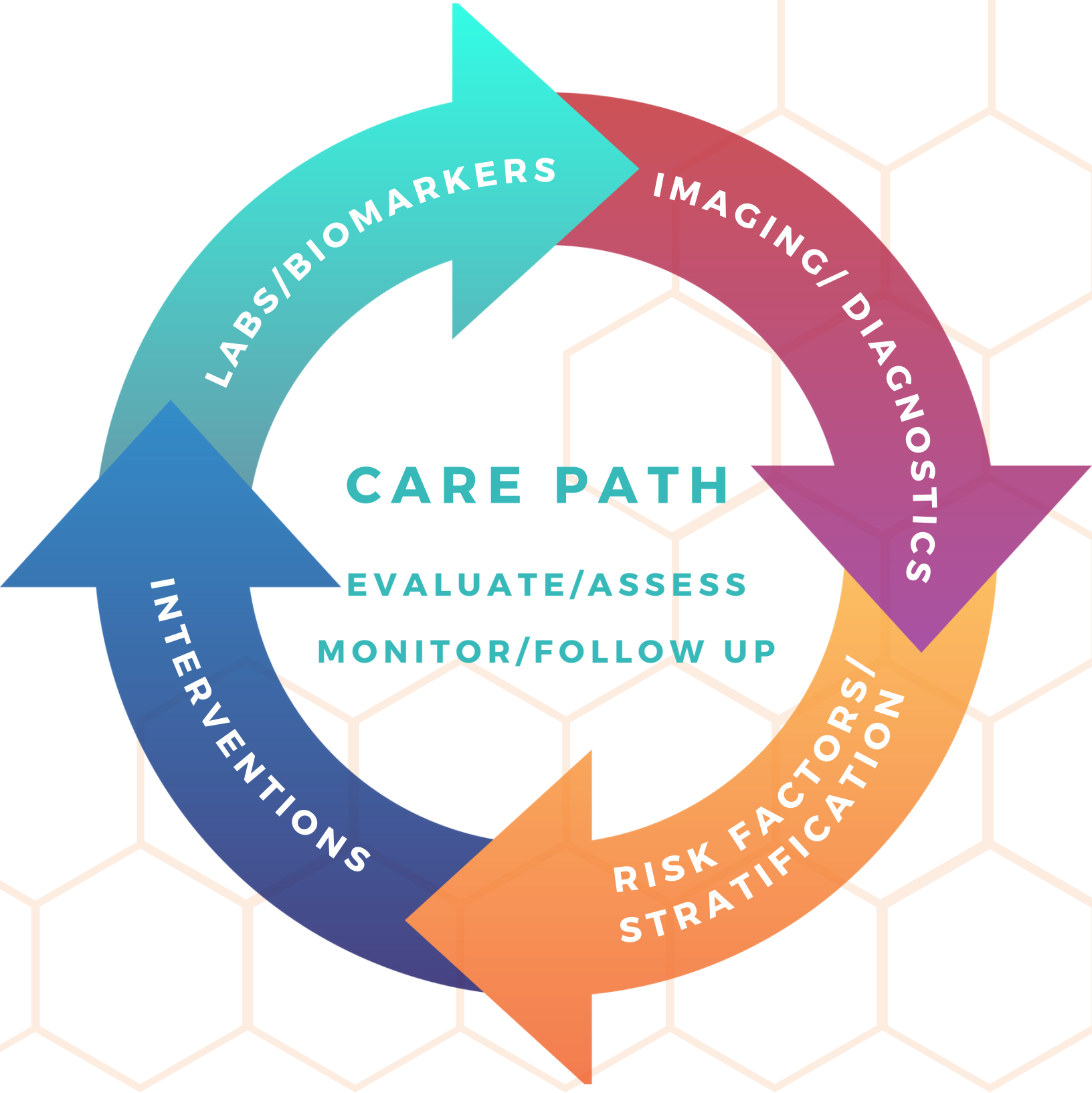

SUMMARY

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LABS/ BIOMARKERS

- hsCRP
- Lipoprotein-Associated Phospholipase A2 (Lp-PLA2)
- Myeloperoxidase (MPO)
- Lab values indicating diabetic, prediabetic, and/or metabolic syndrome conditions should be considered potential indicators of endothelial dysfunction. (6)
- Advanced lipid panel with NMR (includes LDL particle number)
- Lipoprotein(a)
- Asymmetric dimethylarginine (ADMA)
- Microalbumin/creatinine ratio
- Homocysteine

IMAGING/DIAGNOSTICS

- Coronary Artery Calcium Score (CAC)
- Carotid intima-media thickness (CIMT)
- Endothelial Function Tests
- Resonea
- Salivary Nitric Oxide Test Strips

RISK FACTORS/ STRATIFICATION

- Sleep Apnea
- Oral Health
- Genetics, Family History
- Standard American Diet
- Glycemic Load
- Body Composition
- Sedentary Activity Level
- Elevated Lp(a)

INTERVENTIONS

- Movement
- Sleep
- Social Connection
- Stress and Relaxation
- Total Nutrition
  - Arterosil HP®: 1 BID
  - Vascanox HP®: 2 caps once daily
  - Magnesium 500mg BID
  - CoQ10: 300 mg/daily or 200 mg daily to blood level of 3.0
  - Essential Fatty Acids: Up to 2g daily of combined EPA/DHA

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YOUR NOTES AND NEXT STEPS

LABS/ BIOMARKERS

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RISK FACTORS/ STRATIFICATION

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IMAGING/ DIAGNOSTICS

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EVALUATION/ASSESSMENT

LABS/BIOMARKERS

Inflammation: A trio of biomarkers, including hsCRP, Lp-PLA2, and myeloperoxidase, should be evaluated to gain a comprehensive picture of systemic inflammation and its impact on vascular health.

hsCRP:

- Increased risk: >1 mg/L (1)
- Elevated plasma levels are associated with coronary endothelial dysfunction and increased CAD risk and mortality. Levels can correlate with LDL-cholesterol. (2)

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2):

- LpPLA2 is a vascular-specific inflammatory biomarker and participates in the development of plaque. It is mainly released by macrophage foam cells within the endothelium and participates in the oxidative modification of LDL and membrane phospholipids. The presence of elevated LpPLA2 confers a 2-3 fold increased risk of MACE.(3)

Myeloperoxidase (MPO):

- Myeloperoxidase (MPO) serves as a critical biomarker for cardiovascular risk, given its role in producing oxidative substances that diminish NO availability, crucial for vascular function. Elevated MPO levels are often seen in tandem with increased LDL and ADMA, signaling enhanced oxidative stress and endothelial dysfunction. Its elevated presence, particularly in heart failure patients, is indicative of both the severity of the condition and the overall state of endothelial health. (4)

Elevated fasting glucose, hemoglobin A1c, and fasting insulin levels, alongside dyslipidemia markers such as an advanced lipid panel and Lp(a), are indicative of metabolic disturbances that closely interact with endothelial dysfunction through inflammatory pathways. (5)

Lab values indicating diabetic, prediabetic, and/or metabolic syndrome conditions should be considered potential indicators of endothelial dysfunction. (6)

- Fasting Glucose
- GlycoMark®
- Hemoglobin A1C (HbA1c)
- Fasting Insulin

Advanced lipid panel with NMR (includes LDL particle number)

- While lipid profiles with LDL-C <100 mg/dL, HDL-C ≥40/50 mg/dL, and TG <150 mg/dL are targets for endothelial health, the complexity of lipid metabolism—including the influence of genetic mutations and the functional properties of HDL—can affect endothelial function beyond these numbers. (7)

Lipoprotein(a)

- Lipoprotein(a), or Lp(a), carries oxidized phospholipids that favor attachment to Lp(a) rather than LDL, implicating Lp(a) in endothelial dysfunction and atherosclerosis. This binding and transport of atherogenic lipids by Lp(a) suggest its pivotal role in cardiovascular risk, marking high Lp(a) levels as a critical indicator of endothelial health. (8)

LABS/BIOMARKERS

Asymmetric Dimethylarginine (ADMA):

- Typically, ADMA concentrations in the plasma hover around 1 µmol/L under normal conditions. However, in individuals presenting risk factors for vascular diseases, these levels may double. In cases of clinical atherosclerosis, ADMA levels can surge by up to ten times the normal value. (9)
- Elevated plasma levels correlate with risk promoting factors such as intra-plaque lipid and calcification, decreased vascular NO bioavailability, and increased oxidative stress. (10)

Microalbumin/Creatinine Ratio:

- Optimal: <7 mg/g for women and <4 mg/g for men.
- A direct, linear relationship exists between urinary microalbumin level and the risk of heart attack, stroke and death. (59) In otherwise healthy individuals, low levels of urinary microalbumin of ≥3.9 mg/g for men and ≥7.5 mg/g for women, conferred approximately a 3X greater risk for developing cardiovascular disease. (60)

Homocysteine:

- Optimal: <16 umol/L
- Elevated homocysteine levels can lead to endothelial damage by inhibiting endothelial nitric oxide synthase, reducing nitric oxide availability, and promoting thrombotic activity. (12)

CORONARY ARTERY CALCIUM SCORE (CAC)

- This non-invasive examination is performed without contrast or IV injection.
- It takes under a minute, is painless, is not claustrophobic, and has a radiation exposure similar to a mammogram.
- In many cities it costs $100 or less.
- An online calculator (astrocharm.org) uses the CACS and several other clinical markers to predict the 10-year risk of heart attack and stroke
- Results range from the ideal zero to over 1,000

CAROTID INTIMA-MEDIA THICKNESS (CIMT)

- This is an ultrasound examination of the carotid arteries.
- The images are analyzed with digital software and the thickness of the inner 2 layers of the carotids are measured in mm.
- There are databases of normal CIMT by age and gender.
- Many reports include the arterial age measured.
- A healthy measure is around 0.6mm and increased CIMT is a marker of atherosclerosis.
- Contract services often provide reports.
- Vasolabs, CardioRisk, and HeartSmart are possible sources.

ENDOTHELIAL FUNCTIONAL TESTS

EndoPAT

- Non-invasive measurement of arterial tone in peripheral arterial beds to assess arterial elasticity and hyperemia.
- EndoPAT provider is Itamar

Max Pulse

- Non-invasive measurement of arterial and peripheral vessel elasticity.
- Max Pulse is a pulse wave analysis provider

CAPWA

- Computerized Arterial Pulse Wave Analyzer with Cardio Profilor.

ATCOR

- Central blood pressure monitoring

Conneqt Pulse

- Remote Blood Pressure Monitoring

OTHER TESTS

Resonea

- Sleep apnea testing through a phone app

Salivary nitric oxide test strips

- Quick proxy measure of nitric oxide available in the saliva

Sleep Apnea

- Obstructive Sleep Apnea (OSA) is associated with systemic inflammation, endothelial dysfunction, and increased arterial stiffness, as evidenced by higher inflammatory markers and carotid-femoral pulse wave velocities; this condition exacerbates oxidative stress and impairs vascular function, which can be markedly improved with Continuous Positive Airway Pressure (CPAP) therapy. (13,14)

Oral Health

- Periodontitis may precipitate vascular diseases via direct endothelial activation by periodontal pathogens, systemic dissemination of inflammatory mediators from the infected periodontium, and a host immune response that promotes vascular inflammation, complicating the discernment of bacteria from inflammation in endothelial dysfunction (ED). (15)
- Novel research points to the oral-intestinal axis as a potential pathway for periodontitis to impact systemic health, with studies linking elevated levels of the gut microbiota-dependent metabolite TMAO in periodontitis to reduced endothelial progenitor cells and endothelial function, warranting further investigation into this connection. (15)

Genetics, Family History

- Familial hypercholesterolemia (FH) patients experience systemic endothelial dysfunction from birth due to persistently elevated levels of LDL cholesterol (LDL-C), with homozygous individuals (HoFH) at a higher risk than heterozygous (HeFH) ones; this dysfunction is compounded by elevated serum lipoprotein(a) [Lp(a)], necessitating aggressive lipid-lowering strategies to protect vascular health. (16)
- Elevated homocysteine levels, which can coincide with mutations in the Methylenetetrahydrofolate Reductase (MTHFR) gene, contribute to endothelial dysfunction by disrupting nitric oxide production, deregulating gasotransmitter signaling, and inducing oxidative stress, while also promoting the harmful incorporation of homocysteine into proteins, leading to vascular toxicity and atherosclerosis. (17)
- The accumulation of S-adenosylhomocysteine, a metabolic precursor to homocysteine, inhibits cellular methyltransferases, resulting in the production of homocysteine thiolactone, which is toxic to endothelial cells and is linked to increased risks of coronary heart disease and other vascular disorders. (17)
- ApoE is essential for lipid clearance and atherosclerosis prevention, with macrophage-derived apoE playing a pivotal role in cholesterol efflux and anti-inflammatory processes. ApoE polymorphisms, particularly apoE4, are linked to reduced cholesterol efflux and increased inflammation, correlating with a higher risk of coronary artery disease and endothelial dysfunction. (8)

Standard American Diet

- The Standard American Diet, high in advanced gylcation end (AGE) products due to processed foods, is implicated in impaired endothelial function and increased cardiovascular risk; evidence from RCTs supports a shift to low-AGEs diets to enhance insulin sensitivity and mitigate inflammatory and oxidative stress markers associated with endothelial damage. (18)

Glycemic Load

- Studies indicate that fluctuating hyperglycemia, often resulting from high-glycemic and inflammatory diets, is more detrimental to vascular endothelial health than stable high blood sugar levels, leading to increased oxidative stress, reduced nitric oxide availability, and heightened inflammatory responses, which are critical factors in the progression of coronary vascular disease and diabetes-related complications. (19)

Body Composition

- Visceral adiposity is a key driver of systemic inflammation and oxidative stress, leading to the oxidation of low-density lipoprotein (LDL) and subsequent atherogenesis. This process is exacerbated by obesity-related insulin resistance and dyslipidemia, culminating in reduced nitric oxide availability and endothelial dysfunction, which are precursors to atherosclerosis and cardiovascular diseases. (20)

Sedentary Activity Level

- Excessive sedentary behavior, characterized by prolonged sitting during leisure time, has been independently linked to vascular endothelial dysfunction—a key early marker for atherosclerosis & cardiovascular disease. This dysfunction is partly due to reduced muscle activity and peripheral blood flow. This reduction in shear stress on blood vessels, combined with a tendency for higher calorie and sugar intake, can lead to vascular dysfunction, underscoring the need for interventions aimed at reducing sedentary leisure time to improve overall cardiovascular health. (21)

Elevated Lp(a)

- Epidemiological studies support the role of Lp(a) as an independent risk factor for cardiovascular disease. Its ability to deposit in the arterial walls and promote inflammatory pathways makes it a critical marker for assessing the risk of endothelial damage and atherosclerotic progression. (22)

INTERVENTIONS

Movement

- Endurance training markedly strengthens the endothelial glycocalyx layer, as evidenced by reduced serum levels of key components like syndecan-1 and heparan sulfate. This effect, coupled with an upsurge in muscular antioxidant defenses, notably SOD2, mitigates oxidative stress, thereby bolstering the vascular system against the damaging effects of exercise-induced reactive oxygen species. (23)
- Regular moderate-intensity exercise not only preserves the structural integrity of the endothelial glycocalyx layer, crucial for vascular health, but also maintains its functional role in shear-dependent nitric oxide production. Despite no significant changes in nitric oxide metabolites, the training suggests a protective mechanism that may enhance vasodilation and blood flow regulation during physical activity, contributing to cardiovascular disease prevention. (23)
- Active lifestyles are associated with reduced vascular aging and arterial stiffness, with evidence showing that consistent physical activity can reverse age-related endothelial dysfunction and decrease arterial stiffness, emphasizing the critical role of exercise in maintaining vascular health. (24)
- Engaging in regular aerobic exercise can improve arterial elasticity and potentially reduce carotid intima-media thickness, while resistance training should be balanced with aerobic activities to avoid negative impacts on arterial flexibility, highlighting the importance of a varied and sustained exercise regimen for optimal vascular function. (24)

Nutrition

- The Mediterranean diet boosts endothelial function, crucial for cardiovascular health, with studies indicating a potential 18% decrease in cardiovascular disease (CVD) risk due to improved vascular responsiveness. (25)
  - This diet is rich in l-arginine, nitrates, and monounsaturated fats, which not only lowers blood pressure and inflammatory markers but also optimizes lipid profiles by reducing low-density lipoprotein (LDL) and elevating high-density lipoprotein (HDL) levels. This multifaceted approach diminishes oxidative stress and inflammation, fortifying endothelial integrity and reducing atherosclerosis risk. (25)
  - Olive oil rich in phenols has been found to be superior to seed oils and low-phenol olive oils in reducing cardiovascular risk factors, including lowering LDL cholesterol and improving endothelial function. (26)
- Low-fat diets, comprising 30% of total calories from fat, have been shown to restore endothelial function and significantly increase flow-mediated dilation (FMD), while also reducing arterial stiffness as indicated by decreased carotid-femoral pulse wave velocity (cfPWV) and associated inflammatory markers like C-reactive protein (CRP). (24)
- Adopting a caloric restriction diet not only lowers blood pressure and body fat but also bolsters endothelial function by enhancing nitric oxide availability, reducing oxidative stress through decreased NADPH oxidase activity, and elevating antioxidant defenses with increased superoxide dismutase and catalase activities, all contributing to a robust cardiovascular protective strategy. (27)

Nutrition Continued

- Caloric restriction has been effective in delaying vascular aging, with evidence showing improved endothelium-dependent vasodilation and reduced pulse wave velocity (PWV) following low-calorie diets, highlighting its potential for enhancing vascular function. (24)
- Intermittent fasting has shown preliminary benefits in improving markers of endothelial function and increasing FMD, indicating a need for further research to fully understand its impact on vascular aging and potential as a dietary intervention. (24)
- Salt restriction not only enhances arterial elasticity in hypertensive individuals but also delays the progression of arterial stiffness in normotensive individuals, suggesting that low-salt diets confer vascular benefits beyond blood pressure control. (24)
- High-fiber diets correlate with reduced cardiovascular disease risk, improved endothelial function in metabolic syndrome, and protection against endothelial impairment from high-fat meals, underscoring the vascular benefits of fiber-rich foods. (24)

Sleep

- Sleeping less than 7 hours nightly can lead to significant endothelial dysfunction, marked by decreased nitric oxide-mediated vasodilation and increased vasoconstrictor tone. Addressing sleep quality and duration is a vital step in supporting endothelial function and reducing the risk of cardiovascular diseases. Findings indicate that consistent moderate-intensity aerobic exercise can reverse the impaired vasodilator function caused by habitual short sleep durations. This improvement is primarily due to reduced endothelin-1 vasoconstriction, demonstrating that regular physical activity is a viable strategy to support endothelial health in those unable to extend their sleep. (28)

Social Connection

- Loneliness is known to have significant repercussions on vascular health, affecting autonomic responses, HPA axis regulation, vasoconstriction, RAAS involvement, and chronic inflammation, ultimately contributing to cardiovascular conditions. Nevertheless, several interventions have been explored to mitigate the impact of loneliness, particularly on vascular health. These interventions encompass both individual-focused strategies, such as bolstering social support and implementing behavioral interventions aimed at addressing maladaptive social cognition, as well as community-level initiatives. Among these approaches, behavioral interventions have demonstrated the highest degree of efficacy. Additionally, community-based measures, including home visitation, daily contact programs, and telephonic helplines, have proven successful in facilitating social connections. By promoting increased social contact and support, these interventions offer a potential avenue to counteract the adverse effects of loneliness on vascular health. This underscores the imperative for healthcare providers to address social isolation as a means to enhance cardiovascular well-being, providing valuable insights for the healthcare community. (29)

Stress/Relaxation

- The endothelium, crucial for vascular function, is negatively impacted by mental stress (MS), leading to diminished nitric oxide levels, oxidative stress, and heightened vasoconstriction. This dysfunction, coupled with MS-induced parasympathetic nervous system activation and chronic inflammatory cell production, contributes to atherosclerosis and cardiovascular disease (CVD).
- Recognizing MS as a significant CVD risk factor, the 2016 European clinical guidelines recommend targeted management strategies.
    - These include nonpharmacological methods like relaxation techniques, cognitive behavioral therapy (CBT), and physical exercise, along with potential pharmacological interventions. While meditation and CBT show promise in reducing CVD risks, conclusive evidence is limited due to variable study designs and outcomes. However, their low risk and potential for broad application make them valuable adjuncts to conventional lifestyle modifications. Addressing MS and endothelial dysfunction through these diverse approaches is essential for effective CVD risk reduction and overall vascular health. (44)

Arterosil HP®: 1 BID

Rhamnan sulfate from Monostroma nitidum, the key component in Arterosil, exhibits a spectrum of vascular health benefits:*

- Supports a strong and vital glycocalyx – the micro-thin gel lining in your veins and arteries.*
- Modulates inflammation by inhibiting TNF-α-induced NF-κB activation, reducing the expression of pro-inflammatory and pro-coagulant factors, thus supporting endothelial function. (30,31,32)
- Helps maintain a healthy artery wall*
- Arterosil HP supports a healthy heart*

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.

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Vascanox HP®: 2 caps once daily

- Vascanox HP® enhances nitric oxide bioavailability, evidenced by a significant rise in salivary nitrite levels, which peak at two hours post-dose and maintain elevated levels up to 24 hours, supporting sustained endothelial function and cardiovascular health. (33)
- Black garlic, transformed from raw garlic through a meticulous aging process, not only enriches its bioactive profile but also intensifies its antioxidant properties. (34)
- Abundant in phenolic and organosulfur compounds, black garlic provides powerful anti-inflammatory benefits that bolster endothelial function and contribute to improved lipid profiles, supporting heart health and the integrity of blood vessels. (34)
- Nitrates enhance hemodynamic functions and vascular reactivity through the nitrate-nitrite-nitric oxide pathway, offering significant benefits in optimizing endothelial health and nitric oxide levels (35,36)
- Polyphenols, including anthocyanidins found in berries like blueberries and raspberries, support endothelial function, enhance vascular integrity, and contribute to cardiovascular health. (37)

Magnesium Malate: 500 mg BID

- Magnesium is crucial for modulating endothelial function and vascular smooth muscle tone. (38)
- Observational studies have found that increased Mg intake is associated with improved biomarkers of endothelial function (e.x. hs-CRP, IL-6, TNF-a, sVCAM-1). (39)
- A randomized, double-blind, placebo-controlled trial indicated that oral Mg supplementation improved endothelium-dependent brachial artery flow-mediated vasodilation in patients with coronary artery disease. (40)

CoQ10: 300 mg/daily or 200 mg/day to blood level of 3.0 mg/L

- CoQ10 supplementation has been shown in vitro to suppress oxLDL-activated NF-κB and downstream inflammatory mediators like ICAM-1, VCAM-1, IL-6, and TNF-α (41)
- CoQ10 activates the AMPK pathway, which upregulates the Akt/eNOS/NO pathway and attenuates the down-regulation of eNOS and the secretion of endothelin 1 (ET-1), collectively enhancing and supporting endothelial health (42)

Essential Fatty Acids: up to 2g daily of combined EPA/DHA

- N-3 fatty acids enhance endothelial-dependent vasodilation by increasing the expression of endothelial nitric oxide synthase (eNOS). This leads to increased nitric oxide (NO) release, which inhibits platelet aggregation and promotes vasodilation. (43)
- N-3 PUFAs can activate pathways like AMPK/PI3K/Akt/eNOS, offering protection against FFA-induced endothelial dysfunction. (43)
- N-3 PUFAs offer a range of cardiovascular benefits, from antioxidant activity and reduced leukocyte adhesion to anti-thrombotic effects and improved lipid profiles. They inhibit the expression of adhesion molecules like ICAM-1 and VCAM-1, reduce levels of plasma triglycerides and VLDL, and increase antioxidant activity. (43)

Multivitamin high in polyphenols and antioxidants

- The interaction between multivitamins/minerals (MVMs) and macronutrients affects nutrient absorption and metabolism, highlighting the importance of dietary balance. MVMs are beneficial for those with nutritional deficiencies due to restricted diets, aging, or chronic conditions. Incorporating multivitamins with polyphenols and antioxidants can offer additional health benefits for certain individuals.

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