NO Limits: Nitric Oxide and the Future of Cardiovascular Care

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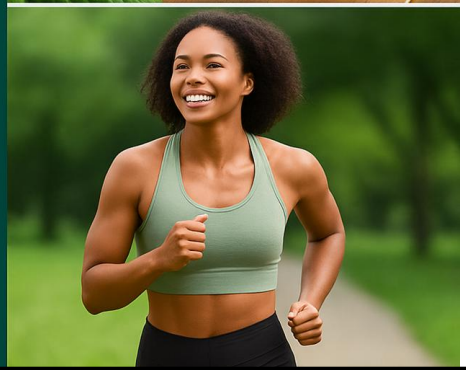
July 17, 2025



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Clinical Takeaways

- What nitric oxide is and why it's important for cardiovascular health
- How the body produces nitric oxide
- Consequences of low nitric oxide levels
- How to measure nitric oxide levels
- Boosting nitric oxide levels naturally

2

Cardiovascular Disease (CVD)

- Leading cause of death in US & globally
- In US, over 941,000 deaths/year (2022)
  - 1 of every 3 deaths in US
  - 2500 people die of CVD *every day*
  - Average of *1 death every 33 seconds*
- CVD kills more people than all cancers & accidental deaths combined (#2 & #3 causes of death)
- Most common conversation patients have with clinicians
- Focus on managing glucose, blood pressure, LDL-C, HDL-C and total cholesterol with Rx
  - Not working

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https://www.heart.org/en/about-us/heart-and-stroke-association-statistics?uid=1740

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CVD: Incidence and Risk

- 48.6% of US adults have CVD
- By 2050, 61%% of the US adult population is projected to have some form of CVD

- Risk increases with age, however:
  - 13% of 20-40 yo have CVD
  - 40% of 40-60 yo have CVD
  - 70% of 60-80 yo have CVD
  - 85% of people over 80 yo have CVD

Benjamin EJ, et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association; Circulation Volume 139, Number 10
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Cardiovascular Disease Continuum

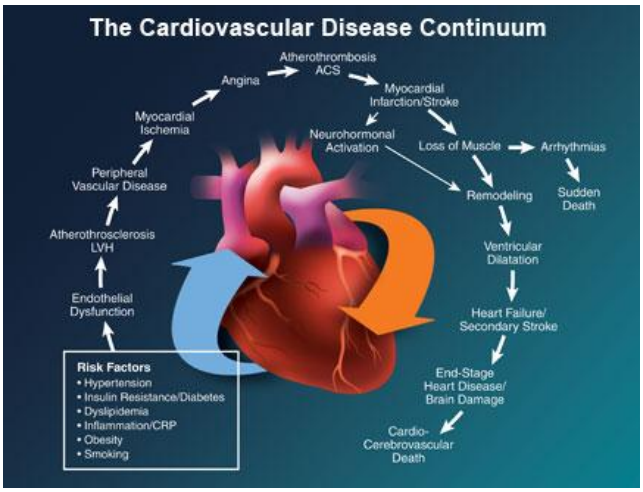

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Figure adapted from: http://www.awaremed.com/tag/diabetes-and-heart-disease/page/4/

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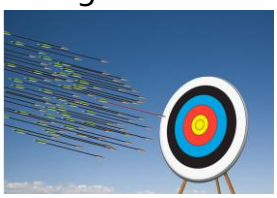
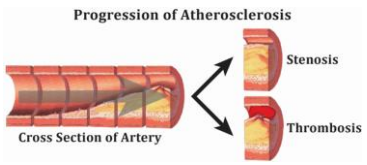
CVD is Preventable & Reversible

- 90% of CVD is preventable/reversible
  - You just need the right keys

- Coronary artery disease and strokes account for 75-80% of CVD deaths
  - Need to target atherosclerosis





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McNeal, Catherine J.; Dajani, Tala; Wilson, Don; et al. "Hypercholesterolemia in youth: opportunities and obstacles to prevent premature atherosclerotic cardiovascular disease". Current Atherosclerosis Reports. 12 (1): 20–28.
Flying arrows picture from www.johnlund.com

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Key Event in Development of Atherosclerosis

- Key event is damage to the endothelium caused by:
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - Toxins (i.e., components of cigarette smoke)
  - ➢ All lead to Nitric Oxide Dysregulation

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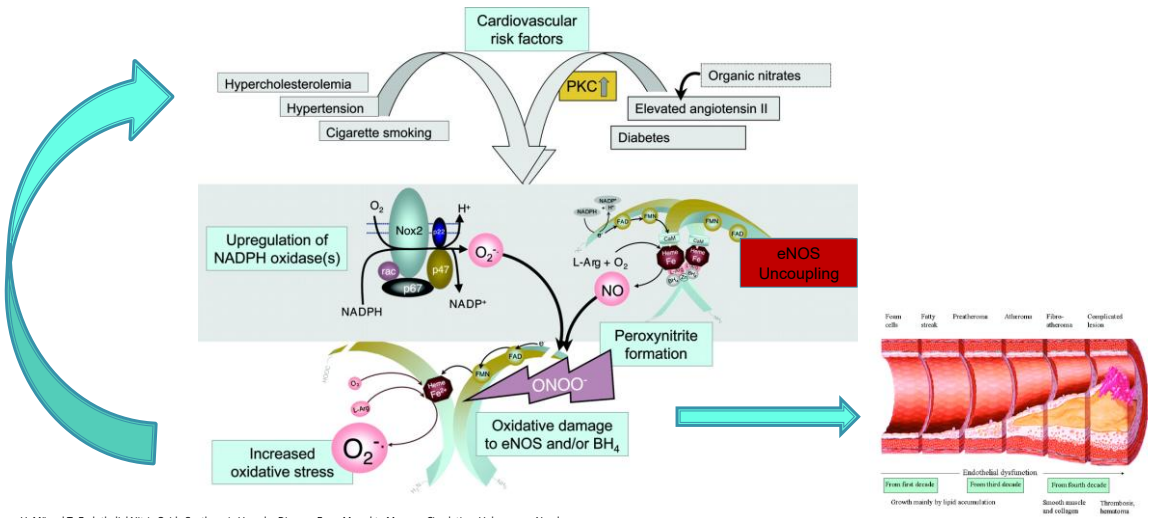
Nitric Oxide Dysregulation: Fundamental Cause of Endothelial Dysfunction



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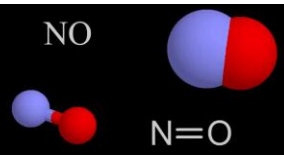
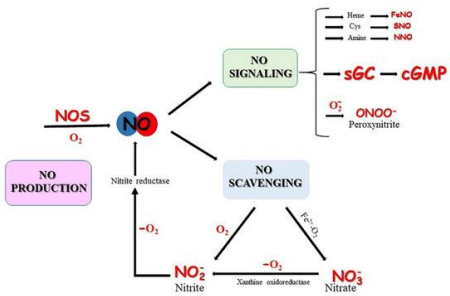
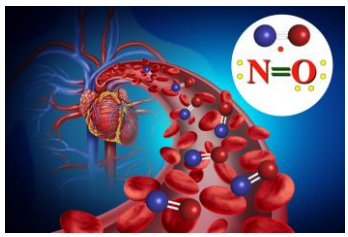
Nitric Oxide (NO)



- Nitric Oxide (NO) is a simple molecule with powerful effects across nearly every system in the body
- NO is a gas & acts as a signaling molecule
- Produced predominantly in the mouth/stomach & lining of blood vessels
- NO is highly reactive
  - NO -> NO2-
    - ½ life is < 1 sec
- Especially important for cardiovascular health





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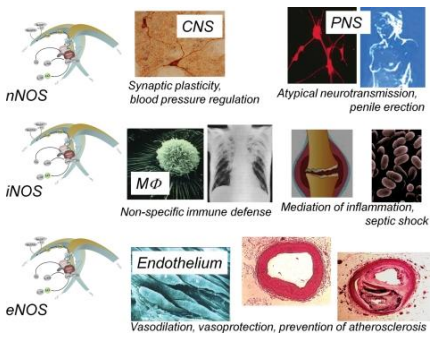
NO Production



- nNOS
  - Important in neurotransmission and brain function
- iNOS
  - Important for immune response
  - Mediates chronic inflammation
    - **Regulation** of iNOS is critical
- eNOS
  - Important for arterial health and CVD prevention

Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. Eur Heart J. 2012 Apr;33(7):829-37, 837a-837d.

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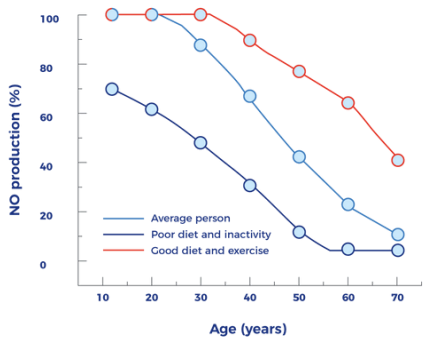
NO Production Decreases with Age



- NO production ↓ 10-12%/decade

- Decreased NO with age occurs because:
  - Increased breakdown of NO
    - Via superoxide free radical
      - Transforms NO -> ONOO–
  - Decreased eNOS & ↓ functionality
  - Reduced building blocks to make NO
    - Nutritional deficiency
      - L-arginine, L-citrulline, B2, B3, folate, Vit C, antioxidants
    - ↑ Arginase causes ↓ L-arginine -> ↓ NO

Arginase Reciprocally Regulates Nitric Oxide Synthase Activity and Contributes to Endothelial Dysfunction in Aging Blood Vessels. Dan E. Berkowitz, Ron White, Dechun Li, Khalid M. Minhas, Amy Cernetich, Soonyul Kim, Sean Burke, Artin A. Shoukas, Daniel Nyhan, Hunter C. Champion, Joshua M. Hare. Circulation. 2003;108:2000–2006.

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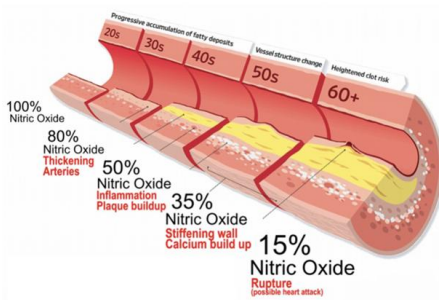
Result of NO decline with age

- Causes endothelial dysfunction
  - 50% decline in endothelial function by age 60
  - 75% loss of endothelium-derived NO in 70 year-olds compared to 20-year olds
- Impairment becomes evident in our 40s
  - ↓ NO = ↓ blood flow
  - *Sexual dysfunction (erectile dysfunction in men/vasculogenic female sexual dysfunction), HBP*, angina, *fatigue, elevated blood sugar, poor wound healing, muscle soreness*, and *memory loss*



- However, the endothelium's responsiveness to NO does NOT change with aging

➢ We can optimize NO production and restore endothelial function by addressing the reason's for this decline

Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. L J Ignarro, G M Buga, K S Wood, R E Byrns, G Chaudhuri. Proc Natl Acad Sci USA. 1987 Dec;84(24):9265-9.
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Effects of age on endothelium-dependent vasodilation of resistance coronary artery by acetylcholine in humans. K Egashira, T Inou, Y Hirooka, et al. Circulation. 1993 Jul;88(1):77-81.
Graphic: https://drnathansbryan.com/nitric-oxide-the-end-of-cardiovascular-disease/

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NO Broad Range of Effects

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NO Broad Range of Effects References

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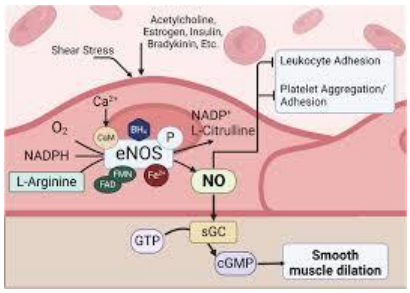
NO and Cardiovascular Health

- Nitric oxide is produced in the endothelial lining of the blood vessels & has widespread effects on the cardiovascular system
  - Vasodilation
    - Improves blood flow & reduces blood pressure
  - Inhibits platelet aggregation
    - Prevents blood clots
  - Regulates vascular wall permeability
    - Reduces monocyte recruitment and adhesion
  - Anti-inflammatory
    - Reduces inflammation in blood vessels
  - Angiogenesis
    - Promotes formation of new blood vessels (tissue repair)
  - Inhibits atherosclerosis
    - Prevents the build up of plaque in the arteries



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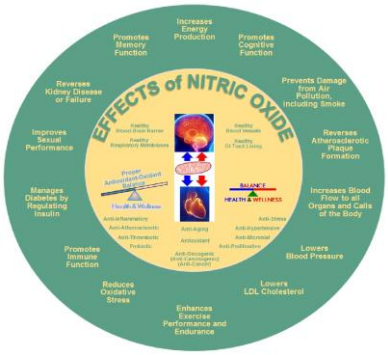
Importance of Nitric Oxide

- Nitric oxide is a simple molecule with broad range benefits
  - It's especially important for cardiovascular health
    - Look for patients with:
      - Erectile/sexual dysfunction
      - Fatigue
      - Muscle soreness
      - High blood pressure
      - Cardiovascular disease: vascular disease, heart attack, stroke
      - Elevated blood sugar
      - Memory loss
  - NO production ↓ with age: ↓ 10-12%/decade
  - However, we can reverse this decline



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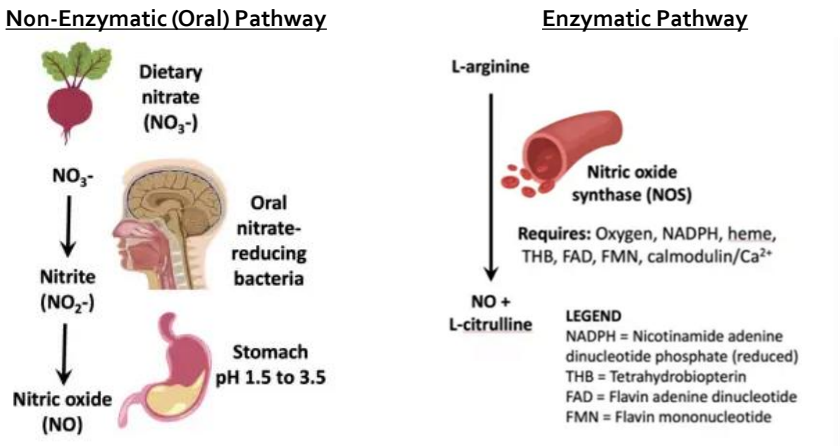
Pathways of NO Production



McKnight GM, et al. Chemical synthesis of nitric oxide in the stomach from dietary nitrate in humans. Gut. 1997 Feb;40(2):211-4.

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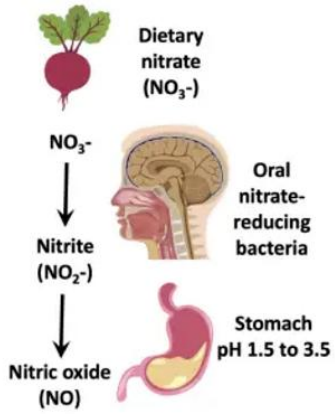
Oral NO Production Pathway

Non-Enzymatic (Oral) Pathway



- Eating nitrate-rich foods can significantly ↑ NO production
  - Can compensate for insufficient enzymatic (eNOS) NO production due to dyslipidemia, HBP, etc.
- Ingested Nitrate -> Nitrite
  - Conversion via salivary bacteria
- Nitrite -> NO in stomach
  - Require stomach acid (pH 1-3)
- Can greatly ↑ NO levels
  - Independent of eNOS
  - Can significantly increase NO levels while correcting other CVD risk factors

McKnight GM, Smith LM, Drummond RS, Duncan CW, Golden M, Benjamin N. Chemical synthesis of nitric oxide in the stomach from dietary nitrate in humans. Gut. 1997 Feb;40(2):211-4.
Sweazea KL, Johnston CS, Miller B, Gumpricht E. Nitrate-Rich Fruit and Vegetable Supplement Reduces Blood Pressure in Normotensive Healthy Young Males without Significantly Altering Flow-Mediated Vasodilation: A Randomized, Double-Blinded, Controlled Trial. J Nutr Metab. 2018 Sep 16;2018

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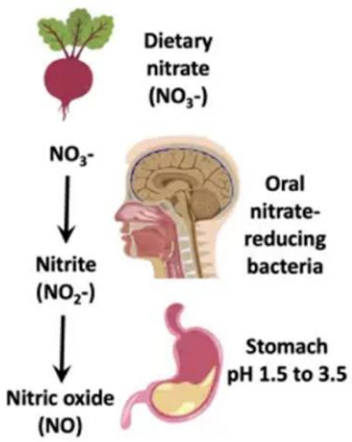
Requirements for Oral NO Production

- Requires:
  - Consumption of nitrate-rich foods/supplements



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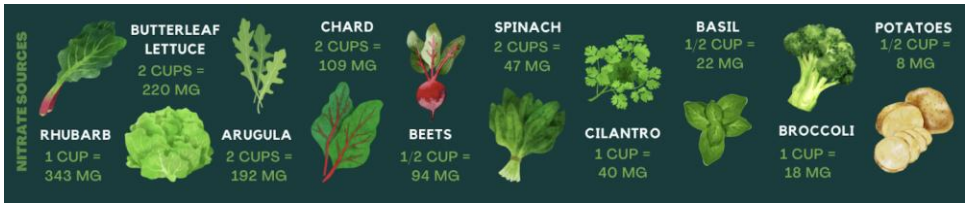
Nitrate-Rich Foods

Nitrate content (mg/100 g fresh weight)	Vegetable varieties
Very low, <20	Artichoke, asparagus, broad bean, eggplant, garlic, onion, green bean, mushroom, pea, pepper, potato, summer squash, sweet potato, tomato, watermelon
Low, 20 to <50	Broccoli, carrot, cauliflower, cucumber, pumpkin, chicory
Middle, 50 to <100	Cabbage, dill, turnip, savoy cabbage
High, 100 to <250	Celeriac, Chinese cabbage, endive, fennel, kohlrabi, leek, parsley
Very high, >250	Celery, cress, chervil, lettuce, red beetroot, spinach, rocket (rucola)



Santamaria P. Nitrate in vegetables: toxicity, content, intake and EC regulation. J Sci Food Agric, 86 (2006), pp. 10-17
Graphic: https://www.craftsbury.com/blog/food-first-nitrates

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Nitrate-Rich Foods

High Nitrate Foods	mg/kg	Moderate Nitrate Foods		Moderate Nitrate Foods	
Arugula	2848	Curly kale	987	Potato	220
Spinach	2500	Broccoli rabe (rapini)	905	Garlic	183
Coriander	2445	Pumpkin	692	Artichoke	174
Basil	2292	Turnip	684	Sweet pepper (colored)	117
Celery	2200	Endive	663	Green sweet pepper	111
Parsley	2134	Cabbage	503		
Radish	2064	Green beans	496		
Butter leaf lettuce	2000	Green onions	485		
Bok choy	1933	Zucchini	416		
Lettuce	1893	Fennel	363		
Beet greens	1852	Asparagus	355		
Kohlrabi	1769	Cauliflower	331		
Swiss chard	1512	Savoy cabbage	324		
Chicory leaf	1452	Eggplant	314		
Beet root	1300	Broccoli	300		
Black radish	1271	Carrot	300		
Mustard greens	1160	Cucumber	240		

Beetroot, arugula and spinach have been the most tested concerning dietary interventions, and all resulted in effective improvements in cardiovascular performance estimated through blood pressure reduction and vascular function amelioration.

dos Santos Baião D, Vieira Teixeira da Silva D, Margaret Flosi Paschoalin V. **A Narrative Review on Dietary Strategies to Provide Nitric Oxide as a Non-Drug Cardiovascular Disease Therapy: Beetroot Formulations—A Smart Nutritional Intervention.** Foods. 2021; 10(4):859. https://doi.org/10.3390/foods10040859

Graphic: Rich Mayfield: 2024 Great Lakes Conference Seminar: Systemic microvascular dysfunction restoration, prebiotic & probiotic management for total body balance

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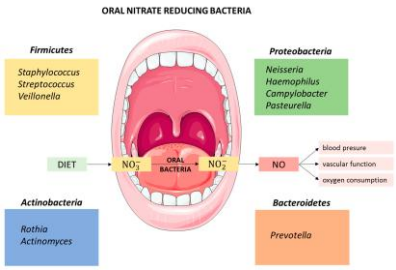
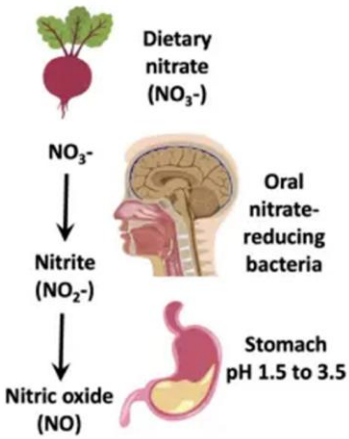
Requirements for Oral NO Production

- Requires:
  - Consumption of nitrate-rich foods/supplements
  - Nitrate-reducing bacteria in the mouth





González-Soltero, R.; Bailén, M.; de Lucas, B.; Ramírez-Goercke, et al. Role of Oral and Gut Microbiota in Dietary Nitrate Metabolism and Its Impact on Sports Performance. Nutrients 2020, 12, 3611.

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Mouthwash, Fluoride Toothpaste & Antibiotics

- Antiseptic/alcohol mouthwash and fluoride-containing toothpastes kill nitrate-reducing bacteria in the mouth
- Antibiotics also kill nitrate-reducing bacteria

➢ Oral flora can be restored within 1-4 weeks after discontinuing mouthwash & fluroide-containing toothpaste & *eating nitrate-rich diet*

  ➢ Studies show significant improvement in nitrate-reducing bacteria within 5 hours of a nitrate rich meal/supplement

Kapil V, et al. Physiological role for nitrate-reducing oral bacteria in blood pressure control. Free Radic Biol Med. 2013 Feb;55:93-100.
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Mouthwash, NO and Blood Pressure

- Antiseptic mouthwashes (containing chlorhexidine, cetylpyridinium) or alcohol/H_2O_2 based mouthwashes:
  - Significantly ↓ oral NO production
  - Significantly ↓ systemic NO levels
  - Significantly ↑ blood pressure
  - If used daily, >200% increased risk of being diagnosed with hypertension within 3 years
- Over 200 million Americans use mouthwash

- Non-antiseptic/non-alcohol/H_2O_2 mouthwash should be better
  - StellaLife (Coconut-based) shown not to decrease oral NO production in one study

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Mouthwash, NO and Blood Pressure References

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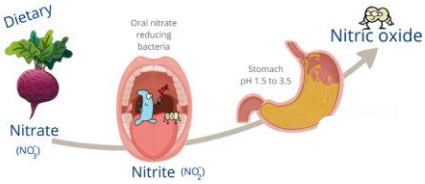
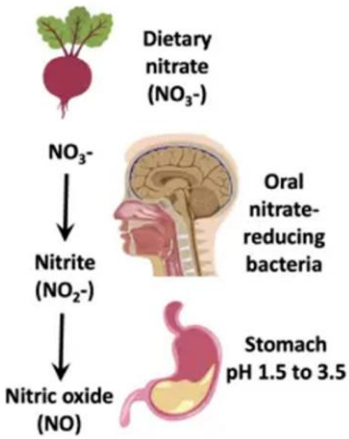
26

Requirements for Oral NO Production

- Requires:
  - Consumption of nitrate-rich foods/supplements
  - Nitrate-reducing bacteria in the mouth
  - Stomach acid





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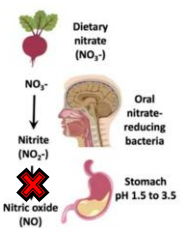
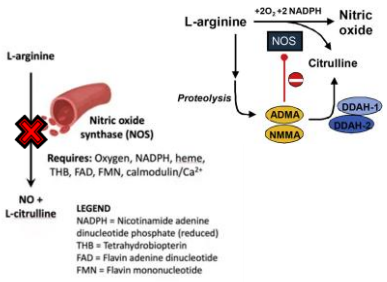
Antacids and PPIs

- Shuts down NO production
  - Prevent conversion of Nitrite -> Nitric Oxide via Oral Pathway
    - Without stomach acid, there is no nitric oxide generated in the stomach
  - Inhibit an enzyme (DDAH) that leads to the accumulation of ADMA
    - ADMA competes with arginine binding to eNOS via Enzymatic Pathway
      - Significantly ↓↓ NO production via enzymatic pathway

DDAH: dimethylarginine dimethyl-aminohydrolase
ADMA: asymmetric dimethylarginine





PPIs shut down total body NO production!

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https://www.researchgate.net/figure/Regulation-of-Nitric-Oxide-synthesis-by-Methylarginines-ADMA-and-L-NMMA-L-arginine-is_fig4_292077217 [accessed 20 Jun 2016]

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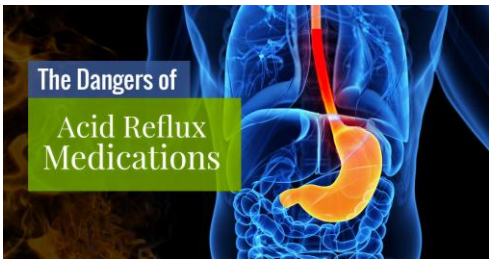
The Dangers of Acid Reflux Meds

- PPIs reduce NO production by 95%
- People on PPIs for 3-5 years have 35-40% ↑ ***incidence*** of heart attacks and strokes
  - Due to ↓ NO production



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29

GI Conditions: Acid Reflux/GERD

- How do you know?
  - HAQ – Part 1
    - Section A – Hypoacidity
    - Section B - Hyperacidity
  - BCA/litmus paper
    - ↓ salivary pH: hyperacidity
    - ↑ salivary pH: hypoacidity
  - H. Pylori (+)

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GERD Medications

- Proton Pump Inhibitors (PPIs)
  - Omeprazole (Prilosec)
  - Lansoprazole (Prevacid)
  - Rabeprazole (Aciphex)
  - Pantoprazole (Protonix)
  - Esomeprazole (Nexium)
- H2 Antagonists
  - Famotidine (Pepcid/Pepcid AC)
  - Cimetidine (Tagamet, Tagamet HB)
  - Ranitidine (Zantac)
  - Nizatidine (Axid/Axid AR)

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PPI Safety Profile

- Possible effects
  - Fatigue!
  - B12 deficiency
  - Magnesium deficiency
  - Increased risk of Clostridia infection
  - Increased risk of pneumonia
  - Increased risk of hip, wrist and spine fracture
  - Increased weight gain
  - Severe reaction with Plavix
  - Increased risk of Alzheimer's disease
  - Increased risk of death after hospitalization
  - …

www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm213259.htm

32

PPI Safety Profile

- "…physicians need to use caution and balance benefits and harms in long-term prescription of high-dose PPIs"
  - JAMA Internal Medicine 2013

Maggio M, Corsonello A, Ceda GP, Cattabiani C, Lauretani F, et al. Proton pump inhibitors and risk of 1-year mortality and rehospitalization in older patients dischrged from actue care hosptials. JAMA Intern Med. 2013;173(7):518-23.

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GI Conditions: Acid Reflux/GERD: Recommendations

- Relax before and during meals
- Chew!
- Hydration
  - Drink ½ your body weight in ounces every day
  - Divided doses – 2-4 oz. every 20-30 minutes ideal
  - Drink minimal water with meals
  - No iced-drinks with meals
- Cook/steam most veggies (& possibly fruit) and add raw as tolerated
- Eat ripe fruit (only) in season daily
- Decrease dairy, red meat, sugar and gluten

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GI Conditions: Hyperacidity: Recommendations

- Dietary recommendations
  - Eat smaller portions/meals
  - Chew food thoroughly
  - Eat a high-fiber, low-grain diet
    - ½-1 cup legumes daily
    - 5-9 cups of veggies daily
    - 1-3 servings whole fruit daily
  - Avoid irritating foods
    - Spicy foods, dairy, alcohol, coffee, strong tea, sugar
  - Cabbage juice – 4-8 oz. 1-2x/day

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Dr. Cheney's Cabbage Cocktail

- ½ head or 2 cups of green cabbage
- 4 sticks of celery
- 2 carrots

- Green cabbages are best, but red cabbages are also useful. Cut the cabbage into long wedges and feed through the juicer followed by the celery and carrots.

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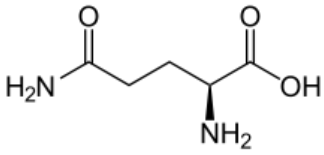
GI Conditions: Hyperacidity: Recommendations

- L-glutamine
  - Source of fuel for enterocytes
    - Need to rebuild and repair
  - Important for immune function
  - Has anti-inflammatory effects
- Aloe vera (solids removed)
  - Anti-inflammatory
  - Promotes healing



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37

GI Conditions: Hyperacidity: Recommendations

- Deglycyrrhizied licorice root (DGL)
  - Soothes inflamed mucous membranes in GI tract
  - Protects stomach and duodenum by increasing production of mucin and secretin
  - Enhances killing of virus that cause cold sores and mouth ulcers
  - Appears to inhibit H. pylori

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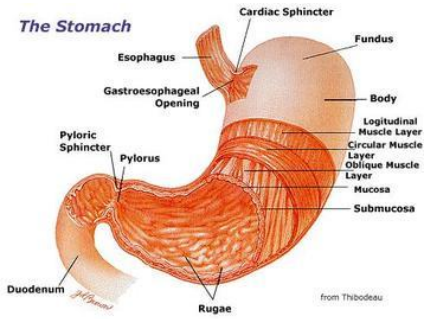
GI Conditions: Hyperacidity: Recommendations

- In order for pepsin/HCl to damage stomach, the mucous layer must be compromised
  - Nourish and protect the mucosal layer
  - Zinc Carnosine



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Hyperacidity: Recommendations

- Zinc carnosine
  - Used in Japan since 1994 to promote healing of gastric mucosal lining and relieve dyspeptic symptoms
  - Over 20 published studies, including 6 human clinical trials
  - Useful with or without conventional treatments

Beneficial Effect	Proposed Mechanism
Inhibits H. Pylori	Anti-urease activity
Attenuates gastric inflammation	Inhibits expression of TNF-α and IL-8 cytokines, without affecting PGE2 production
Protects cellular integrity	Antioxidant activity
Protects gastric epithelium	Stimulates mucus secretion
Adheres to wound site	L-carnosine transports zinc to would site; zinc is an important cofactor for many proteins

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GI Conditions: Hyperacidity: Recommendations

Recommendation	Dosage
Ultra Biotic Complete – empty stomach	1 capsules QD/BID
Zinc Carnosine	2 tablets 2x/day for 2 bottles, then 1 BID
GI Integrity	1 scoop before or between meals BID/TID
Melatonin TR Pro	1-2 tablets b4 bed
Anti-inflammatory diet; eliminate food triggers; avoid cow's dairy, red meat and gluten	
Focus on chewing food until it is a liquid; at LEAST 30 times before swallowing	
Small meals (don't overeat); high fiber diet (esp soluble fiber); cabbage juice – 4-8 oz. 1-2x/day (esp if suspect ulcer); avoid irritating foods	
Water – ½ body weight in ounces/day; ~1/4-½ cup every ½ hour; swish in mouth	

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Hypoacidity: Recommendations

- CHEW!
- Dietary recommendations
  - Eat smaller portions/meals
  - Eat only when hungry
  - Do not eat when upset
  - Limit liquids with meals (dilute digestive juices)
- Apple cider vinegar – 1 Tbsp b4 meals
- Exercise – 15-20 min walk after eating
- Supplement when necessary

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Hypoacidity: Recommendations

- Replace HCl – HCl Challenge
  - Begin with 1 tablet HCl Support with meals; if no burning or warmth sensation within 2 hours, increase by 1 tablet with meals until experience warmth or burning sensation in stomach/abdomen OR reach 6 tablets HCl Support with meals
  - If/when experience warmth or burning sensation, decrease by 1 tablet with meals and continue
  - May need to heal/repair stomach/GI tract first
    - Use GI Integrity and Zinc Carnosine for 2 weeks prior to HCl Challenge
    - Continue with one or both formulas during challenge PRN

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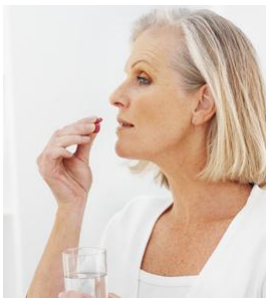
HCl Challenge Example

- Jane begins with 1 tablet HCl Support with breakfast and does not experience warmth/burning in abdomen
- Increases to 2 tablets with lunch; no burning
- Increases to 3 tablets with dinner; has some mild warmth/burning
- Takes 2 tablets with meals ongoing until warmth/burning returns, then continues to decrease PRN



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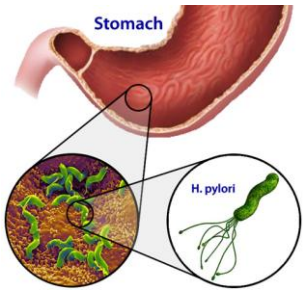
Hypoacidity: H. pylori

- Helicobacter pylori (H. pylori)
  - 2/3 of people infected with H. pylori
  - Increases risk of non-ulcer dyspepsia, peptic ulcers and gastritis
  - Leading cause of peptic ulcers
    - 80% of gastric ulcers & 90% of duodenal ulcers
  - Produces an enzyme that neutralizes stomach acid
  - Regular use of antacids increases risk of infection
  - Amoxicillin successful in only 60% of cases
  - Zinc-carnosine can help eliminate



45

Hypoacidity: Recommendations

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Beneficial Effect	Proposed Mechanism
Inhibits H. Pylori	Anti-urease activity
Attenuates gastric inflammation	Inhibits expression of TNF-α and IL-8 cytokines, without affecting PGE2 production
Protects cellular integrity	Antioxidant activity
Protects gastric epithelium	Stimulates mucus secretion
Adheres to wound site	L-carnosine transports zinc to would site; zinc is an important cofactor for many proteins

46

Hypoacidity: Recommendations

Recommendation	Dosage
Ultra Biotic Complete – empty stomach	1 capsules QD/BID
GI Integrity	1 scoop before or between meals BID/TID
HCl Support	Per HCl Challenge
Zinc Carnosine	2 tablets 2x/day for 2 bottles, then 1 BID
Melatonin TR Pro	1-2 tablets before bed
Anti-inflammatory diet; eliminate food triggers; avoid cow's dairy, red meat and gluten	
Focus on chewing food until it is a liquid; at LEAST 30 times before swallowing	
Small meals (don't overeat); high fiber diet (esp soluble fiber); cabbage juice – 4-8 oz. 1-2x/day (esp if suspect ulcer); avoid irritating foods; apple cider vinegar – 1 Tbsp/meal	
Water – ½ body weight in ounces/day; ~1/4-½ cup every ½ hour; swish in mouth	

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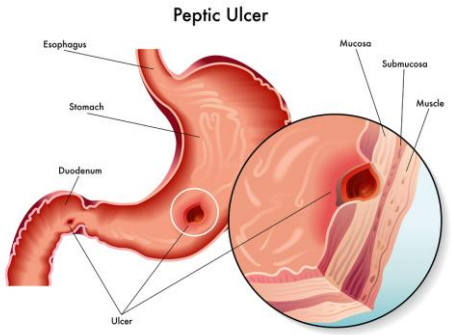
GI Conditions: Ulcers

- Gastric ulcer
  - Lesion in stomach
  - Often worse with food
  - Burning, cramping
  - Causes: stress, H. Pylori
- Duodenal ulcer
  - Lesion in duodenum
  - Often worse on empty stomach
  - Causes: alcohol, caffeine, NSAIDS, stress



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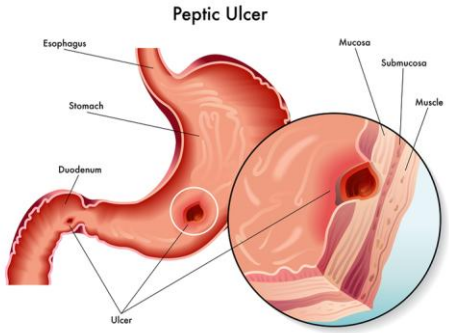
GI Conditions: Ulcers: Recommendations

- Address underlying dietary/lifestyle causes
  - Eliminate alcohol, caffeine, need for NSAIDs
  - Improve stress management
- Address inflammation/Heal Ulcer
  - Cabbage juice
  - Ginger, curcumin, bioflavonoids,
  - L-glutamine, DGL, Licorice
  - Chinese Herbal Formula
  - Probiotics
  - EFAs



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GI Conditions: Ulcers: Recommendations

Recommendation	Dosage
Ultra Biotic Complete – empty stomach	1 capsules QD/BID
Infam-Eze	1 scoop BID
GI Integrity	1 scoop before or between meals BID/TID
Omega Pure EPA-DHA 720	1-2 gelcaps BID with meals
Anti-inflammatory diet; eliminate food triggers; avoid cow's dairy, red meat and gluten	
Focus on chewing food until it is a liquid; at LEAST 30 times before swallowing	
Small meals (don't overeat); high fiber diet (esp soluble fiber); cabbage juice – 4-8 oz. 1-2x/day (esp if suspect ulcer); avoid irritating foods	
Water – ½ body weight in ounces/day; ~1/4-½ cup every ½ hour; swish in mouth	

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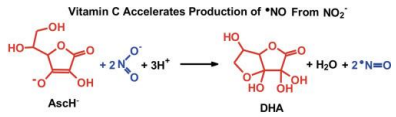
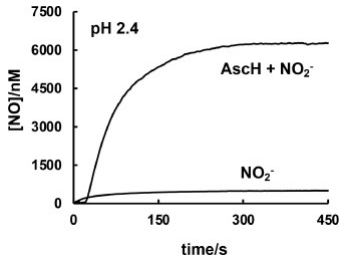
Ascorbate and NO production

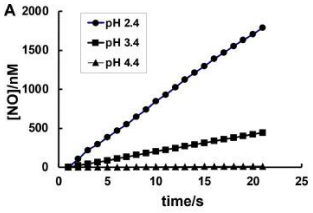
- Ascorbate (Vit C)



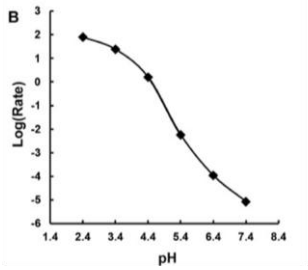
- Ascorbate ↑↑ NO production



Ascorbate-Induced NO Production vs. pH



Rate of ascorbate-induced NO Production vs. pH



Juan Du, Milos R. Filipović, Brett A. Wagner, Garry R. Buettner, Ascorbate mediates the non-enzymatic reduction of nitrite to nitric oxide, Advances in Redox Research, Volume 9, 2023.

51

Optimizing Oral NO Production

- Avoid:
  - Antiseptic and/or alcohol/H2O2-based mouthwashes
  - Fluoride
  - Antacids and PPIs

- Consume:
  - Lots of nitrate-rich foods
  - Ascorbate (foods/supplements)
  - Supplementation

Du J, Filipović MR, Wagner BA, Buettner GR. Ascorbate mediates the non-enzymatic reduction of nitrite to nitric oxide. Adv Redox Res. 2023 Dec;9:100079.

52

Optimizing Oral NO Production References

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- Bryan NS. Nitric oxide enhancement strategies. Future Sci OA. 2015 Aug 1;1(1):FSO48.

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Nitric Boost: Optimizing NO Production

Ingredients
Vitamin D_3 (as cholecalciferol) (from lichen)
Thiamin (as thiamin mononitrate)
Vitamin B12 (as adenosylcobalamin)
Magnesium (as magnesium ascorbate)
Zinc (as zinc ascorbate)
Potassium (as potassium nitrate)
Beet Root Extract
Pomegranate Extract (fruit; *Punica granatum*; 30% punicalagins) (P
Montmorency Tart Cherry Extract (fruit; *Prunus cerasus*)
French Maritime Pine Bark Extract (*Pinus pinaster*; 65-75% procyan (Pycnogenol®)
Grape Seed Extract (*Vitis vinifera*; 95% proanthocyanidins)

- Patients with:
  - Erectile/sexual dysfunction
  - Cardiovascular Disease
    - High blood pressure
    - Atherosclerosis
    - Heart failure/heart attacks
  - Past/current PPI/ antacid use
    - Ideally during/after tapering off

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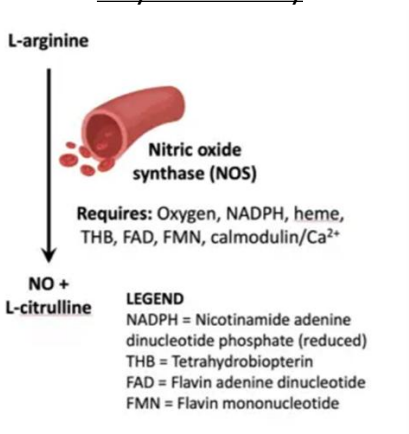
Optimizing Enzymatic Production of NO

- Increase substrate availability:
  - L-arginine
  - L-citrulline
- Support eNOS activity
  - Ascorbate/antioxidants
  - B-vitamins (B2, B3, MTHF)
  - Exercise (O_2)
  - Deep nasal breathing
  - Humming
  - Sunshine (UV-A)
- Minimize Inhibitory Factors
  - Arginase activity
  - Inflammation
  - Smoking

Enzymatic Pathway



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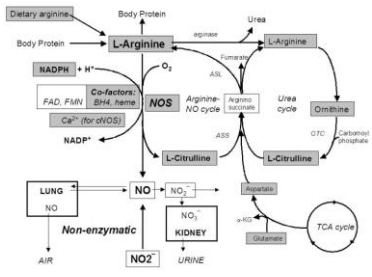
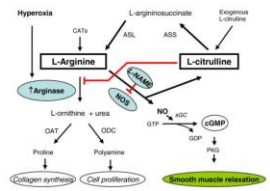
Increasing NO Substrates: L-Arginine & L-Citrulline

- NO production requires L-arginine
  - Also produces L-citrulline
- L-citrulline can be converted back into L-arginine by the kidneys
  - Requires ascorbate (Vit C)
- Taking both has synergistic effects
  - L-citrulline can replenish L-arginine
  - L-citrulline more bioavailable
    - Fewer competing reactions
  - L-citrulline blocks arginase (competes with eNOS)
    - Increases L-arginine available





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Summar M. Potential therapeutic uses of L-citrulline beyond genetic urea cycle disorders. J Inherit Metab Dis. 2024; 47(6): 1260-1268.

56

L-Arginine: Sources

- Food sources:
  - Red meat, poultry, fish/seafood, dairy products
  - Wheat germ, oatmeal, nuts & seeds, chickpeas

- Supplementation
  - Typically, 1-6 grams/day in divided doses
  - Post workout or injury: 1-3 grams
  - To increase NO production: 1-3 grams L-arginine with 1-3 grams L-citrulline, 200-400 mg magnesium glycinate & 1-3 grams ascorbate

Andrew, P.J.; Myer, B. (August 15 1999). "Enzymatic function of nitric oxide synthases". Cardiovascular Research 43 (3): 521–531
Stechmiller, J.K.; et al. (February 2005). "Arginine supplementation and wound healing". Nutrition in Clinical Practice 20 (13): 52–61

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L-Citrulline

- Precursor to L-Arginine
- Can be recycled into L-Arginine
- Reduces breakdown of Arginine by Arginase
- Shown to increase levels of L-Arginine & NO availability
- Therapeutic dose: ~1-3 grams
  - 1.5 kg of fresh watermelon = ~3 grams
- Combine with 1-6 grams of L-Arginine
  - 1:1-1:3 L-citrulline: L-Arginine

Castillo L., Chapman T.E., Yu Y.M., Ajami A., Burke J.F., Young V.R. Dietary arginine uptake by the splanchnic region in adult humans. Am. J. Physiol. 1993;265:E532–E539.
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Park HY, Kim SW, Seo J, Jung YP, Kim H, Kim AJ, Kim S, Lim K. Dietary Arginine and Citrulline Supplements for Cardiovascular Health and Athletic Performance: A Narrative Review. Nutrients. 2023 Mar 3;15(5):1268.
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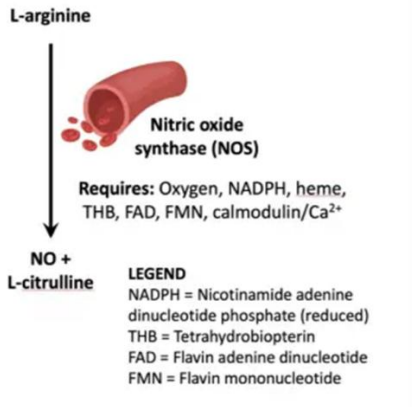
  - Smoking

Enzymatic Pathway



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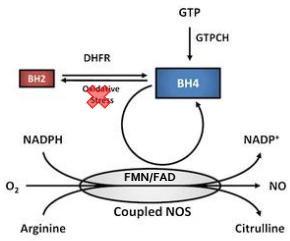
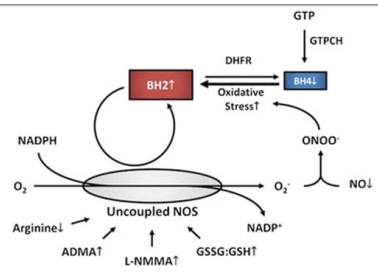
Nutrients to Optimize Enzymatic NO Pathway





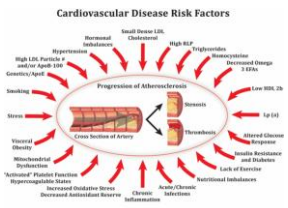
Coupled NOS

- L-Arginine + O_2 -> L-Citrulline + NO
- BH_4 (tetrahydrobiopterin) availability crucial
  - Requires methyl folate, ascorbate/antioxidants
- NADPH – nicotinamide (B_3)
- FMN/FAD – both derived from riboflavin (B_2)

DHFR: dihydrofolate reductase NADPH: nicotinamide adenine diphosphate
FMN: flavin mononucleotide FAD: flavin adenine dinucleotide

Uncoupled NOS

- Triggered by oxidative stress for CVD risk factors
- Generates free radicals that further degrade NO levels
- Therapeutic interventions:
  - **L-Arginine & L-Citrulline + O_2**
  - **↑BH_4 (tetrahydrobiopterin) availability**
    - **Ascorbate/antioxidants**
    - **Methyl folate**
  - **Vit B_2 & B_3**
  - **Address CVD risk factors**



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NO Boosting Supplementation

- Ascorbate
  - Protects NO from inactivation from ROS
  - Necessary for L-citrulline -> L-arginine recycling
  - Increases NO production via Oral Pathway
  - Supports eNOS activity
  - Improves NO synthesis via eNOS up to 300%
    - Shown to reduce blood pressure in hypertension (500 mg/day)
      - Systolic: ↓ 10-12 mmHg; Diastolic: ↓ 5-6 mmHg
      - No effect on those with normal blood pressure
  - Halt progression of coronary calcification
    - Reduces arterial stiffness

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NO Boosting Supplementation

- Antioxidants
  - Grape seed extract
    - Improves activity of endothelial NOS
    - Increases NO levels
    - Acts as calcium channel blocker
  - Pomegranate extract
    - Improves activity of endothelial NOS
      - Makes more NO available

de Nigris F, et al. The influence of pomegranate fruit extract in comparison to regular pomegranate juice and seed oil on nitric oxide and arterial function in obese Zucker rats. Nitric Oxide. 2007 Aug;17(1):50-4.
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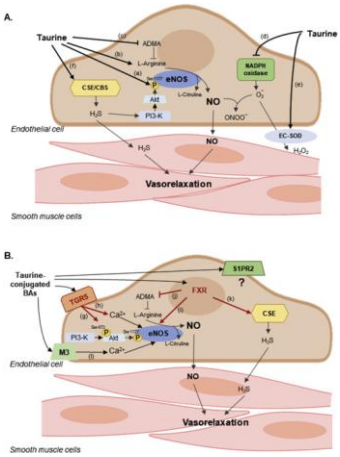
NO Boosting Supplementation

- Taurine – semi-essential amino acid
  - ~50% of total fee amino acids in the heart
    - Shown to improve heart function
  - Increased NO production
    - ↑ eNOS expression
    - ↑ eNOS phosphorylation
      - ↑ eNOS activation
    - ↑ NO bioavailability
      - Potent antioxidant
    - Modulate L-arginine/ADMA ratio
      - ADMA inhibits eNOS and competes with L-arginine
      - Taurine can ↑ available L-arginine and ↓ ADMA
  - Dosing: 1-3 grams/day



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NO Boosting Supplementation

- CoQ10 – 100-250 mg/day
  - Decrease free radical damage in arterial wall & oxidized lipoproteins
  - Significantly decrease Lp(a) 31%
  - Decrease blood viscosity and improve blood flow
  - Improve cellular energy production
  - Significant improvement in arterial function
  - Shown to reduce:
    - SBP: 11-17 mmHg
    - DBP: 8-10 mmHg
  - Safe with no significant side effects

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Nitric Boost to Help Recouple NO Synthesis

Ingredients	Amount
Vitamin D_3 (as cholecalciferol) (from lichen)	15 mcg
Thiamin (as thiamin mononitrate)	100 mg
Vitamin B12 (as adenosylcobalamin)	50 mcg
Magnesium (as magnesium ascorbate)	120 mg
Zinc (as zinc ascorbate)	7 mg
Potassium (as potassium nitrate)	150 mg
Beet Root Extract	375 mg
Pomegranate Extract (fruit; *Punica granatum*; 30% punicalagins) (Pomanox®)	200 mg
Montmorency Tart Cherry Extract (fruit; *Prunus cerasus*)	200 mg
French Maritime Pine Bark Extract (*Pinus pinaster*; 65-75% procyanidins) (Pycnogenol®)	50 mg
Grape Seed Extract (*Vitis vinifera*; 95% proanthocyanidins)	50 mg

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Cardio Flow

Ingredient	Amount
Calories	15
Total Carbohydrate	4 g
Dietary Fiber	<1 g
Folate (as calcium L-5-methyltetrahydrofolate) (BioFolate®)	200 mcg DFE
Calcium	55 mg
Iron	1.3 mg
Magnesium (as magnesium bisglycinate chelate) (TRAACS™)	100 mg
Sodium	45 mg
L-Arginine	3 g
Beet Root Powder	2 g
Hibiscus Flower Powder	1.5 g
Taurine	1 g
L-Citrulline	1 g

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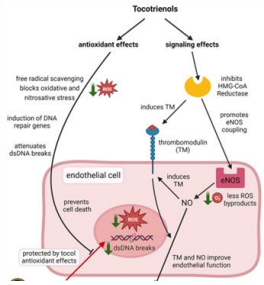
Annatto Pro 125

Ingredients	Amount
Tocotrienols (from annatto seed; *Bixa orellana*; 90% delta tocotrienols and 10% gamma tocotrienols) (DeltaGold®)	125 mg

- Target:
  - Cardiovascular health & lipid metabolism
    - ↑ BH_4
    - ↑ eNOS activity
    - ↓ Removal of NO by ↓ free radicals
    - ↑ nitric oxide
  - Liver health: NAFLD
  - Blood sugar imbalances, T2D
  - Brain health & cognition
  - Bone health: osteopenia/osteoporosis
  - Inflammatory conditions
  - Cancer



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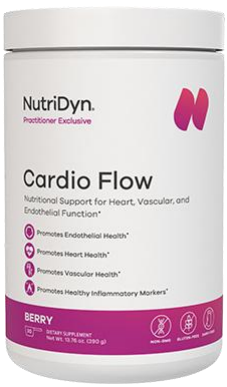
Foundational Support to Optimize NO Levels

- Incredible Foundation to recouple (repair) nitric oxide pathways and optimize NO levels



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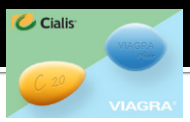
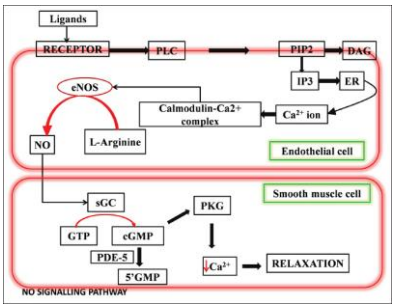
Nitric Oxide & PDE5-Inhibitors



- Phosphodiesterase type 5 (PDE5) inhibitors (Cialis®, Viagra®, Levitra®) enhance the effects of nitric oxide
  - Prevent breakdown of cGMP



- Significant ↑ in NO + PDE5-I =
- ~40% of men don't respond
  - Endothelial dysfunction, metabolic syndrome, diabetes, atherosclerosis
  - Need to increase NO production first to improve efficacy

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Nitric Oxide and PDE5-Inhibitors References

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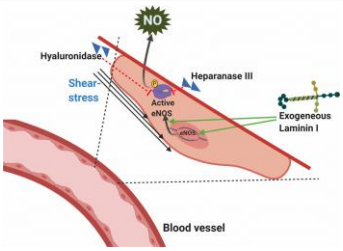
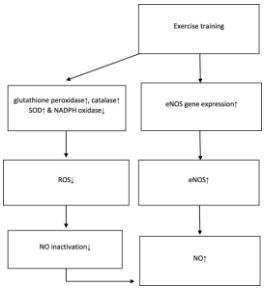
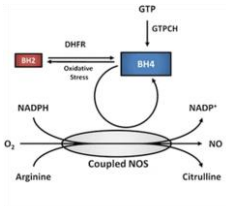
Exercise Increases NO Production

- Exercise increases the force of blood against the blood vessel walls (shear stress)
  - Causes a chain of reactions that activates eNOS
  - Increases the production of NO
- Exercise also increases eNOS gene expression & improves NO availability
- Provides O2 to drive enzymatic NO production

- Moderate intensity; >40 min 3+x/week for >8 weeks
- HIIT: powerful way to boost NO levels
  - 2-3x more NO produced vs. moderate intensity training
  - 1 min hard:easy cycling – 10 intervals; 2-3 days/week
  - 75 min/week, 30 min high intensity (max)







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Exercise Increases NO Production References

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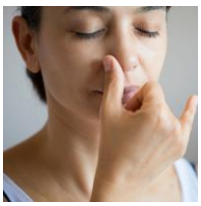
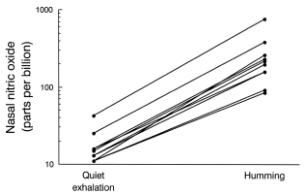
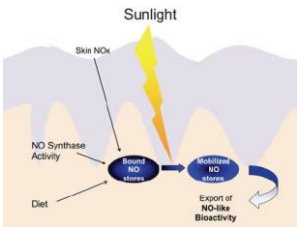
Lifestyle Interventions to ↑ NO

- Nasal breathing
  - Diaphragmatic breathing
  - Alternate nostril breathing
- Humming
  - Can ↑ NO production by 15x
- Stress management
  - Short term: ↑ NO
  - Long term: ↓ NO - must manage
- Sunshine
  - Can increase NO production in skin cells & release *stored* NO
    - Optimize by ↑ NO via Oral (non-enzymatic) route







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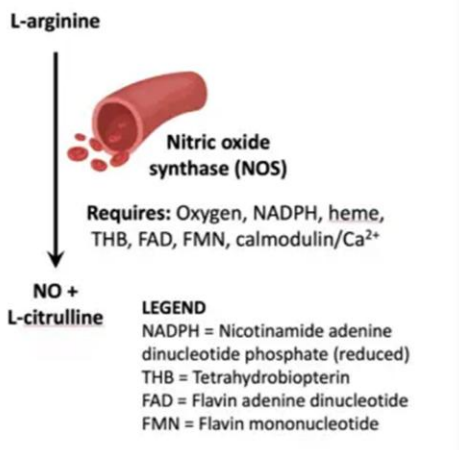
Optimizing Enzymatic Production of NO

- Increase substrate availability:
  - L-arginine
  - Nitrates
  - L-citrulline
- Support NOS activity
  - Deep nasal breathing
  - Ascorbate/antioxidants
  - B-vitamins (B_2, B_3, MTHF)
  - Exercise (O_2)
  - Humming
  - Sunshine (UV-A)
- Minimize Inhibitory Factors
  - Arginase activity
  - Inflammation
  - Smoking

Enzymatic Pathway



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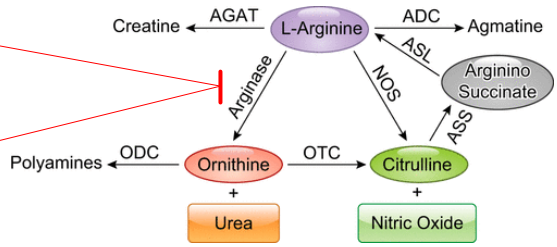
Inhibiting Arginase Activity

- Arginase competes with eNOS
  - Converts L-arginine -> Ornithine & Urea
  - Arginine available for NO via eNOS
- Compounds that inhibit arginase activity
  - L-citrulline
  - Taurine
  - γ-tocotrienol
  - Ginger
  - Turmeric
  - Resveratrol
  - EGCG



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Additional Support if needed

4 Capsules Supply:

Ingredients	Amount
Turmeric Extract (rhizome; *Curcuma longa*) (BCM-95® CURCUGREEN®)	500 mg
Resveratrol (root; *Polygonum cuspidatum*)	500 mg
Chinese Skullcap Extract (root; *Scutellaria baicalensis*)	450 mg
EGCG (epigallocatechin-3-gallate) (from green tea extract; leaf; *Camellia sinensis*)	400 mg
Sage Extract (leaf; *Salvia officinalis*) (SIBELIUS™:SAGE)	333 mg

- Especially useful for neuroprotection and cognition

3 Capsules Supply:

Ingredient	Amount
Ginger Powder (root; *Zingiber officinale*)	800 mg
Proprietary Mix of Curcumin Extract (rhizome; *Curcuma longa* L.; 35% curcuminoids) and Fenugreek Galactomannans Extract (seed; *Trigonella foenum-graecum*) (CurQfen®)	250 mg
Boswellia serrata Gum Extract (65% boswellic acid)	250 mg
White Willow Extract (bark; *Salix alba*; 25% salicin)	200 mg
Hops Extract (flower; *Humulus lupulus*; 2% xanthohumol)	150 mg
Devil's Claw Extract (root; *Harpagophytum procumbens*; 1.2% harpagosides)	60 mg

- Especially useful for inflammation (high hs-CRP)

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Inhibiting Arginase Activity References

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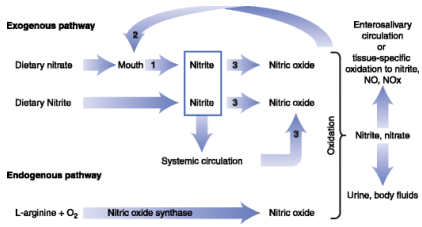
Testing Nitric Oxide

- No standard lab tests

NO_x species	Fasting plasma	Half-life	Exogenous or endogenous source
	nmol/L		
Nitrate	20–50,000	5–8 h	Diet or endogenous oxidation of nitrite
Nitrite	100–500	1–5 min	Endogenous nitrate, diet, oxidation of nitrite
Nitric oxide	<1	1–2 ms	Endogenous nitrite



- Serum nitrite
  - Surrogate for NO production and eNOS activity
- Fractional Exhaled Nitric Oxide testing
  - Useful in management of asthma
  - Does NOT correlate with Oral or Enzymatic NO production
- Nitric Oxide Indicator Strips

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Nitric Oxide Indicator Strips

- Nitric Oxide Indicator Strips
  - Measure nitrite (NO_2^-) in the saliva
  - Helps determine oral conversion of nitrate (NO_3^-) into nitrite (NO_2^-)
  - **Measure of NO production via Oral NO Pathway**
    - Identify need for dietary nitrates , supplementation
    - Need to avoid mouthwash, F-toothpaste, PPIs
    - Can compensate for insufficient enzymatic (eNOS) NO production
  - Not a measure:
    - Serum nitrite or systemic NO levels
    - eNOS activity

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Nitric Oxide Strips: Understanding the Results

- Oral NO Levels Low (↓ with age)
  - ↑ nitrate-rich foods
  - ↑ Regular exercise (aerobic and HIIT)
  - Supplementation (Nitric Boost, Cardio Flow, Ascorbate)
  - Avoid antiseptic mouthwash, fluoride, antacids/PPIs
- Oral NO Level High (above Target range)
  - Effectively converting nitrate -> nitrite -> NO
    - Sufficient intake of nitrate-rich foods or supplements
    - Acute effect from exercise

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Nitric Oxide Strips: Indications

- Use/recommend NO Indicator Strips to:
  - Monitor Oral NO production
    - Decreases with age, CVD, ED, etc.
  - Assess dietary intake of nitrates
    - Can increase nitrate rich foods or supplement accordingly
  - Measure the effect that various exercises have on Oral NO production
    - Moderate vs. high-intensity; weight training vs. aerobic training
- Personalized dietary, supplement and exercise recommendations

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Optimize NO to Improve Cardiovascular Health

- Nitric oxide has widespread effects on the cardiovascular system
  - Vasodilation
    - Improves blood flow & reduces blood pressure
  - Inhibits platelet aggregation
    - Prevents blood clots
  - Anti-inflammatory
    - Reduces inflammation in blood vessels
  - Angiogenesis
    - Promotes formation of new blood vessels
  - Inhibits atherosclerosis
    - Prevents the build up of plaque in the arteries

Graphic: Creator: HitToon Credit: Getty Images/iStockphoto

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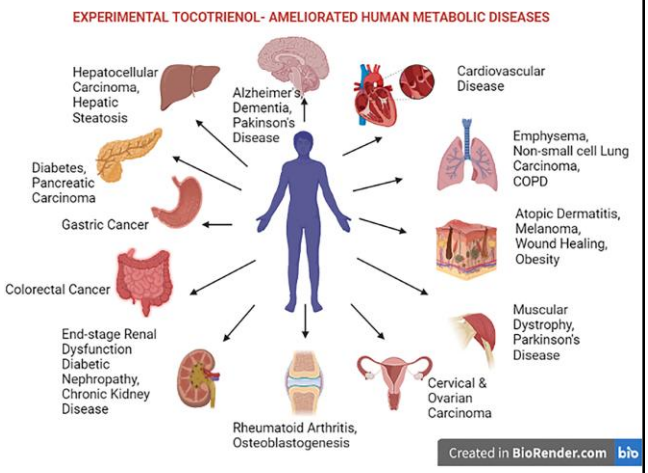
NO & Tocotrienols: 1-2 Health Punch



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NO Boosting Supplementation

Recommendation	Dosage
Cardio Flow powder	***1 scoop QD (or ½ scoop BID)***
Nitric Boost	***3 caps/day wf***
Annatto Pro 125	***1 gelcap QD/BID wf***
C Aspa Scorb	½ tsp BID wf
Brain Support	2 caps BID (esp for cognition)
Inflam-Eze Plus	1-2 caps BID/TID (esp for inflammation)
Diet – Modified Mediterranean: lots of low GI deep colored vegetables/fruit (esp. berries/pomegranates); focus on MUFA (Oleic acid (olives/olive oil, avocado/oil) – 1-2 Tbsp/day) and Fish/fish oils; nitrate-rich foods daily: Beets, carrots, lettuce, spinach, walnuts	
Exercise – moderate aerobic exercise – 30 min 5x/week; HIIT 2-3x/week	
Stress management – daily; deep nasal breathing, humming, meditation, yoga, etc.	
Avoid: Antiseptic and/or alcohol/H_2O_2-based mouthwashes, Fluoride toothpaste, Antacids and PPIs	

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Benefits of Improving NO

- "We can significantly improve endothelial function by improving NO production via both the Oral and Enzymatic pathways with just a few supplements"
- "Your patients will see a dramatic improvement in NO production."
  - Measure with Nitric Oxide Indicator Strips
- "This protocol provides your patients a powerful way to significantly improve their blood pressure and dramatically reduce their cardiovascular disease risk."

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Benefits of Improving NO

- "Nitric oxide has such a powerful and widespread effect on the CV system, optimizing nitric oxide production is one of THE most important factors *we have to address* with your patients for preventing and reversing CVD."

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NO Limits Smoothie

- Mix in blender:
  - ½ cup frozen spinach
  - ½ cup frozen blueberries
  - ½-1 cup yogurt/kefir
  - 1-2 Tbsp nut butter
  - Liquid of choice
  - 1 scoop Fruits & Greens
    - Berry or Espresso are favorites
  - ½-1 scoop Cardio Flow
  - ½-1 tsp C Aspa Scorb
  - 1 scoop protein powder and/or Functional Food (Cardio Metabolic, Infam-Eze)

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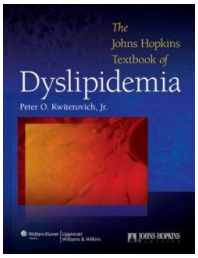
Addressing the Causes of CVD

- Nitric Oxide Dysfunction
- Nutritional Imbalances
- Dyslipidemia
- High blood pressure
- Blood sugar/insulin resistance
- Chronic Inflammation/Infection
- Mitochondrial Dysfunction
- Hormone Imbalances
- Visceral obesity



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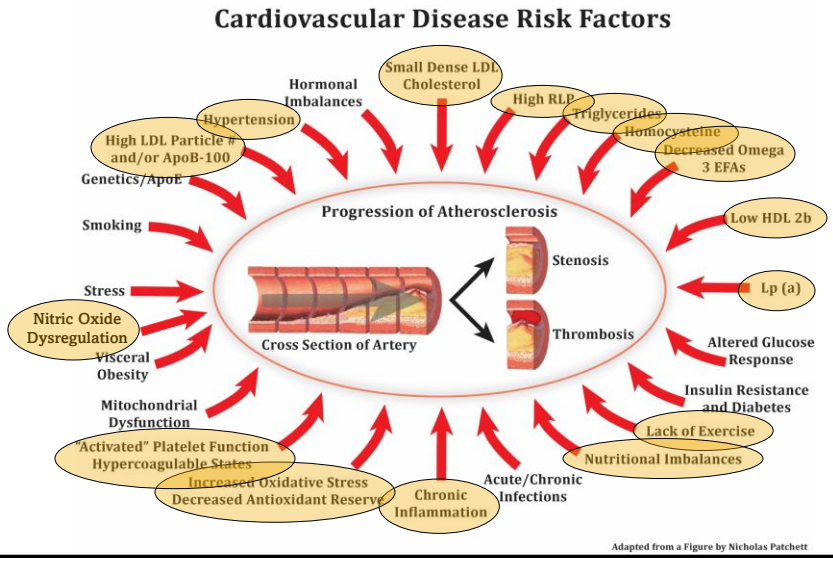
Cardiovascular Disease Risk Factors



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Correcting Cardiovascular Disease
Using Advanced Assessments to Address Endothelial Dysfunction
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Questions???

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