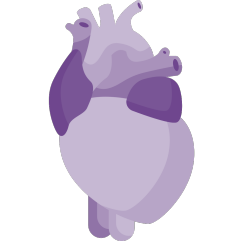


**Cardiovascular Health Supplement Guide**

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Written By: Michael Hull, Wyatt Brown, Mike Murray, Antonis Damianou, & Adel Moussa Edited By: Molly Gregas

Reviewed By: Wyatt Brown, & Molly Gregas

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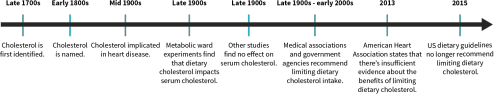
**Introduction**

For three decades, the cholesterol issue was clear: too much cholesterol in your blood is bad, and both dietary cholesterol and saturated fat should be kept to a minimum. But in recent years, the media have changed their tune: dietary cholesterol and fat — even saturated fat — aren’t so dangerous after all; they can even be good for you!

A typical nutrition enthusiast tends to take sides, either shying away from butter or adding some to everything, even their coffee. Some low carbers tend to downplay cholesterol concerns — or even celebrate their high numbers[1] — while some vegans brandish their rock-bottom numbers[2][3] as proof that eggs and meat are better avoided.

If it’s your first time at Cholesterol Club, you have to fight — fight dogma, that is — with scientific evidence as your only weapon. You have to dare to consider cardiovascular health as a whole, rather than either magnify or ignore the role of dietary fat and serum cholesterol.

**Timeline of cholesterol research and guidelines**

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References: Olson. J Nutr. 1998.[4] ● Duff. Am J Med. 1951.[5] ● Clarke et al. BMJ. 1997.[6] ● Brownawell and Falk. Nutr Rev. 2010.[7] ● Stone et al. J Am Coll Cardiol. 2014.[8]

**The diet-heart hypothesis was wrong**

First published in 1970, the Seven Countries Study led by Ancel Keys suggested that dietary saturated fat raised serum cholesterol levels and therefore increased the risk of cardiovascular disease.[9] Within the academic and medical communities, this conclusion was widely accepted as fact, and it influences official dietary guidelines even today.

However, recent evidence does not clearly support a connection between saturated-fat intake and cardiovascular disease.[10][11] Whether serum cholesterol and heart health are affected by saturated-fat intake appears to depend on what saturated fat is replacing (or is being replaced by).[12]

Even the source of the saturated fat matters. Randomized controlled trials have shown that a diet high in saturated fat from butter led to an increase in LDL-C (the “bad cholesterol”) but that a diet equally high in saturated fat from cheese might not.[13] And to add to the confusion, the most recent evidence suggests that butter has, at worst, a minor effect on cardiovascular health,[14] despite its tendency to increase LDL-C more than olive oil and coconut oil and to increase HDL-C] (the “good cholesterol”) less than coconut oil.[15]

The evidence on coconut products is equally conflicted. Although purified oil tends to perform worse than coconut meat, the magnitude of its effect on cardiovascular health is uncertain — probably because wider dietary patterns have a much greater impact on cardiovascular health.[16]

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| **Digging Deeper: Are you cuckoo for coconuts?**  You may love coconuts or might even guzzle coconut oil for its health benefits, but have you ever eaten an entire coconut in one sitting? Probably not. A single coconut of average size contains 400 grams of coconut meat (1,400 kcal). Aside from water, this coconut meat is composed of fat (133 grams, including 18 grams of MCTs (medium-chain triglycerides), carbs (35 grams of fiber and 25 grams of sugar), and more protein than you’d expect (13 grams). Combined, coconut’s fiber, sorbitol (a sugar alcohol that naturally occurs in some plants), and MCTs can result in a prolonged stay on the toilet.  Consuming the equivalent amount of fat through a few tablespoons of coconut oil might not cause any digestive issues because fiber and sorbitol are both subtracted, but the evidence linking coconut oil with a reduction in cardiovascular risk factors is mixed.[17] Although there is evidence of good health in island cultures with high coconut intakes,[18] we cannot conclude that these cultures owe their good health to coconuts. And even if coconuts are a healthy component of these cultures’ diets, it doesn’t follow that isolated coconut oil is healthy too — especially when added to most modern diets.  Still, when it comes to its effect on your cholesterol, coconut oil compares favorably to both butter and olive oil.[19] Compared to butter, it causes a higher increase in HDL-C (the “good cholesterol”) and a lower increase in LDL-C (the “bad cholesterol”). Compared to olive oil, it causes a higher increase in HDL-C and a smaller increase in LDL-C. |
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**Test results matter, but they can be misleading**

The standard lipid panel is a relatively poor reflection of your cardiovascular health. It estimates how much cholesterol, triglycerides, LDL-C, and HDL-C are in your blood, but it ignores better indicators of cardiovascular health.

LDL particle count is far more important than LDL-C levels. LDL infiltration is a major cause of inflammation, which is a precursor to atherosclerosis (a hardening and narrowing of the arteries),[20] and the more particles you have, the more can infiltrate your artery walls. LDL particle size is another potentially important factor because the smaller and denser LDL particles might find infiltration easier, but its predictive ability is greatly reduced once particle number is accounted for.[21]

So, simply keeping your LDL-C levels in check won’t protect you from heart attacks. In fact, one study found that nearly half of hospital patients admitted for cardiovascular disease had ideal levels of LDL-C.[22] Furthermore, some studies have associated low LDL-C levels with cancer, depression, and infectious diseases — although whether low LDL-C is a cause or a consequence of these conditions is uncertain.[23]

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| **Digging Deeper: Is LDL-C really “bad cholesterol”?**  Low-density lipoprotein (LDL) delivers cholesterol to the cells that need it. High-density lipoprotein (HDL) removes excess cholesterol from the bloodstream.  A quick Internet search will probably convince you that LDL cholesterol (LDL-C) is nefarious. It’s beyond question at this point that, in certain populations, lowering LDL-C helps reduce the risk of coronary events.[24]  But cholesterol is also key to hormone production and the structure of cell membranes, so it certainly isn’t inherently bad. LDL particles ferry cholesterol over to cells where it can be used.  If your LDL-C is extremely low, that could even be a sign that something is wonky within your body. One reason relates to infection: both HDL and LDL are needed to fight infection, and severe infection is linked to a reduction in both. Very low LDL-C levels (≤70 mg/dL) have been associated with higher risks of both cancer malignancy and sepsis (a life-threatening complication of infection),[25] not to mention an overall higher risk of death;[26] however, it is possible that the diseases cause low LDL-C, rather than the reverse.  Not everyone agrees that very low LDL-C levels are risky,[27] but it should be noted that some of the reviews concluding that risks are low were funded by companies that produce LDL-C–lowering drugs.[23] The overall takeaway is that the health effects of low LDL-C levels are far from certain, with well-documented cardiovascular benefits on one side and less-well-quantified risks on the other. If your LDL levels are very low, you should probably do a little bit of digging into these topics. |
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Still, even the standard lipid panel can provide useful information — if we look at ratios. On their own, cholesterol, triglycerides, LDL-C, and HDL-C are relatively poor indicators of cardiovascular health, but the ratio of total cholesterol to HDL-C is a strong indicator of heart disease risk,[28] and the ratio of triglycerides to HDL-C is a strong predictor of heart disease severity,[29][30]insulin resistance,[31] and LDL particle size.[32]

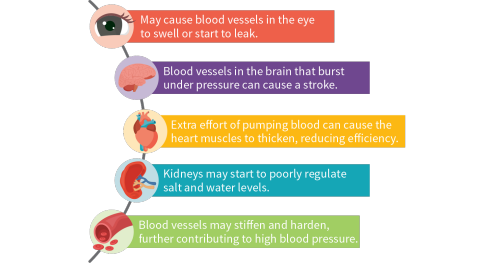
**Beyond blood lipids**

Even a savvy member of Cholesterol Club — a veteran who looks at ratios and LDL particle size — needs to realize that there’s more to cardiovascular health than blood lipids.

For instance, LDL particles aren’t the only factor involved in the inflammation necessary for arterial plaque formation. And of course, blood pressure (BP) also plays a central role in heart health: cardiovascular disease risk is strongly associated with an increase in BP, even when BP is still within normal range.[33]

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**Complications of high blood pressure**

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| **Digging Deeper: What’s a clinically significant reduction in blood pressure?”?**  A study may report a statistically significant reduction in blood pressure, but that doesn’t necessarily mean that the results are clinically significant, (i.e., practically meaningful to you). In the context of blood pressure, a clinically significant reduction would translate into a worthwhile benefit, such as a reduced risk of a major CVD event, CVD, or death due to CVD.  A reduction in blood pressure as small as ≥2 mmHg has been considered clinically significant and associated with a notable reduction in the risk of CVD and major CVD events.[34]  Most recently, a meta-analysis of 48 randomized clinical trials published in 2021 reported that in participants without and with a history of CVD across a range of SBP categories (i.e., <120 to ≥ 170 mmHg), a 5 mmHg reduction of SBP reduced the risk of major CVD events by 9% and 11%, respectively.[35] More specifically, the risk of stroke, heart failure, ischemic heart disease, and cardiovascular death were reduced by 13%, 13%, 8%, and 5%, respectively. |
| --- |

In sum, blood lipids are but one piece of the cardiovascular health puzzle: they shouldn’t be ignored, but neither should they turn into an obsession. Some supplements show evidence for potentially aiding cardiovascular health through a variety of mechanisms — some involving blood lipids, some not. However, none of these supplements will be able to counteract an unhealthy diet; rather, they should be seen as helpful adjuncts to a healthy diet and lifestyle.

Healthy foods and well-chosen supplements may complicate your life a little, but they can prolong it too. Published in 2019, a research letter on the “trends in cardiometabolic mortality in the United States, 1999– 2017”[36] reports that, “while cardiovascular disease (CVD) death rates declined by approximately 36% from 2000 to 2014,[37] CVD remains the leading cause of mortality among US adults."

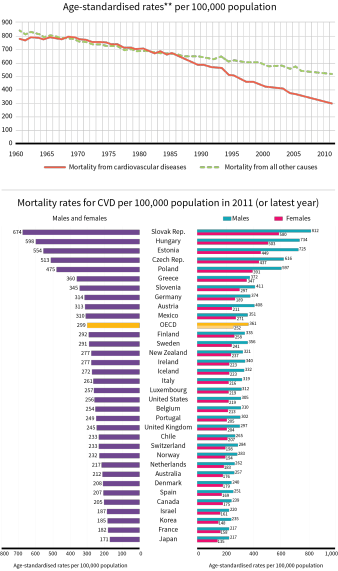
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**Kamal Patel**, Co-founder and Director

MBA, MPH, PhD(c) in Nutrition

**Mortality rates for cardiovascular diseases and all other causes of death in OECD countries\\***

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\* In 2013, the Organization for Economic Cooperation and Development comprises 36 member countries. \*\* Age-adjusted rates are a statistical tool that allows us to compare different age groups while reducing the potential confounding effect age may have on a health outcome.

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Reference: OECD Health Statistics. 2013. DOI:10.1787/health-data-en

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**Combos**

**Disclaimer about supplement quality**

We expect that readers will do their due diligence when choosing products. Depending on the manufacturer, supplements may have inaccurate labels (i.e., they contain too much or too little of the ingredients they claim, or in some cases, significant amounts of other ingredients not listed). They may also contain significant amounts of contaminants such as heavy metals or pesticides. It is also possible for supplements to contain ingredients that people are commonly allergic to, and it’s important to be aware of the nonmedicinal ingredients as well. As a brief introduction to vetting manufacturers, we drew up a short list of steps you should take if a product has caught your interest.

| **Tip: Why don’t you recommend brands or specific products?**  For two reasons:  We don’t test physical products. What our researchers do — all day, every day — is analyze peer-reviewed studies on supplements and nutrition.  We go to great lengths to protect our integrity. As you’ve probably noticed, we don’t sell supplements or even show ads from supplement companies, even though either option would generate a lot more money than our Supplement Guides ever will — and for a lot less work, too.  If we recommended any brands or specific products, our integrity would be called into question, so… we can’t do it. |
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**Core Combo**

Take 200–1000 mg of cocoa polyphenols, for instance, by eating about 10–30 grams of cocoa powder or 10–40 grams of dark chocolate with a 75% cocoa content.

If, for whatever reason, you can’t or don’t want to take chocolate, grape seed extract may be substituted. In that case, take 200–400 mg of grape seed extract.

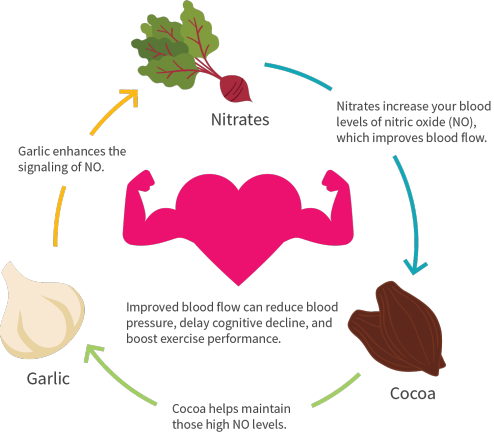
Take at least 1000 mg of aged garlic extract or garlic powder, to a maximum of 2400 mg. However, you may want to start with a smaller dose to avoid any gastrointestinal upset. It is unclear what dose is best for whole garlic.

Eat nitrate-rich vegetables. Aim for 6.4–12.8 mg of nitrates per kilogram of body weight per day (2.9–5.8 mg/lb/day), either over several meals or in one sitting a couple of hours before exercise.

Those three supplements are hypotensive agents, so start at the low end of the dosage range and monitor your blood pressure.

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**Core supplement synergy**

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| **Tip: Try one combo alone for a few weeks**  Taking too many supplements at once may prevent you from determining which ones are truly working. Start with just one of the combos suggested here for a couple of weeks before you consider making any modification, such as adding another supplement, altering a supplement dosage, or incorporating the supplements from an additional combo.  When adding another supplement to your regimen, be methodical. For example, you may want to take all the supplements from two combos. Select the combo that you wish to try first and take this for a couple of weeks. Then, add one supplement from the second combo and wait another week to see how it affects you. Continue this process until you’ve added all the supplements that you wish to.  If a supplement appears in two combos that you wish to combine, don’t stack the doses; instead, combine the ranges. For instance, if the range is 2–4 mg in one combo and 3–6 mg in the other, your new range becomes 2–6 mg. Always start with the lower end of the range — especially in this case, because the reason why one of the ranges has a lower ceiling in one combo may be due to a synergy with another supplement in the same combo. Reading through the full supplement entry may help you decide which dose to aim for, but if you’re not sure, lower is usually safer. |
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**Specialized Combos**

**For people with high blood pressure**

In addition to the core combo, take 3 grams of L-arginine three times per day for a total daily dose of 9 grams. It is possible that L-citrulline could also work, at 3–6 grams per day, but there is more evidence behind L-arginine. That said, L-citrulline likely has a lower risk for gastrointestinal upset, so if you are having problems with that arginine dose, citrulline may be a good substitute. These supplements are likely not redundant with nitrates because they are turned into nitric oxide via a different mechanism.

It is important to be wary of using this many antihypertensive supplements due to a theoretical risk for hypotension, especially if combined with blood pressure medication.

**For people who have experienced a heart attack**

After consultation with your physician, take the core supplements with 5–9 grams of carnitine, 1.5–4.5 grams of taurine, and 15 grams of D-ribose, in three divided doses spread through the day.

**For people with varicose veins or with leg swelling caused by sitting**

If the core supplements do not solve the problem within a month, adding a venotropic may help, though this is speculative. Take either 100–200 mg of pycnogenol at breakfast or one of the following options

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twice per day, 12 hours apart.

375–750 mg of butcher’s broom (i.e., 750–1,500 mg/day)

50–75 mg of horse chestnut (i.e., 100–150 mg/day)

400 mg of diosmin with 100 mg of hesperidin (i.e., 1,000 mg/day in total)

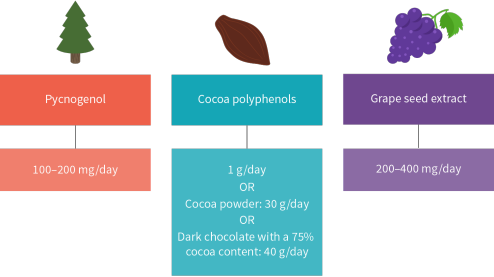
Like the core supplements (cocoa, garlic, and nitrates), Pycnogenol is a hypotensive agent. **Other Options**

People with elevated triglycerides can add fish oil to any combo. In general, taking in 4 grams of combined EPA and DHA per day by eating fatty fish (e.g., 280 grams of salmon or by taking fish oil softgels (with food, to reduce the chance of fishy burps) will have the greatest effect, but it is still unclear to what extent fish oil may increase the risk of arrhythmia in people without cardiovascular disease, so it may be best to exhaust all other options before trying this supplement. Vegans and vegetarians have the option of taking algal oil softgels.

Because glutathione may slow the rate of nitric oxide (NO) breakdown in the bloodstream, adding 200 mg of glutathione to your nitrates might prove synergistic.

Should cocoa polyphenols (1 gram) fail to help you after a month, you could try replacing them with a grape seed extract (200–400 mg). Should the grape seed extract fail to help you after a month, you could try replacing it with Pycnogenol (100–200 mg). Take your grape seed extract or pycnogenol once per day with a meal.

**Procyanidin dose chart**

**What has changed since the last time?**

It should be noted that we changed the names of our ranking categories. “Core” (the highest) is now “primary”, “primary” is now “secondary”, and “secondary” is now “promising”. This nomenclature has already

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been implemented for some guides, but this is the first update to the Cardiovascular Health Guide that uses this new terminology. For example, if it was a core supplement in the previous issue and is now a secondary supplement in this issue, we’ll say that it was a primary supplement in the previous issue and is now a secondary supplement.

Added:

L-arginine

L-citrulline

Vitamin D

Spirulina

Changed ranking:

CoQ10

Downgraded from secondary to unproven. We found that based on a new review, we weren’t able to say that it improved general cardiovascular risk factors. There may be some utility in cases such as heart failure, but we haven’t reviewed that yet.

Resveratrol

Downgraded from secondary to unproven. It doesn’t appear to consistently improve risk factors, especially compared with cocoa and grape seed extract.

Vitamin K

Downgraded from secondary to unproven. It is possible that it can decrease arterial calcification, but we will need more high-quality research before we can say so.

Arjuna

Upgraded from unproven to promising. Additional evidence increased our confidence in it somewhat. 13

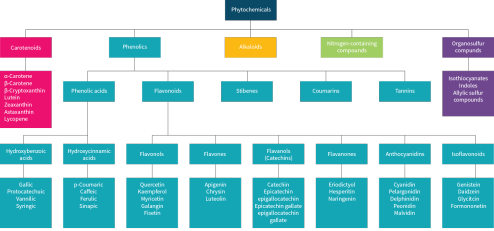
**Primary Supplements**

**Cocoa**

**What makes cocoa a primary supplement**

Cocoa’s cardioprotective effects can be primarily attributed to its polyphenol content, most notably, flavanols — of which, (-)-epicatechin is the most predominant constituent (up to 35%), and proanthocyanidins.[38]

**Classification hierarchy of polyphenols**

****Flavanols can help to reduce cardiovascular disease (CVD) risk by boosting nitric oxide (NO) levels[39][40] — which increases vasodilation (i.e., relaxation of the blood vessels) and can subsequently improve blood pressure. Correspondingly, research supports that acute and chronic cocoa consumption leads to a small improvement in flow-mediated dilation and arterial stiffness.[41][42]

The flavanols in cocoa may also provide benefit by scavenging free radicals, thereby reducing oxidative stress,[43] as well as inhibiting low-density lipoprotein (LDL) oxidation.[44][45][46]

In line with cocoa’s effects on blood vessels, it reduces blood pressure by a couple of points.[47][48] The most notable effect (−4 and −2 mmHg for systolic and diastolic blood pressure, respectively) has been reported in people with hypertension and older adults (age ≥65).

In contrast, the effect of cocoa on blood lipids is controversial. Most evidence points toward little to no effect on LDL-C (low density lipoprotein cholesterol), HDL-C (high density lipoprotein cholesterol), or triglycerides.[49][50][51][52] However, population differences may moderate the effect.

For example, a 2021 meta-analysis that focused on participants with type 2 diabetes reported that cocoa consumption reduced LDL-C by 15.49 mg/dL, on average.[53] Due to heterogeneity between studies, further

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research is needed to fully determine the potential benefits of cocoa on blood lipids in specific populations.

Although the effects of cocoa consumption on cardiovascular risk factors are generally marginal, a potentially more important question is whether the consumption of cocoa is associated with a reduced risk of CVD and cardiovascular events.

The largest and most consistent protective effect has been reported for stroke. Meta-analyses of prospective cohort studies have found that compared to the lowest category of chocolate intake, the highest category was associated with a 13%–17% lower risk of stroke, with a larger effect for hemorrhagic stroke, specifically.[54][55][56]

With respect to heart disease, the highest category of intake was associated with an 8%–10% lower risk compared to the lowest category.[56][54] For CVD overall — which includes heart disease, stroke and its subtypes, heart failure, and heart attack — the highest category of chocolate intake was associated with a 12% reduced risk compared to the lowest category.[55]

A central limitation of observational studies is that the methods used to assess dietary intake (e.g., food frequency questionnaires) do not distinguish between dark and milk chocolate consumption. This is noteworthy because dark chocolate contains a higher amount of cocoa and flavanols than milk chocolate (which are responsible for chocolate’s cardioprotective effects), so the effect of dark chocolate on cardiovascular disease risk may be underestimated.

**Warnings about cocoa**

Because cocoa contains caffeine, it has potential safety concerns related to caffeine itself. Caffeine is generally considered to be safe when the daily dose does not exceed 400 mg in adults[57]. One cup of unsweetened dry cocoa powder can contain up to 198 mg of caffeine, so up to two cups (or around 180 grams) of cocoa is relatively safe from a caffeine standpoint. But with increasing doses, expect to see some of the effects of caffeine. For anyone with sensitivities to caffeine, caution is particularly important. Cocoa flavonol, an extract of cocoa powder, is generally well tolerated in dosages up to 2000 mg per day,[58] which is the rough equivalent of 400 grams of cocoa powder. However, there are still some side effects to watch out for, like gastrointestinal discomfort.[59] Because cocoa has been shown to have antiplatelet effects,[60]it should be used cautiously if taking any other anticoagulant medications (e.g. warfarin/Coumadin/Jantoven) or (aspirin)(https://medlineplus.gov/druginfo/meds/a682878.html)) due to the increased risk of bleeding. Consult with a doctor if taking any other supplements with these medications. Taking cocoa with other hypotensive agents could cause low blood pressure. Hypotensive agents can be pharmaceuticals but also supplements — garlic, notably, but also nitrates, grape seed extracts, or pine bark extracts, to mention only the supplements presented in this guide. Cocoa is high in oxalates. People already at an increased risk of forming kidney stones, as well as people with oxalosis or hyperoxaluria, should keep their oxalate intake to a minimum.

**How to take cocoa**

In 2012, the European Food and Safety Authority stated that 200 mg of cocoa flavanols should be consumed daily to help maintain endothelium-dependent vasodilation in the general population. This amount of flavanols can be obtained from 2.5 grams of high-flavanol cocoa powder or 10 grams of high flavanol dark chocolate.

Since this statement was released, a number of dose-response meta-analyses have been conducted to 15

determine the optimal intake of chocolate needed to reduce the risk of CVD. A 2020 meta-analysis of observational studies reported that the risk of heart disease and stroke decreased by 7%–8% with increasing chocolate intake but flatlined at 20 g/day.[54]

In comparison, a separate meta-analysis of observational studies published in 2019 reported that the optimal intake of chocolate needed to reduce CVD risk was approximately 45 g/week, and risk reduction was maintained at up to 90 g/week.[55]

| **Digging Deeper: What’s in your chocolate bar?**  To obtain the potential cardiovascular effects of consuming chocolate, it’s essential that the chocolate is rich in polyphenols, but unfortunately, this is easier said than done. Several factors influence the polyphenol content of chocolate, including the cultivar, growing conditions (e.g., soil, climate), maturity of the cocoa bean, and processing and form (e.g., cocoa liquor, cocoa powder, chocolate bar).[61][62][63][64]  For example, a study conducted in 2019 reported the following:[65]  Proanthocyanidin content increased with maturation (i.e., fully ripe cocoa beans contained the most proanthocyanidins) in unfermented cocoa beans.  Proanthocyanidin content and total antioxidant capacity decreased with maturation when cocoa beans were fermented.  Fermentation reduced proanthocyanidin content, and the longer the duration, the greater the reduction.  Using an enzyme in the fermentation process (i.e., pectinase) reduced proanthocyanidin content and antioxidant capacity.  Generally speaking, polyphenol content and the antioxidant capacity of chocolate increases proportionally with the amount of nonfat cocoa solids,[66][63][67] but the provenance and quality are also influential. For example, one study found a higher polyphenol content in 60% (60% cacao) organic dark chocolate than in 72% conventional dark chocolate and a higher polyphenol content in 70% dark chocolate from Madagascar than in 80% dark chocolate from Trinidad.[64] |
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Collectively, the evidence suggests that daily consumption of a small amount of dark chocolate (≥70% cacao) may have cardioprotective effects. Higher intakes may not be detrimental per se,[56] but chocolate products are relatively energy dense and can be easy to overeat. Because weight gain typically increases the risk of CVD, it’s likely best to stick to the minimally effective dose for chocolate consumption.

**Garlic**

**What makes garlic a primary supplement**

The use of garlic as a spice, food, and medicine dates back over 5,000 years. It’s been traditionally used in Ayurvedic and Chinese medicine for the prevention and treatment of a variety of diseases.[68][69]

Garlic’s beneficial properties are primarily attributed to its high content of sulfur-containing compounds, 16

namely, alliin, which produces allicin –– the main active metabolite responsible for most of garlic's biological activities –– when physically disturbed through chewing, slicing, or crushing.

Mechanistically, there is great interest in garlic for therapeutic use due to its ability to produce hydrogen sulfide (H2S), which can relax blood vessels,[70] and upregulate nitric oxide (NO) production.[71] Notably, dysregulated production of NO and H2S is linked to several diseases, including cardiovascular disease.[72]

In people with elevated blood lipids, garlic has a large effect on total cholesterol and LDL reduction.[73][74] Based on the results from one meta-analysis, garlic reduced total cholesterol and LDL by approximately 17 mg/dL and 10 mg/dL, respectively, on average.[73] Moreover, garlic has a considerable positive effect on blood pressure. In the context of hypertension (defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg), garlic supplementation reduced systolic blood pressure and diastolic blood pressure by about 8 mmHg and 5.5 mmHg, respectively, on average.[75]

With regard to markers of inflammation, garlic reduced C-reactive protein (−0.53 mg/L) compared to placebo,[76] with a larger effect reported for garlic products than aged garlic extract. However, garlic has demonstrated unreliable effects on other markers of inflammation (i.e., tumor necrosis factor alpha (TNF-α) , interleukin-6 (IL-6).

Garlic is also helpful for reducing oxidative stress, as evidenced by a very large effect on increasing total antioxidant capacity in both healthy individuals and those with different disease states.[77] Similarly, garlic reduced malondialdehyde levels, but this outcome was based on low-quality evidence.

**Warnings about garlic**

One to two cloves of raw garlic per day is considered safe in adults.[78] Side effects noted with garlic include abdominal pain, flatulence, and body odor, as well as bad breath.[79] Garlic has been linked with bleeding due to its antiplatelet activity.[80] Therefore, garlic should be stopped 7–10 days before undergoing surgery.[81] Additionally, garlic may be dangerous if taking any other anticoagulant medications (e.g. coumadin/Warfarin/Jantoven or aspirin due to the risk of bleeding. Garlic may also reduce the efficacy of antiretroviral medications.[82] Consult with a doctor about any other supplements taken alongside medications. The same principle applies to blood pressure medications, as well as the other blood pressure-reducing supplements in this guide. Garlic extract has been observed to reduce CYP2C9 expression, which means that it could reduce the rate of detoxification of drugs and potentially lead to overdose effects.[83] Some examples of drugs metabolized by CYP2C9 can be found here in Table 1. But it is important to always talk to a doctor or a pharmacist about supplements if a person is taking any medications.

**How to take garlic**

A wide variety of garlic products and doses have been used in research settings. Clinical trials have most commonly used either garlic powder (typically in the form of a tablet or capsule) in a daily dose of 600– 900 mg or aged garlic extract in a daily dose of approximately 1,200–2,400 mg. Concerning total antioxidant capacity specifically, it appears prudent to supplement with at least 1,000 mg/day of a chosen garlic product.[77]

Whole garlic hasn’t been sufficiently studied, but if it’s the only option, start small and increase up to the most that can be tolerated. First cut or crush whole garlic cloves, to activate their bioactive compounds, 17

and then cook them or eat them raw.

**Nitrates**

**What makes nitrates a primary supplement**

Nitrates break down into nitrites, which circulate in the body and are turned into the vasodilator nitric oxide (NO) as needed.

**How nitrates are converted into nitric oxide**

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To date, a handful of meta-analyses have looked at the effects of nitrates on blood pressure, with most reporting small beneficial effects. For example, a 2020 meta-analysis of 47 randomized controlled trials found that nitrates (taken primarily from beetroot juice) reduced systolic blood pressure by 2.9 mmHg and diastolic blood pressure by 1.5 mmHg.[84] Similarly, 3 other meta-analyses examining the effects of nitrates (mainly from beetroot, but also from other vegetables or from sodium nitrate) have reported improvements in systolic blood pressure in the range of 3.4 to 3.9 mmHg and in diastolic blood pressure in the range of 1.7 to 2.6 mmHg.[85][86][87]. It’s also worth noting that one of 2 meta-analyses did not find statistically significant improvements in blood pressure but trended towards statistical significance.[88][89] 18

With the aforementioned research in mind, we can be fairly confident that nitrates can improve blood pressure to a small, but clinically meaningful, degree.

**Warnings about nitrates**

Nitrates are prevalent in many foods, and an intake above the acceptable daily intake is important to consider for safety measures. The acceptable daily intake set by the European Food Safety Authority of nitrates is 3.7 mg (or 0.06 mmol) per kilogram of bodyweight.[90] For example, a 50 kg person would have an acceptable daily intake of 185 mg of nitrates. However, this value was derived from animal studies in the 1960s, which found that the highest tested dose had no adverse effects, so this is actually a lower bound for safe intake. Taking nitrates with other hypotensive agents could cause low blood pressure. Hypotensive agents can be pharmaceuticals but also supplements — garlic, notably, but also cocoa, grape seed extracts, or pine bark extracts, to mention only the supplements presented in this guide.

Leafy greens are often rich in vitamin K~~1~~, a fat-soluble vitamin that helps with blood clotting and so might decrease the effectiveness of blood thinners, especially anticoagulants (such as

warfarin/Coumadin/Jantoven and acenocoumarol/Sintrom/Nicoumalone. People who take a blood thinner should consult with a physician before consuming a lot of leafy greens.

Due to their goitrogen content, cruciferous vegetables can reduce thyroid hormone production if regularly consumed in high amounts, such as those needed for nitrate supplementation. People who tend to eat a lot of cruciferous vegetables (such as cabbage, collard greens, or kale) should make sure to also get enough iodine via iodine-rich foods (such as cod, shrimp, milk, yogurt, or cottage cheese), iodine-fortified foods (such as iodized salt), or supplements (75–150 μg/day). Although dosing can vary, nitrate toxicity may lead to an increased risk of methemoglobinemia, a disorder in which hemoglobin cannot transport oxygen.[91] However, this condition is rarely due to dietary nitrates; instead, it’s usually caused by drinking water contaminated with high levels of nitrates, and the disease is most often seen in infants and children. Nitrates are reduced to nitrites, which eventually can form nitrosamines in the acidic environment of the stomach.[92] These nitrosamines have been studied and determined to have carcinogenic potential.[93] Particularly, nitrates have been linked to an increased risk of thyroid cancers.[94] Therefore, it is important to consider the different dosages of nitrates available in foods prior to consumption. Nitrates tend to get most of the attention when it comes to the subject of red/processed meat and colorectal cancer/other cancers; however, vegetables with many more nitrates aren't convincingly tied to carcinogenesis. Evidence suggests that the heme iron in meat acts as an important catalyst of nitrosamine formation when it reacts with nitrates and nitrites.[95] For this reason, it might be particularly harmful to consume a large amount of nitrates with red meat, though the presence of calcium salts, chlorophyll, vitamin C, and various polyphenols inhibit this reaction, so it is less likely that combining red meat and high-nitrate vegetables would form large amounts. That said, it is currently unclear whether these factors can entirely mitigate nitrosamine formation when red meat and high amounts of nitrates are consumed simultaneously. Beetroot juice is rich in inorganic nitrates and has been used as a supplement to reduce blood pressure in adults. However, side effects of red urine and red stools can be seen with beetroot supplementation.[96] Most vegetables rich in nitrates are also rich in oxalate, which can increase the risk of kidney stones. People who are already at an increased risk of forming kidney stones, as well as people with oxalosis or hyperoxaluria, should keep their oxalate intake to a minimum.

Other people need not ban all oxalate from their diet, but individuals who consume high amounts of nitrates (and the dosage range in this guide certainly qualifies) more than twice per week should favor oxalate-poor vegetables. People who do eat oxalate-rich foods on occasion should consider cooking them and/or

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pairing them with calcium-rich foods to reduce oxalate absorption.

Vegetables sorted by total oxalate content (mg per 100 grams)

| **OXALATE CONTENT** | **VEGETABLES** |
| --- | --- |
| Very high (100+) | Beetroot, collard greens, dill, mustard greens, parsley, rhubarb, spinach, swiss chard, turnips |
| High (10 to <100) | Cauliflower, celery, kale, lettuce, turnip greens |
| Moderate (2 to <10) | Arugula/rocket, asparagus, carrot, radish, sweet potato, watercress |
| Low (<2) | Bok choy, cabbage, radicchio |

**How to take nitrates**

Aim for 6.4–12.8 mg of nitrates per kilogram of body weight (2.9–5.8 mg/lb).

Because the nitrate content of beet-based sports supplements (juice, powder, concentrate) varies so greatly,[97]it's important to check the amount of nitrate that the product delivers per serving. Remember to follow these guidelines to find a quality supplement.

Nitrate intake by body weight

| **BODYWEIGHT**  **lb/kg** | **2.9**  **(6.4)** | **3.4**  **(7.5)** | **3.9**  **(8.5)** | **4.3**  **(9.5)** | **4.8**  **(10.5)** | **5.2**  **(11.5)** | **5.8**  **(12.8)** | **mg/lb**  **(mg/kg)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 100/45 | 288 | 338 | 383 | 428 | 473 | 518 | 576 | mg |
| 125/57 | 365 | 428 | 485 | 542 | 599 | 656 | 730 | mg |
| 150/68 | 435 | 510 | 578 | 646 | 714 | 782 | 870 | mg |
| 175/79 | 506 | 593 | 672 | 751 | 830 | 909 | 1,011 | mg |
| 200/91 | 582 | 683 | 774 | 865 | 956 | 1,047 | 1,165 | mg |
| 225/102 | 653 | 765 | 867 | 969 | 1,071 | 1,173 | 1,306 | mg |
| 250/113 | 723 | 848 | 961 | 1,074 | 1,187 | 1,300 | 1,446 | mg |
| 275/125 | 800 | 938 | 1,063 | 1,188 | 1,313 | 1,438 | 1,600 | mg |

Nitrate-rich vegetables (mg per 100 grams)

| **NITRATE-RICH VEGETABLES** | **Nitrates (mg)** | **Total Oxalate (mg)** | **Soluble Oxalate (mg)** | **Vitamin K~1~ (μg)** |
| --- | --- | --- | --- | --- |
| Arugula/rocket | 362.4 | 7.1 | <0.5 | 108.6 |
| Turnip greens | 346.7 | 50 | — | 251 |
| Dill | 259 | 159 | 60 | 0 |
| Collard greens | 254.5 | 450 | — | 437.1 |
| Spinach | 248.5 | 656 | 542.6 | 482.9 |
| Swiss chard | 236.3 | 964 | 207.7 | 830 |
| Turnips | 217.4 | 210 | — | 0.1 |
| Rhubarb | 199.9 | 805 | 223 | 29.3 |
| Beetroot | 199.2 | 121 | 74.9 | 0.2 |
| Celery | 196.4 | 17.5 | <0.5 | 29.3 |

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| **NITRATE-RICH VEGETABLES** | **Nitrates (mg)** | **Total Oxalate (mg)** | **Soluble Oxalate (mg)** | **Vitamin K~1~ (μg)** |
| --- | --- | --- | --- | --- |
| Mustard greens | 187.5 | 128.7 | — | 257.5 |
| Radish | 177.3 | 9.2 | <0.5 | 1.3 |
| Lettuce | 168.9 | 13.6 | <0.5 | 126.3 |
| Watercress | 164 | 10 | <0.5 | 250 |
| Bok choy | 162 | 2 | — | 45.5 |
| Kale | 137.5 | 20 | — | 704.8 |
| Parsley | 130.47 | 136 | 76 | 1640 |

This table is composed of averages from multiple samples. Farming techniques, transport, storage conditions, and cooking methods can all greatly affect the actual nitrate and oxalate content of your food.

References: Jackson et al. Nutr Res Rev. 2017.[98] ● Lidder and Webb. Br J Clin Pharmacol. 2013.[90] ● Griesenbeck et al. Nutr J. 2009.[99] ● Tamme et al. Food Addit Contam. 2006.[100] ● Siener et al. Food Chem. 2006.

DOI:https://doi.org/10.1016/j.foodchem.2005.05.059 ● Hönow and Hesse. Food Chem. 2002.[101] ● Santamaria et al. J. Sci. Food Agric. 1999.[102] ● [https://phytochem.nal.usda.gov/phytochem/search](Dr. Duke's Phytochemical and Ethnobotanical databases) ● [https://fdc.nal.usda.gov/](FoodData Central)

Those vegetables can be consumed whole or in liquid form (juice, shake, or purée) over several meals. They can also be drunk in one sitting a couple of hours before exercise.

Because the bacteria in saliva play a role in activating dietary nitrates, do not use an antibacterial mouthwash too often and especially not shortly before consuming nitrate-rich foods.[103] Moreover, the cooking time, if any, should be brief: although cooking reduces the oxalate content more than the nitrate content, the loss of nitrates after 15 minutes of cooking can still exceed 50%.

Vegetables sorted by nitrate content (mg per 100 grams)

| **NITRATE**  **CONTENT** | **VEGETABLES** |
| --- | --- |
| Very high  (250+) | Arugula/rocket, collard greens, dill, turnip greens |
| High  (100 to  <250) | Beetroot, bok choy, celeriac, celery, kale, kohlrabi, lettuce, mustard greens, parsley, radish, rhubarb, spinach, swiss chard, turnip, watercress |
| Moderate  (50 to  <100) | Broccoli, cabbage, cauliflower, endive, savoy cabbage |
| Low  (20 to <50) | Chicory, eggplant, fennel, green beans, green onion, leek, pumpkin/squash |
| Very low  (<20) | Artichoke, asparagus, broad bean, brussels sprouts, carrot, cucumber, dry beans, garlic, lima beans, maize, mushroom, onion, peas, pepper, sweet potato, tomato, white potato |

References: Jackson et al. Nutr Res Rev. 2017.[98] ● Hord et al. Am J Clin Nutr. 2009.[104] ● Jones. Sports Med. 2014.[105]

Most vegetables that are rich in nitrates are also rich in oxalate, which can increase the risk of kidney stones. People who are already at an increased risk of forming kidney stones, as well as people with oxalosis or hyperoxaluria, should keep their oxalate intake to a minimum.

Other people need not ban all oxalate from their diet, but individuals who consume high amounts of nitrates 21

(and the dosage range in this guide certainly qualifies) more than twice a week should favor oxalate-poor vegetables. People who do eat oxalate-rich foods on occasion should consider cooking them and/or pairing them with calcium-rich foods, to reduce oxalate absorption.

Vegetables sorted by total oxalate content (mg per 100 grams)

| **OXALATE CONTENT** | **VEGETABLES** |
| --- | --- |
| Very high (100+) | Beetroot, collard greens, dill, mustard greens, parsley, rhubarb, spinach, swiss chard, turnips |
| High (10 to <100) | Cauliflower, celery, kale, lettuce, turnip greens |
| Moderate (2 to <10) | Arugula/rocket, asparagus, carrot, radish, sweet potato, watercress |
| Low (<2) | Bok choy, cabbage, radicchio |

Because glutathione may slow the rate of NO breakdown in the bloodstream, adding 200 mg of N acetylcysteine (NAC) to your nitrates might prove synergistic.

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**Secondary Supplements**

**Carnitine**

**What makes L-carnitine a secondary**

**supplement**

L-Carnitine is a compound produced by the body from the amino acids lysine and methionine. It’s also found in animal-based foods and is most prevalent in beef. L-Carnitine is most notable for its role in fat metabolism. More specifically, it transports long-chain fatty acids into mitochondria to be broken down into ATP.

The heart has very high energy demands, and long-chain fatty acids are a significant source of energy. In a healthy heart, the vast majority of ATP production in the mitochondria comes from the beta-oxidation of fatty acids.[106] Consequently, in people who have had a heart attack –– an event characterized by a progressive loss of ATP –– L-carnitine may be an effective add-on treatment.[107][108]In people with chronic heart failure, L-carnitine has been shown to decrease the New York Heart Association Classification (a measure of the extent of heart failure) as well as levels of brain natriuretic peptide (−124.60 pg/mL) and N terminal pro--type natriuretic peptide (−510.36 pg/mL), which are two hormones produced in higher concentrations when the heart is working harder than usual.[109] L-Carnitine also improved the heart's ability to pump blood, as evidenced by increases in left ventricular ejection fraction.

Related to L-carnitine’s involvement in the breakdown of fatty acids, it’s also hypothesized that it could be effective for treating elevated blood lipids (i.e., dyslipidemia) and related disorders. The available evidence reports that it can decrease LDL-C and triglycerides in the range of −5.48 to −6.25 mg/dL and −9.44 to −10.35 mg/dL, respectively, on average.[110][111]In contrast, L-carnitine does not appear to improve apolipoprotein B levels.[112]In fact, a small number of long-term studies (>3 months) suggest that L-carnitine may slightly increase apolipoprotein B levels (+2.62 mg/dL). Moreover, L-carnitine does not meaningfully affect blood pressure.[113]

With respect to markers of oxidative stress and inflammation, L-carnitine has a small positive effect. For instance, it may decrease C-reactive protein, interleukin 6, and tumor necrosis factor alpha levels by approximately −0.10 mg/dL, −1.87 pg/mL, and −1.43 pg/mL, respectively.[114] L-Carnitine can also slightly decrease malondialdehyde (a marker of oxidative stress) levels and increase superoxide dismutase (an antioxidant enzyme) activity.[114]

However, it must be cautioned that in the meta-analysis that reported these results, there was wide variation among studies in the participants' ages and health conditions, the doses of L-carnitine, the types of L-carnitine, the administration routes (e.g., oral, intravenous), and the durations of the intervention. Also, many of the included studies combined L-carnitine with other compounds.

There is some speculation that the conversion of L-carnitine to trimethylamine N-oxide (TMAO) in the digestive tract can accelerate atherosclerosis, but the direct evidence is mixed. In one study, supplementing with 250 mg of L-carnitine for 12 weeks coincided with a reduction in atherosclerosis, but in another study, taking 2 grams of L-carnitine daily for 6 months coincided with an increase in some measures, though not 23

overall plaque volume.[115][116] There may very well be a dose-dependent effect that further studies could elucidate.

**Warnings about carnitine**

Adverse effects are generally rare, but some cases of upset stomachs have been reported. Higher dosages of L-carnitine (2 g/day or more) can be converted into the compound trimethylamine, which in some people can give a fishy odor to urine, sweat, or breath.[117]

Carnitine and its derivatives might interact negatively with some pharmaceuticals, including anticoagulants (such as warfarin/Coumadin/Jantoven and acenocoumarol/Sintrom/Nicoumalone). People on thyroid medication or with hypothyroidism may also wish to forgo carnitine because it might depress thyroid hormone levels.[118]

**How to take carnitine**

In people at risk but who have not yet experienced cardiovascular complications, 500 mg of L-carnitine per day might offer some protection when taken in conjunction with prescribed medical therapies. People who have already experienced a heart attack, however, would need at least 2,000 mg (i.e., 2 grams) and preferably 5,000–9,000 mg (i.e., 5–9 grams) to see a reduction in arrhythmia, angina, and all-cause mortality. However, in this case, it is best to defer to the instructions of a doctor.

L-carnitine can also be consumed as L-carnitine L-tartrate (LCLT) or glycine propionyl-L-carnitine (GPLC).

It is possible to supplement 500 mg of L-carnitine through 750 of LCLT or GPLC.

It is possible to supplement 5,000–9,000 mg of L-carnitine through 7,500–1,350 mg of LCLT or GPLC.

However, neither LCLT nor GPLC has proven advantages over regular L-carnitine, both are more expensive, and GPLC also clumps easily in moist environments.

Food can sometimes provide significant amounts of carnitine. Because the participants in trials on carnitine typically have had an average dietary intake, doses from food should not affect the amount a person takes from supplements.

Selected food sources of carnitine

| **FOOD** | **PORTION** | **MILLIGRAMS (mg)** |
| --- | --- | --- |
| Beefsteak, cooked | 4 oz | 56–162 |
| Ground beef, cooked | 4 oz | 87–99 |
| Whole milk | 1 cup | 8 |
| Codfish, cooked | 4 oz | 4–7 |
| Chicken breast, cooked | 4 oz | 3–5 |
| Ice cream | ½ cup | 3 |
| Cheddar cheese | 2 oz | 2 |
| Whole-wheat bread | 2 slices | 0.2 |
| Asparagus, cooked | ½ cup | 0.1 |

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Adapted from [https://ods.od.nih.gov/factsheets/Carnitine-HealthProfessional/#h3](Carnitine: Fact Sheet for Health Professionals). NIH ODS. Last updated October 10, 2017; accessed October 27, 2019

**Digging Deeper: Levels of prevention for CVD**

Public health and medical interventions are often focused on preventing negative health outcomes. There are multiple types of prevention: primordial, primary, and secondary. These types of prevention are summarized below.

**Levels of prevention in cardiovascular disease**

****Reference: Hong et al. J Am Coll Cardiol. 2017.[119]

**Primordial** prevention is aimed at stopping the risk factors for CVD from ever developing. An example would be aiming to maintain blood pressure in someone who already has normal blood pressure.

**Primary** prevention means preventing an initial event from happening, like getting heart disease or a first heart attack, by modifying its risk factors. An example would be lowering high cholesterol to prevent a first heart attack.

**Secondary** prevention aims to prevent the progression or another occurrence of an existing disease, like preventing a second stroke in someone who’s already had one.

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**Fish Oil**

**What makes fish oil a secondary supplement**

Essential fatty acids (EFAs) are polyunsaturated fatty acids (PUFAs) that your body needs and cannot produce. There are only two kinds of EFAs: linoleic acid (LA) and alpha-linolenic acid (ALA). Neither is very active, so your body transforms the former into notably arachidonic acid (AA) and the latter into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). LA and AA are omega-6 fatty acids, and ALA, EPA, and DHA are omega-3 fatty acids. EPA and DHA make up most of the PUFAs in fish oil.

A 2020 Cochrane meta-analysis of 78 randomized controlled trials found low-moderate certainty evidence that higher (compared to lower) intakes of the omega−3s EPA and DHA (from supplements or food) in adults at risk of cardiovascular disease slightly reduced the risks of death from cardiovascular disease, death from coronary heart disease, and coronary heart disease events.[120] Similarly, another 2020 meta analysis of 40 randomized controlled trials found that taking EPA and DHA supplements reduced the risks of heart attack and coronary heart disease events (high-certainty evidence) and that they also reduced the risks of fatal heart attack and death from coronary heart disease (moderate-certainty and low-certainty evidence, respectively).[121] Although the former meta-analysis did not detect a dose-response relationship between omega−3 intake and the size of the effects, the latter meta-analysis found that the reduction in heart attack risk was dose dependent, with every 1 gram of omega−3s per day (up to 5.5 grams) reducing the risk of heart attacks by 9%.

A number of proposed mechanisms may explain howomega−3s from fish oil can improve cardiovascular health. One mechanism is the reduction of triglyceride levels, with the aforementioned Cochrane meta analysis reporting an average reduction in triglycerides of 0.24 mmol/L with supplemental omega−3. It’s also worth noting that a dose-response relationship has been reported, with omega−3 dosages of 4.4–5.5 grams/day reducing triglyceride levels the most (−0.41 mmol/L), followed by 2.4–4.4 grams/day (−0.36 mmol/L) and 0.4–2.4 grams/day (−0.18 mmol/L). Moreover, omega−3s may improve cardiovascular health by reducing inflammation and oxidative stress and by preventing plaque formation, thereby reducing the risk of atherosclerosis (hardening and narrowing of the arteries).[122]

Although most trials looking at the effects of omega−3s on cardiovascular health have used combinations of EPA and DHA, the two fatty acids may have distinct effects on membrane structure, rates of lipid oxidation, inflammatory biomarkers, and endothelial function, which means that their effects on cardiovascular health may also differ.[122]Indeed, although a 2021 meta-analysis of 38 randomized controlled trials found that supplementation with EPA and DHA reduced the risks of heart attack, coronary heart disease events, major adverse cardiovascular events, and death from cardiovascular events, the subgroup analyses of trials that used EPA alone showed greater risk reductions in the aforementioned outcomes.[123] This result might be explained by DHA’s potential LDL-increasing effects.[124] On the other hand, some evidence suggests that DHA may be more effective than EPA at reducing triglyceride levels.[125][126]

**Warnings about fish oil**

Fish oil is known to cause gastrointestinal side effects, including abdominal pain and diarrhea, in some people.[127][128] Taking fish oil with food may help avoid these unwanted side effects.[129]

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Although rare, some cases suggest that fish oil interacts with anticoagulants like

warfarin/Coumadin/Jantoven and antiplatelets like aspirin and can increase the risk of bleeding when used together.[130][131][132], especially at daily doses above 1 gram.[133] Taking fish oil alone does not appear to have this risk.[134][135] Consult with a prescriber or medical professional before taking fish oil with any of these medications.

| **Digging Deeper: Oxidized fish oil**  Fish oil can become rancid and oxidize when exposed to oxygen, heat, or light. These oils are particularly susceptible to oxidation because of their very-long-chain polyunsaturated fatty acids. The oxidation level is measured using three values.  Peroxide value (PV)  Anisidine value (AV)  Total oxidation value (TOTOX)  The PV is a measure of primary oxidation products (peroxides), and AV is a measure of secondary oxidation (aldehydes and ketones). The TOTOX value is calculated using the formula AV + 2PV. The lower the TOTOX value, the better the oil quality will be. The Global Organization for EPA and DHA Omega-3 recommends a TOTOX value of no more than 26.  Oxidation of fish oils can be highly variable. One 2015 study found that nearly 50% of commercial fish oils exceeded the maximum recommended TOTOX value,[136] whereas others have found very good compliance with TOTOX limits.[137][138] Taken together, the divergent results demonstrate just how widely the quality of commercially available fish oil supplement can be.  Evidence for the health effects of consuming oxidized fish oils is a bit mixed. For healthy individuals, it appears that there is an absence of obvious short-term health damage from consuming oxidized fish oil. One study showed no difference in circulating levels of oxidized LDL-C or inflammatory markers after 7 weeks of supplementation with oxidized fish oil.[139]  However, in people with high levels of cholesterol and triglycerides, consumption of highly oxidized fish oils can minimize its efficiency in improving metabolic markers like fasting glucose, total cholesterol, and triglycerides.[140] |
| --- |

There is some evidence of fish oil increasing the risk of atrial fibrillation, as detailed elsewhere by Examine. The risk seems to be present even at dosages as low as 1 gram/day and may be greater with EPA-only supplements than with combined EPA and DHA supplements.[123] There are still many uncertainties, including the magnitude of risk and whether or not this risk is present in people without cardiovascular disease or who are not at a high risk of cardiovascular disease.

Although DHA is marginally better than EPA at reducing triglyceride levels, it can cause a modest increase in low-density lipoprotein (LDL-C, the “bad cholesterol”).[124]

**How to take fish oil**

To support cardiovascular health, take at least 250 mg of combined EPA and DHA per day. This dose can 27

be achieved simply by eating fatty fish several times a week. Note that higher daily doses (up to 5.5 grams) may have greater effects for protection against heart attacks, but the risk-benefit relationship isn’t well understood. Due to the potential risk of atrial fibrillation, and the current uncertainty, taking such high doses — especially for the sake of prevention — may be counterproductive.

To reduce triglyceride levels, the most effective daily dose is 4.4–5.5 grams of combined EPA and DHA from eating fatty fish (e.g., 300–375 grams of salmon) or taking fish oil softgels. Again, due to the risk of atrial fibrillation, taking such high doses may be counterproductive.

Vegans and vegetarians have the option of taking algal oil softgels.

People whose LDL levels are too high could replace the EPA+DHA combination with an equal dose of just EPA.

Taking fish oil with food reduces the chance of fishy burps.

**Grape Seed**

**What makes grape seed a secondary**

**supplement**

Grape seed extract contains a high level of polyphenols, particularly proanthocyanidins, which have a number of potential beneficial effects, including facilitating nitric oxide production (thereby helping blood vessels dilate), ACE inhibition (another way it can affect blood vessel function), and antioxidative and anti inflammatory effects.[141]

A meta-analysis of randomized controlled trials found a notable reduction in systolic (−6.57; 95% CI: −10.80, −2.34) and diastolic blood pressure (−3.83; 95% CI: −5.33, −2.34) based on 15 trials.[142] An effect was found for both participants with and without hypertension, though the effect was greater for participants with higher blood pressure. The major caveat is that much of the evidence carries a notable risk of bias due to nonrigorous methods.

A meta-analysis of 11 randomized controlled trials found a small improvement in LDL cholesterol and a smaller reduction in triglycerides, without an effect on HDL.[143] Yet another meta-analysis came to similar conclusions.[144]Improving these lipids isn’t a reason to take grape seed extract, but it may be a small, gratuitous perk.

Interestingly, another meta-analysis found some evidence of a reduction in oxidized LDL when taking grape seed extract, as well as a general reduction in oxidative stress and inflammation, with all effects modest but noteworthy.[145] So although grape seed extract might not have much of an effect on lipid levels, it may prevent lipids from contributing to atherosclerosis in other ways.

For these reasons, grape seed extract is a solid secondary option. Higher quality evidence would increase our confidence in it, though its effects would most likely still be modest and potentially even smaller in more rigorous trials, as tends to be the trend in research.

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**Warnings about grape seed**

Grape seed is generally well tolerated.[146][147] One study found that a small number of participants had gastrointestinal side effects, but this was relatively uncommon.[148] Another study found headache to be an uncommon side effect, starting at doses of at least 1,500 mg, though this high of a dose is unlikely to be used by most people.[147]

Grape seed extract has been observed to inhibit CYP2C9, CYP2D6, and CYP3A4 in vitro, though it’s unclear what effects on drug metabolism this may have in the real world.[149][150] One study found that despite its effect on GYP2D6 in vitro, 300 mg of grape seed extract didn’t meaningfully affect dextromethorphan pharmacokinetics in human participants, suggesting that its effect on CYPD6 may not hold for most people. A list of drugs metabolized by various enzymes can be found here.

Taking a grape seed extract with other hypotensive agents could cause low blood pressure. Hypotensive agents can be pharmaceuticals but also supplements (e.g., garlic, notably, but also nitrates, cocoa, or pine bark extracts, to mention only the supplements presented in this guide).

**How to take grape seed**

Take 200–400 mg of a grape seed extract once per day with a meal. The higher end of this dose range may be more beneficial, but for people without elevated blood pressure, it may not confer additional benefits.

**Taurine**

**What makes taurine a secondary supplement**

Taurine is a conditionally essential, sulfur-containing amino acid that is abundant in the body –– particularly in the heart. It can be endogenously produced from methionine and cysteine and obtained from food sources such as seafood. Interest in taurine stems from its role as a cell-protecting agent by modulating cell membrane fluidity.[151]It also exerts antioxidant-like effects.[152]

Taurine has been mostly studied for its potential to reduce blood pressure. Taurine deficiency has been found to accelerate the onset of hypertension in rats on a high-salt diet and decrease blood pressure in rats with hypertension.[153][154]

Similarly, observational evidence in humans suggests that plasma taurine levels are reduced in people with hypertension.[155]

It's believed that taurine may lower blood pressure mainly by enhancing vasodilation.[156][157][158]

Taurine has also exhibited the potential to improve blood lipids by enhancing the conversion of cholesterol to bile acid in combination with increasing fecal excretion.[159][160][161]

Taurine's most notable effect in humans is blood pressure reduction. The available evidence suggests that in people with cardiometabolic abnormalities (e.g., type 2 diabetes, cardiovascular disease, liver disease), taurine reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP) by approximately 3–4.67 29

mmHg and 3 mmHg, respectively, on average.[162][163]

In the most well-conducted trial to date, supplementing with 1.6 grams/day of taurine for 12 weeks reduced SBP and DBP in people with prehypertension (i.e., SBP of 120–139 and DBP of 80–89) by 7.20 and 4.70 mmHg, respectively, on average, with larger effects in people with higher blood pressure at baseline.[164] Taurine also improved flow-mediated dilation by 3.2% compared to placebo.

For blood lipid parameters, taurine reduced total cholesterol and triglycerides by 10.87 mg/dL and 13.05 mg/dL, respectively, on average, in people with cardiometabolic abnormalities.[162] However, it doesn’t appear to have an effect on LDL-C.

**Warnings about taurine**

Trials have not found convincing evidence of adverse events that exceed those with placebo. Adverse events associated with taurine are more likely due to other ingredients in energy drinks, such as high doses of caffeine.

Taurine is generally well tolerated within the recommended dose range of up to 3 grams.[165] More research is needed to determine the maximum safe dose.[166]

Note that many energy drinks contain approximately 750 mg of taurine per serving, so people who consume energy drinks should be sure to take this source into account.[166]

Taurine can reduce blood pressure, and therefore, it’s possible that it could lead to hypotension when combined with blood pressure medication. However, this is a speculative risk and not a well-documented phenomenon.

**How to take taurine**

The daily dose typically ranges from 0.5 to 6 grams, with no reported adverse side effects across doses and supplementation periods, which is unsurprising because these amounts are significantly below the upper tolerable limit of 10 g/day.[165] The most common dosing protocol is 1.5 g/day evenly split into 3 doses.

**Venotropics**

**What makes venotropics a secondary supplement**

Note: This entry is more speculative than the others because it is based primarily on a mechanistic understanding that may not be significant in the real world. Nonetheless, it is included because it is a unique area of interest.

Venotropics can improve the rate at which the blood returns to the heart. They are used to treat chronic venous insufficiency (CVI), which is characterized by blood pooling in the extremities. Venotropics can also 30

be used to treat leg swelling caused by prolonged sitting or to reduce varicose veins.

Daflon (90% diosmin, 10% hesperidin) was the first venotropic, but it is slightly less effective than Pycnogenol. Butcher’s broom (Ruscus aculeatus) and horse chestnut (Aesculus hippocastanum) also have venotropic properties.

Pycnogenol is a patented pine bark extract standardized to 65%–75% procyanidin. Grape seed extracts, which are also rich in procyanidins, might offer similar benefits, but there is currently no study on the subject.

**Warnings about venotropics**

Reported side effects from pycnogenol use are rare but include gastrointestinal discomfort, nausea, headache, and dizziness.[167] Taking pycnogenol with food could decrease your chances of having adverse GI effects.[168]

Horse chestnut seems to be well tolerated, but some individuals may experience side effects that include gastrointestinal discomfort, headache, dizziness and itchy skin.[169]

Butcher’s broom is generally well tolerated, but more research on its safety is needed.[170][171] A case of diabetic ketoacidosis was reported in a patient who was taking butcher’s broom. People with diabetes should be cautious with butcher’s broom.[172]

Taking a combination of diosmin and hesperidin could cause gastrointestinalside effects in some people.[173][174] Diosmin may inhibit the activity of CYP3A4 and other CYPs, which are enzymes used by the body to break down many kinds of medications ranging from blood pressure medication to antibiotics.[175][176][177] People who are currently taking any prescription drugs should consult with a healthcare professional before taking diosmin.

**How to take venotropics**

Take 100–200 mg of Pycnogenol with breakfast. Alternatively, take one of the following options twice per day, 12 hours apart.

375–750 mg of butcher’s broom (i.e., 750–1,500 mg/day)

50–75 mg of horse chestnut (i.e., 100–150 mg/day)

400 mg of diosmin with 100 mg of hesperidin (i.e., 1,000 mg/day in total).

**Arginine**

**What makes arginine a secondary supplement**

Arginine (or L-arginine) is an amino acid found in protein-rich foods, including meat, poultry, fish, and some seeds and nuts. Because it is a precursor of nitric oxide (a vasodilator), arginine has been investigated for its potential effects on blood pressure. Also, some trials have looked at the potential effects of supplemental arginine on other cardiovascular risk markers, such as blood lipids, and inflammatory markers. 31

| **Question: Why the discrepancy with the Muscle Gain & Exercise Performance guide?**  Our Muscle Gain & Exercise Performance guide says that arginine likely has limited efficacy on exercise performance and cites studies suggesting limited effects of supplemental arginine on arginine status. To be honest, we don’t really know how to explain the discrepancy, but it’s possible that arginine functions differently in different contexts and may not have much additional benefit for healthy and active people, but it may very well work in the case of people with high blood pressure. What’s most important is that the evidence supports it in this context, and nitric oxide synthesis is our best explanation for why. |
| --- |

A 2011 meta-analysis of 11 randomized controlled controlled trials involving a total of 387 participants who received a median daily L-arginine dose of 9 grams (range: 4 to 24 grams/day) for a median of 4 weeks (range: 2 to 24 weeks) found that supplementation with L-arginine improved systolic blood pressure by 5.4 mmHg and diastolic blood pressure by 2.67 mmHg.[178] Although there was considerable heterogeneity in the analysis of systolic blood pressure, when 2 trials (which were the source of the heterogeneity) were excluded from the analysis, the effect of arginine on systolic blood pressure remained statistically significant but was smaller in size (−3.3 mmHg). It’s worth noting that most of the participants had normal baseline blood pressure, which means that the effects of arginine on blood pressure in people with hypertension may be more pronounced.

According to two 2019 meta-analyses, L-arginine supplementation had no effect on the concentrations of total, LDL, or HDL cholesterol in adults aged 21–74 years but improved triglyceride concentrations to a trivial degree (by approximately 6–7 mg/dL).[179][180]

One of the aforementioned meta-analyses and another 2019 meta-analysis found that supplemental L arginine had no effect on markers of inflammation (C-reactive protein, tumor necrosis factor alpha, and interleukin 6).[180][181]

With the above research in mind, we can be fairly confident that supplementation with L-arginine can improve blood pressure to a small but likely clinically meaningful degree and that it’s unlikely to meaningfully improve blood lipids or inflammatory markers.

**Warnings about arginine**

Arginine can cause adverse gastrointestinal effects such as diarrhea, nausea, and vomiting, particularly when taken as a single dose of approximately 9 grams or more, but the amount will vary among individuals.[182]

Because of arginine’s effects on blood pressure, people who are taking blood pressure medication, should talk to a doctor before taking arginine because the combination might lead to hypotension.

**How to take arginine**

Take 3 grams of L-arginine three times per day for a total daily dose of 9 grams.

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**Promising Supplements**

**D-Ribose**

**What makes D-Ribose a promising supplement**

Adenosine triphosphate (ATP) has been called “life’s energy currency” because it powers our cells. ATP levels remain depressed after events that damage the heart tissue, such as heart attacks. Without enough ATP, the heart can suffer from dysfunctions such as the inability to pump properly (and thus fill up with adequate amounts of blood).

D-Ribose is a monosaccharide that helps replenish ATP stores. Supplementation with D-ribose when ATP levels are depressed looks beneficial, but research is still limited. To date, only a handful of studies have investigated the effects of supplemental D-ribose in participants with congestive heart failure, all of whom were taking various medications to treat their condition. The majority of the participants were middle-aged or older-aged men. Preliminary evidence from the available studies suggests that D-ribose may help the heart pump blood, with results ranging from very minor effects to moderate improvements.

For example, in a 1992 trial, 20 men with coronary artery disease took either 60 grams of D-ribose or placebo daily (in four 15-gram doses) for 3 days and then performed a treadmill test. During the test, only the participants who took D-ribose showed improvement in the time it took to report moderate chest pain and in the time to ST-segment depression.[183] Moreover, in a 2003 crossover trial, 15 adults (14 men and 1 woman) with coronary artery disease and congestive heart failure took either 15 grams of D-ribose or placebo daily (in three 5-gram doses) for 3 weeks. Before and after the intervention, the researchers assessed the participants’ myocardial function and exercise capacity. D-ribose, but not placebo, improved indices of diastolic heart function and exercise tolerance.[184]

Because only a few small studies have examined the effects of D-ribose in individuals with heart failure, D ribose can only rank as a promising supplement.

**Warnings about D-Ribose**

D-ribose may lower blood sugar in a dose-dependent fashion.[185] People with diabetes or who are taking drugs that could lower blood sugar, like metformin or insulin should consult with a physician before taking D-ribose. D-ribose also may cause mild stomach upset, though it’s not clear if it’s a common occurrence. One study found this effect in 1 of 11 participants who took 20 g/day,[186], while another found this effect in 2 of 20 participants after an initial dose of 15 grams, but the effect didn’t persist throughout the study,[183] and another found no notable symptoms when taking 20 g/day.[187]

**How to take D-Ribose**

Take 5 grams of D-ribose three times per day (i.e., 15 g/day) with or without food.

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**Olive Leaf**

**What makes olive leaf a promising supplement**

The leaves of the olive tree (Olea europaea) have a high content of phenolic compounds, the most abundant of which is oleuropein.[188] Due to the potential hypotensive, antilipidemic, anti-inflammatory, and antioxidant properties of these phenolic compounds, supplementation with olive leaf extract has been purported to lower blood pressure, improve blood lipids, and modulate inflammation, thereby reducing cardiovascular risk.

**Blood pressure**: The effect of olive leaf extract supplementation on blood pressure was assessed in a 2021 meta-analysis of 2 randomized controlled trials involving a total of 80 participants with prehypertension or hypertension.[189] Compared to placebo, supplementation with 500 milligrams of olive leaf extract for 8–12 weeks reduced systolic, but not diastolic, blood pressure by an average of 5.8 mmHg. However, the certainty of the evidence was low.

**Blood lipids**: The aforementioned meta-analysis also examined the effect of olive leaf extract supplementation on blood lipids and found no benefit.

**Inflammatory markers**: The same meta-analysis also looked at the effect of olive leaf extract supplementation on three proinflammatory markers (interleukin 6, interleukin 8, and tumor necrosis factor alpha), and found that olive leaf extract reduced all three proinflammatory markers, compared to placebo,. However, these results were based on only one trial, and the certainty of the evidence was low.

Although the available research suggests that supplementing with olive leaf extract may improve systolic blood pressure and some markers of inflammation, the certainty of the evidence is low. As such, olive leaf can only rank as a promising supplement.

**Warnings about olive leaf**

One study found that some participants experienced stomach aches and headaches while taking olive leaf.[190] Overall, more research needs to be conducted because evidence is lacking on the safety of olive leaf.

Olive leaf could decrease blood pressure.[189] People who are taking blood pressure medication should talk to a doctor before starting an olive leaf supplement.

**How to take olive leaf**

Choose an olive leaf extract standardized to at least 16% oleuropein, and take 500 mg 1–2 times/day with a meal.

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**Pycnogenol**

**What makes Pycnogenol a promising supplement**

Low nitric oxide (NO) levels can cause blood vessels to narrow, leading to reduced blood flow and a higher risk for cardiovascular diseases. Like the flavonoids in cocoa and grape seeds, procyanidins and other flavonoids in pine bark can theoretically help support NO synthesis via their interaction with nitric oxide synthase. Pycnogenol is a patented pine bark extract standardized to 65%–75% procyanidin. It is the best studied source of procyanidins but is also the most expensive.

Several meta-analyses have been published on Pycnogenol’s effects on blood pressure, but the most rigorous one (which required the included trials to be randomized and double blinded) didn’t find a meaningful effect on blood pressure,[191] whereas the others found a small but notable effect.[192][193]It’s possible that more high-quality trials, particularly in participants with hypertension, could yield different results; of the trials evaluated by the more rigorous meta-analysis, only 1 trial recruited participants with hypertension, but just barely surpassing the 140 mmHG systolic blood pressure, while 2 trials recruited participants with prehypertension. However, these studies didn’t observe greater effects, so it can’t be said that this result is likely.

The effects of Pycnogenol on blood lipids were reviewed in a meta-analysis of randomized controlled trials that included 14 studies with a total of 1,065 participants.[194]It was unable to confirm an improvement in LDL or triglycerides, but there was a small but statistically significant increase in HDL.

A meta-analysis of 5 controlled trials with a total of 324 participants found a reduction in C-reactive protein, though more high-quality trials are needed to confirm this.[195]

Overall, Pycnogenol may have some benefits, but the evidence doesn’t make it look very useful, especially compared with mechanistically similar (cocoa, grape seed extract) supplements in this guide.

**Warnings about Pycnogenol**

The reported side effects from Pycnogenol use are rare but include gastrointestinal discomfort, nausea, headache, and dizziness.[167] Taking Pycnogenol with food could decrease the chances of having adverse gastrointestinal effects.[168]

Taking a pine bark extract with other hypotensive agents could cause low blood pressure. Hypotensive agents can be pharmaceuticals but also supplements (e.g., garlic, notably, but also nitrates, cocoa, or grape seed extracts, to mention only the supplements presented in this guide).

**How to take Pycnogenol**

Take 100–200 mg of Pycnogenol once per day with a meal.

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**Citrulline**

**What makes citrulline a promising supplement**

Citrulline (or L-citrulline) is an amino acid found primarily in cucurbits, such as watermelons, cucumbers, and other melons. By increasing the endogenous synthesis of L-arginine and, ultimately, nitric oxide levels, supplementation with L-citrulline supplementation may improve blood pressure. However, the research examining the potential hypotensive properties of L-citrulline has provided mixed results.

More specifically, a 2018 meta-analysis of 5 randomized controlled trials in 114 participants found that daily supplementation with 3–6 grams of L-citrulline for 1–8 weeks in healthy adults had no effect on central or peripheral systolic or diastolic blood pressure.[196] On the other hand, a more recent (2019) meta-analysis of 8 randomized controlled trials in 204 participants found that supplementation with 3–9 grams per day of L citrulline for 1–17 weeks in (mostly) healthy adults improved systolic, but not diastolic, blood pressure.[197] However, the improvement (decrease) in systolic blood pressure was only −4.1 mmHg, which is less than with many other supplements, though likely clinically meaningful.[35] With the above said, it’s worth keeping in mind that the 95% confidence intervals ranged from −8.0 to −0.3 mmHg and that there was considerable heterogeneity in the analysis (the source of which was not identified). This means that the effect of L citrulline on systolic blood pressure may range from small (but clinically meaningful) to trivial and that the factors that can affect this variability in effect size are currently unknown.

With the above in mind, L-citrulline can currently only rank as a promising supplement. **Warnings about citrulline**

Unlike arginine, citrulline doesn’t seem to have the same negative effects on gastrointestinal health at high doses.[198]

Because of citrulline’s effects on blood pressure, people who are taking blood pressure medication should talk to a doctor before taking arginine because the combination might lead to hypotension.

**How to take citrulline**

Take 3 grams of L-citrulline two times per day (with or without food) for a total daily dose of 6 grams.

**Spirulina**

**What makes spirulina a promising supplement**

Spirulina (Arthrospira platensis) is a common species of cyanobacteria. This blue-green algae is thought to be one of the oldest lifeforms on Earth. Spirulina grows in both fresh and saltwater sources and is known for its high micronutrient content — including carotenoids, phycocyanin, tocopherols, B vitamins, copper, manganese, magnesium, iron, selenium, and zinc, as well as various phenolic compounds.[199][200], With a 36

protein content of 71%, spirulina also represents one of the richest natural sources of protein ever discovered. Its high nutritive value has made spirulina attractive as a food supplement and nutraceutical — so attractive, in fact, that blue/green algae have been considered as a food supplement for long-term space travel by both NASA and the European Space Agency.[199] Here on Earth, spirulina is still better known for its application in the prevention and treatment of various aspects of metabolic disease, including obesity, type II diabetes, and hyperlipidemia.[201][199] Efforts to pinpoint the metabolic benefits of spirulina to one of its various chemical constituents have been futile. Research does point to specific phycocyanins, which are pigment-binding proteins that contribute to spirulina's characteristic blue(-ish)/green color. In view of these proteins’ extraordinary antioxidant, anti-inflammatory, and antitumor effects in laboratory studies,[202] supplement producers have also started to offer products that are standardized for a given phycocyanin content. However, any putative advantages of higher phycocyanin contents have not been confirmed in clinical trials. Moreover, it cannot be excluded that either individual or synergistic effects due to other chemicals in the algae might contribute to its reported health benefits. If this is the case, purified extracts may even be less effective than regular freeze-dried or spray-dried preparations. There's good evidence that spirulina supplements at dosages of 1–19 g/day promote a healthier lipid profile in various subject populations. A 2018 review and meta-analysis of 12 clinical trials with study durations of 2–24 weeks found significantly lowered total cholesterol (TC) (−36.60 mg/dL; p=0.0001), low-density lipoprotein cholesterol (LDL-C) (−33.16 mg/dL; p=0.0002), triglycerides (−39.2 mg/dL; p=0.0001), and very-low density lipoprotein cholesterol (VLDL-C) (−8.02 mg/dL; p=0.0001) but only barely significant increases in high-density lipoprotein cholesterol (HDL-C) (+5.81 mg/dL; p=0.05).[203]In this meta-analysis, larger improvements of blood lipids were reported by studies using 2 grams per day or more of spirulina and intervention lengths of 12 weeks or longer. Similarly significant but generally smaller benefits have been reported in a more recent meta-analysis by Hamedifard et al.[201]. Unlike the previously cited meta analysis,[203] which also included studies in healthy and normal-weight participants, as well as participants with HIV infection, ischemic heart disease, and hyperlipidemic nephrotic syndrome, this more recent 2019 meta-analysis focused on clinical trials in participants with overweight and obesity. Compared to the effects on lipid levels, spirulina’s antihypertensive (blood pressure lowering) effects must be considered as less well established. There are two clinical trials showing reductions in systolic blood pressure (SBP) ranging from 6 mmHg to 14 mmHg.[204][205] One of these studies reported a concomitant improvement in arterial stiffness.[204] None of the studies reported a significant treatment effect on diastolic blood pressure. Moreover, at least 3 related studies report no significant effects of spirulina powder or extracts on either SBP or DBP.[206][207][208] Based on that background, it should be clear that more research is necessary to determine whether spirulina has general hypotonic effects or if these effects occur only in specific participant groups. Even less evidence is available on spirulina's effects on lipid oxidation. Only 2 studies measured its effects on cholesterol oxidation.[209][210] Both studies reported reduced oxidative damage to blood lipids, but their generalizability is very limited because both measured the increase in lipid oxidation after intense exercise interventions. Studies investigating the long-term effects of chronic spirulina supplementation on the actual risk of CVD, CAD, or stroke are not available. In the absence of this kind of “hard evidence” of heart-protective effects, spirulina should be classified as a promising (but not a secondary or primary) supplement for heart health, with effects that are primarily mediated by its established lipid-lowering effects in people with overweight/obesity and with preexisting heart problems.

**Warnings about spirulina**

Spirulina supplements can become contaminated with toxic microcystins and BMAA from other types of cyanobacteria and microorganisms.[211][212] Early testing in 1998 and 1999 discovered potentially worrisome levels of microcystins.[213] However, the supplement industry seems to have largely cleaned up the production process, and in 2017, a report found that only 3 out of 14 products had meaningful levels of 37

microcystins. Additionally, other reports from the U.S., German, and Italian markets didn’t find detectable levels of microcystins.[214][215][216] Similar information isn’t available for BMAA contamination, but the same methods used to reduce other cyanobacteria and microorganisms in spirulina will likely also help to reduce BMAA contamination.

Mercury, platinum, lead, and arsenic levels in spirulina products don’t appear to be excessively high, though it is possible that some products could be dangerous.[217][218] Needless to say, it’s always wise to purchase supplements from brands that do rigorous third-party testing to ensure safe products.

Spirulina has been found to reduce the activity of CYP1A2, CYP2E1 and CYP2C6, enzymes that are responsible for metabolizing a variety of drugs and whose inhibition may lead to overdose-like effects. Some of the relevant drugs can be found here, but people who take medications should talk to a doctor or a pharmacist.

**How to take spirulina**

Take at least 2 grams per day of spirulina powder split across meals, preferably for at least 3 months. Although studies report the use of up to 19 grams of spirulina powder per day[219], the results of the previously cited meta-analyses suggest that a comparatively moderate dose of 2 or more grams per day of spirulina powder with meals will suffice to elicit significant and potentially health-relevant beneficial effects on blood lipids. Evidence of a linear dose-response relationship does not exist. Longer studies (≥12 weeks) have yielded better results than short interventions. Whether the currently available supplements with standardized amounts of phycocyanins offer a significant advantage over the regular freeze-dried or spray-dried formulations has not been tested in clinical trials. Moreover, phycocyanins are only one group of molecules that could be responsible for the heart health effects of spirulina supplements, and individual or synergistic contributions of other chemicals cannot be excluded.

**Arjuna**

**What makes arjuna a promising supplement**

Water extracts from the bark of the arjuna (Terminalia arjuna) tree have long been used in Ayurvedic medicine to improve cardiovascular health. Preliminary studies support this traditional use, but the quality and generalizability of the few existing human studies raises questions about its usefulness as a dietary supplement — particularly as a preventative measure in healthy individuals. Several studies have reported measurable beneficial effects of arjuna powder or extracts on heart disease risk markers in participants with preexisting heart conditions, including those with established heart failure[220] and participants with stable coronary artery disease (CAD)[221] or coronary heart disease (CHD).[222] Benefits were also observed in a group of participants with overweight/obesity and hypertension or prehypertension.[223] Clinical trials with healthy participants are not available. Compared to placebo, Arjuna supplements triggered significant improvements in blood lipids in 3 studies,[222][221][223] and an improvement in the exercise capacity of participants with chronic stable angina in 1 study.[224] Two studies reported large reductions (more than −30%) in triglycerides[221][223] and VLDL-C.[221] Significant reductions were also observed for LDL-C and total cholesterol levels,[221][225][222] as well as lipid oxidation and selected markers of inflammation.[222][221][222] When an active comparator in the form of statins was used, however, neither reductions in blood lipids nor direct 38

beneficial effects on blood flow were observed.[220] Overall, the evidence on the usefulness of Arjuna supplements to promote heart health and reduce cardiovascular disease risk must be considered preliminary. Additional clinical studies should recruit ethnically more diverse subject groups, include (or at least facilitate) dose-response analyses, and investigate the use of Arjuna supplements as a preventative measure in heart-healthy individuals.

**Warnings about arjuna**

There is insufficient evidence for adverse events in human trials, so Arjuna can’t be considered to be particularly dangerous or particularly safe.

Arjuna was found to inhibit CYP1A, CYP3A, and CYP2D enzymes in rat liver microsomes in vitro.[226][227][228] Some drug interactions associated with various CYP enzymes are listed here.

**How to take arjuna**

Take 1.5 g/day of an Arjuna extract, divided into 2 or 3 servings per day, with water. The amount of Arjuna used in the 4-week to 12-week studies ranged from 500 mg/day of Arjuna bark powder to 2x5000 mg/day of Arjuna powder with a median dosage of 1.5 g/day of different Arjuna extracts. All supplements came in capsule form, and the total amount was often split across the day and taken with water in 2-3 smaller servings. In the absence of dose-response studies and in view of the heterogeneous participants pools in the existing clinical trials, it is difficult to estimate the optimal supplementation protocol. In this context, it may be noteworthy that the most recent study of Arjuna’s heart health benefits used 5 g/day of regular Arjuna powder.[223] These results raise the question as to whether extracts, especially those that are standardized for Arjunetin (one of Arjuna’s purported primary active ingredients[229]~~)~~, which were used in two of the previously discussed studies,[220][224] offer relevant advantages over standard preparations.

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**Unproven Supplements**

**CoQ10**

**What makes CoQ~10 an unproven supplement**

Coenzyme Q10 (CoQ10) is a molecule with vitamin-like properties. Although it is nonessential, CoQ10 is vital in the body. It is most abundant in mitochondria and is critical for ATP production due its participation in the electron transport chain.

CoQ10 is also an important part of the body’s antioxidant system. It helps to protect mitochondrial and cell membranes from oxidative stress and can recycle other powerful antioxidants (e.g., vitamin E) back to their active form.[230]

CoQ10 can be endogenously synthesized by all human cells. However, its synthesis appears to diminish with aging, with increased stress from chronic disease, and with statin therapy,[231] which has led to interest in its use as a coadjuvant treatment for a variety of conditions.[232]

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**How statins lower CoQ~10~**

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The effect of CoQ10 on blood lipids has been investigated in participants with various cardiometabolic conditions (e.g., coronary artery disease, type 2 diabetes). The results have been inconsistent but generally point toward little to no beneficial effect.[233][234][235]

When a positive result has been reported, either the magnitude of effect was small and unlikely to be clinically meaningful or the effect was driven by an outlier study, and the removal of said outlier made the result no longer statistically significant. With respect to blood pressure, it’s a similar story.[236]

However, in people with cardiometabolic conditions, CoQ10 appears to reduce oxidative stress and boost the activity of enzymes involved in the antioxidant defense system. More specifically, CoQ10 has a large effect on reducing malondialdehyde levels (a marker of lipid peroxidation; the process by which free

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radicals attack the fatty acids that make up cell membranes) in addition to increasing total antioxidant capacity and superoxide dismutase activity with a small to large effect, depending on the unique disease state.[237][238]

CoQ10 also has a small positive effect on inflammation. It’s been found to reduce tumor necrosis factor alpha and interleukin 6 levels,[239] and limited evidence suggests it can reduce C-reactive protein in people with elevated levels (>3 mg/L) at baseline.[240]

CoQ10 may be a secondary supplement for reducing oxidative stress, but its minor effect on inflammation and lack of influence on blood lipids and blood pressure makes it an unproven supplement overall for cardiovascular health.

**Resveratrol**

**What makes resveratrol an unproven supplement**

Resveratrol is a natural polyphenol found in grapes, nuts, and berries, and most notably, red wine. Resveratrol is produced by plants as a defense mechanism against environmental threats and exists as two isomers: trans-resveratrol and cis-resveratrol, and the former is responsible for resveratrol’s effects in the body.

The buzz surrounding resveratrol stems from its impressive and wide-ranging effects in cell culture and animal studies, namely, reductions in oxidative stress and inflammation, which play major roles in the development of cardiovascular disease.[241]It does this by directly scavenging free radicals,[242][243] reducing the production of reactive oxygen species,[244] upregulating antioxidant enzymes,[245] and inhibiting the production of proinflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin 6).[246]

Resveratrol has also been shown to improve markers of insulin sensitivity, blood pressure, and blood lipids in rodents.[247][248][249][250][251]

Despite abundant mechanisms and a robust body of evidence from nonhuman studies, human trials have not panned out as might be expected. Most notably, resveratrol supplementation has little to no effect on blood lipids or blood pressure,[252][253][254][255][256][257] although limited evidence suggests it may improve flow mediated dilation in people with metabolic syndrome.[257]

With respect to markers of inflammation, resveratrol has a small effect on high sensitivity C-reactive protein (−0.40 mg/L) in people with systemic inflammation due to various conditions.[258] Resveratrol may also reduce tumor necrosis factor alpha in people with overweight (−0.56 pg/mL) and interleukin 6 in people with elevated levels (≥3 pg/mL).[259][252][259]

Overall, the current evidence does not support the use of resveratrol for managing cardiovascular disease risk. It has failed to improve critical outcomes, and for other outcomes, either the certainty of evidence was low (i.e., based on a small number of studies and/or substantial heterogeneity in the analysis) or the magnitude of effect was unlikely to be clinically meaningful.

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**Vitamin K**

**What makes vitamin K an unproven**

**supplement**

Vitamin K is an umbrella term for a group of fat-soluble molecules with similar but distinct structures:

K1(phylloquinone) is found in plants and is mainly derived from dark-green leafy vegetables.

K2 (menaquinone) refers to several molecules that differ in the number of isoprenoid units in the side chain and is mainly derived from dairy products, meat, and eggs.

**The K vitamins**

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Vitamin K is thought to reduce the risk of cardiovascular disease (CVD) because there are vitamin K dependent proteins in vascular tissue, such as \_matrix Gla protein\_ (MGP), that inhibit calcification, and vascular calcification is indicative of atherosclerotic CVD.[260][261]

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| **Digging Deeper: How does vitamin K affect calcification?**  Vitamin K is a necessary cofactor for enzymes that catalyze some carboxylation reactions, a process in which a molecule of carbon dioxide is transferred onto one of over a dozen different proteins in the body.  In the case of the enzyme gamma-glutamyl carboxylase (GGCX), for example, vitamin K likely gets oxidized to facilitate the removal of a proton from a glutamate residue in a protein — a removal needed for GGCX to carboxylate the protein in a following step.[262][263]  On the protein, this process creates a chemical group resembling a two-pronged claw and carrying two negative charges. This group can grab free calcium ions, which each carry two positive charges. The protein can then transport these ions and utilize them as needed, resulting in effects on blood coagulation, bone metabolism, and possibly the removal of calcium from arteries.  **The carboxylation mechanism of vitamin K**    Put simply, vitamin K makes a bunch of proteins that are good at grabbing calcium and moving it around in the body as needed. |
| --- |

In support of this theory, evidence from prospective cohort studies suggested that higher dietary intakes of phylloquinone and menaquinone were associated with an 8% and 30% lower risk of coronary heart disease, respectively.[264]

Moreover, higher plasma dephospho-uncarboxylated MGP levels (dp-ucMGP; a marker of vitamin K deficiency; when vitamin K status is low, less MGP gets carboxylated, resulting in elevated levels of up ucMGP) are associated with the development and progression of CVD in addition to an increased risk of mortality.[265][264]

Based on this information, it’s clear that getting enough vitamin K from the diet is important, but the question remains, does supplementing with vitamin K above the minimum amount needed to avoid deficiency-related issues reduce the risk of CVD?

A 2020 systematic review investigated the effect of vitamin K supplementation on cardiovascular 44

parameters.[266]It included 9 randomized controlled trials, 3 of which had participants supplement with 500– 2,000 µg/day of vitamin K1, and the other 6 had participants supplement with 90–2,000 ug/day of vitamin K2. All of the studies were at least 12 weeks long, and most studies included healthy participants (5 studies), whereas the rest included people with impaired kidney function or type 2 diabetes.

At large, vitamin K supplementation had little-to-no effect on vascular calcification, atherosclerosis, or arterial stiffness. Positive results were in short supply, but we mention a couple of thought-provoking findings.

In a 3-year randomized controlled trial, 388 healthy older adults (ages 60–80) received a daily multivitamin with or without 500 µg of vitamin K1.[267]In the participants who took the supplement at least 85% of the time and had mild coronary artery calcification (CAC) at baseline, vitamin K1reduced the progression of CAC by 6% compared with the control group.

In another 3-year randomized controlled trial, 180 µg/day of MK-7 improved arterial stiffness in healthy postmenopausal women.[268] MK-7 also improved the elastic properties of the carotid artery in women with high arterial stiffness at baseline.

Together, these studies suggest that long-term vitamin K supplementation (≥3 years) may improve cardiovascular parameters in relatively healthy older adults with mild risk factors. However, due to an absence of evidence to support that these changes lead to a reduced risk of CVD events, in combination with a lack of effect of vitamin K supplementation in many other studies, vitamin K is currently listed as an unproven supplement.

For people still considering supplementing with vitamin K, it’s important to mention that this strategy is ill advised if taking a blood thinner (e.g., warfarin/Coumadin/Jantoven and

acenocoumarol/Sintrom/Nicoumalone) because they produce their effect by impairing vitamin K’s blood clotting properties.

Micrograms of vitamin K per 100 grams of food

| **FOODS** | **K~1~** | **K~2~ MK-4** | **K~2~ MK-7** |
| --- | --- | --- | --- |
| Collards | 440 | 0 | 0 |
| Spinach | 360–380 | 0 | 0 |
| Broccoli | 113–180 | 0 | 0 |
| Cabbage | 98–145 | 0 | 0 |
| Natto | Not measured | 0 | 939–998 |
| Chicken | 0–4.5 | 8.5–60 | 0 |
| Pork | 0–3.4 | 2.1–6 | 0.5–0.12 |
| Beef | 0.7–2.4 | 1.1–15 | 0–0.12 |
| Beef liver | 2.7 | 0.82 | 18.2 |
| Egg | 0.3–12 | 7–9 | Not measured |
| Egg yolk | Not measured | 15.5–64 | 0 |
| Butter | 7 | 15–21 | 0 |
| Blue cheese | Not measured | Not measured | 2.5–22 |
| Cheddar | 2.1 | 10.2 | 0–2.3 |

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**Inadvisable Supplements**

**Caffeine**

**What makes caffeine an inadvisable supplement**

People with heart problems are more likely to suffer from the adverse effects of high doses of caffeine, which include increased blood pressure and potentially a greater risk of traumatic cardiovascular injuries such as heart attacks, though this is still speculative, and studies are mixed and inconsistent.[278]

People who choose to take caffeine should respect the recommended dose (typically no more than 400 mg per day). If tolerance develops, do not increase the dosage, but stop using the stimulant long enough for sensitivity to return.

It’s easy to inadvertently consume too much caffeine When calculating daily intake, consider all beverages, foods, and supplements. Bear in mind that caffeine can be “hidden” in a product — for instance, if “guarana seeds” appears on a label, remember that they are richer in caffeine than coffee beans.

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**Caffeine upper limit (400 mg) in number of drinks**

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References: McCusker et al. J Anal Toxicol. 2006.[279] ● Desbrow et al. Nutr Health. 2019.[280] ● Ludwig et al. Food Funct. 2014.[281] ● Fox et al. J Agric Food Chem. 2013.[282] ● McCusker et al. J Anal Toxicol. 2003.[283] ● Angeloni et al. Food Res Int. 2019.[284]

**Vitamin D**

**What makes vitamin D an inadvisable supplement**

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Vitamin D is a cholesterol-based fat-soluble vitamin that is essential for human survival. It is unique in that it can be consumed via foods like fish and eggs and can also be synthesized in the skin by ultraviolet light from sun exposure.

Vitamin D receptors (VDR) are found in almost all human tissues, including in the cardiovascular system.[285][286] The interaction between vitamin D and VDR produces several beneficial effects, including a reduction in blood clotting, an inhibition of oxidative stress, an improvement of endothelial repair, and vascular relaxation and dilation.[287][288]

Along with vitamin D’s pivotal role in cardiac and vascular function, observational studies have consistently reported an inverse association between 25-hydroxyvitamin D (25(OH)D) levels and cardiovascular disease (CVD) risk factors, events, and mortality.[289][290]

The optimal 25(OH)D level needed to support overall health is individual and debatable. Nevertheless, the Endocrine Society recommends that 25(OH)D levels should exceed 30 ng/mL.[291] At the very least, it’s generally agreed that greater than 20 ng/mL is sufficient for the vast majority of people, and the risk of adverse effects associated with deficiency incrementally increases below this threshold.[292][293]

In terms of the prevalence of vitamin D inadequacy (i.e., <20 ng/mL), it’s estimated that approximately 24%, 37%, and 40% of the population of the United States, Canada, and Europe, respectively, do not meet adequate 25(OH)D levels.[294][295][296]In other parts of the world, the prevalence of vitamin D inadequacy has been estimated to be even greater, such as in Israel (50%),[297] Japan (54%), and northwestern China (75.2%).[298]

Because vitamin D is critical for cardiovascular health, and because most people do not have sufficient 25(OH)D levels, supplementing with vitamin D may be a feasible solution to improve CVD-related outcomes.

With respect to CVD risk factors, vitamin D supplementation was found to trivially decrease total cholesterol (–3.69 mg/dL), low-density lipoprotein cholesterol (–2.92 mg/dL), and triglyceride (–6.92 mg/dL) levels.[299] However, these beneficial effects were only apparent in individuals with vitamin D inadequacy (≤20 ng/mL) at baseline. Vitamin D supplementation also largely does not affect endothelial function.[300]

In line with its paltry effects on blood lipids and endothelial function, a 2021 meta-analysis of 65 randomized controlled trials demonstrated that vitamin D supplementation does not affect the risk of CVD events or CVD mortality.[301] However, most of the included studies had a short intervention duration (<1 year). Does long-term vitamin D supplementation reduce the risk of CVD events and/or CVD mortality?

The short answer is no.

In a 2022 randomized controlled trial, 2,495 white Finnish older adults (average age of 68) with an average baseline 25(OH)D level of 30 ng/mL who were free of CVD ingested a placebo, 1,600 IU of vitamin D3, or 3,200 IU of vitamin D3 daily for an average of 4.3 years.[302] There was no difference between groups for the incidence of major CVD events (i.e., heart attack, stroke, CVD mortality).

In another 2022 randomized controlled trial, 21,310 Australian older adults (average age of 69) ingested either a placebo or 60,000 IU of vitamin D3 monthly for 5 years. There was no difference between groups for CVD mortality.[303] A limitation of this trial was that 25(OH)D levels were not assessed at baseline, but they were measured on a yearly basis, and the researchers used the average levels at year one (31 ng/mL) in the placebo group to estimate baseline levels in both groups. It was estimated that 24% of participants 49

had 25(OH)D levels of <20 ng/mL.

In a 2019 randomized controlled trial, 25,871 participants (average age of 67; 20% African American), with median 25(OH)D levels of 31 ng/mL who were free of CVD, ingested a placebo, 2,000 IU of vitamin D3, or 1,000 mg of fish oil daily for a median of 5.3 years.[304] There was no difference between the vitamin D3 and placebo groups for the incidence of major CVD events, and the results did not differ when the participants were stratified by baseline 25(OH)D levels (i.e., below or above the cohort median of 31 ng/mL).

In a 2017 randomized controlled trial, 5,108 participants (average age of 66) with an average baseline 25(OH)D level of 25 ng/mL ingested either a placebo or 100,000 IU of vitamin D3 monthly for a median of 3.3 years.[305] There was no difference between groups for the incidence of CVD events, and the results did not differ in participants with vitamin D inadequacy or previous CVD.

Collectively, these trials demonstrate that in populations of older adults with a relatively low prevalence of vitamin D inadequacy at baseline, vitamin D supplementation does not reduce the risk of CVD events or CVD mortality. Additionally, subgroup analyses indicated that the results did not differ according to baseline 25(OH)D levels. With that said, it remains possible that a trial in a large number of participants with extremely low vitamin D levels (i.e., <12 ng/mL) would show stronger CVD risk reduction with vitamin D supplementation.

Vitamin D supplementation may provide benefit in the latter stages of CVD. Heart failure is characterized by structural and/or functional abnormalities in the heart that impair ventricular filling or the ejection of blood to the rest of the body. In this population, evidence suggests that vitamin D supplementation may increase ejection fraction by 3.3%, on average.[306]

Additionally, vitamin D may indirectly improve CVD outcomes. Statins are generally well tolerated, but there is a subset of individuals who experience side effects, most commonly muscle aches and weakness, which can lead them to stop using the medication.

Low 25(OH)D levels have been associated with statin intolerance, and evidence suggests that vitamin D supplementation can improve statin tolerance. More specifically, in individuals with 25(OH)D levels of 21–23 ng/mL, increasing 25(OH)D levels to at least 40 ng/mL improved statin tolerance in 87%–88% of cases.[307][308]

Overall, for people whose 25(OH)D levels are low and who are unable to alter their diet to get more vitamin D or spend more time in the sun, it’s a good idea to supplement with vitamin D to support overall health. However, the current evidence suggests that vitamin D supplementation is unlikely to significantly improve CVD risk factors or reduce the risk of CVD events or mortality. There may be niche cases in which vitamin D supplementation can provide CVD-related benefits, but for most people, supplementing with vitamin D is inadvisable to improve CVD outcomes.

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**FAQ**

**Q. What about the supplements not covered in this guide?**

Our guides are regularly updated, often with new supplements. We prioritize assessing (and reassessing) the most popular of them and those most likely to work. However, if there is a specific supplement you’d like to see covered in a future update, please let us know by filling out this survey.

**Q. Can I add a supplement not covered in this guide to my combo?**

Supplement with your current combo for a few weeks before attempting any change. Talk to your physician and research each potential addition. Check for known negative interactions with other supplements and pharmaceuticals in your current combo, but also for synergies. If two supplements are synergistic or additive in their effects, you might want to use lower doses of each.

**Q. Can I modify the recommended doses?**

If a supplement has a recommended dose range, stay within that range. If a supplement has a precise recommended dose, stay within 10% of that dose. Taking more than recommended could be counterproductive or even dangerous. Taking less could render the supplement ineffective, yet starting with half the regular dose could be prudent — especially if you know you tend to react strongly to supplements or pharmaceuticals.

**Q. At what time should I take my supplements?**

The answer is provided in the “How to take” section of a supplement entry whenever the evidence permits. Too often, however, the evidence is either mixed or absent. Starting with half the regular dose can help minimize the harm a supplement may cause when taken during the day (e.g., fatigue) or in the evening (e.g., insomnia).

**Q. Should I take my supplements with or without food?**

The answer is provided in the “How to take” section of a supplement entry whenever the evidence permits. Too often, however, the evidence is either mixed or absent. Besides, a supplement’s digestion, absorption, and metabolism can be affected differently by different foods. Fat-soluble vitamins (A, D, E, K), for instance, are better absorbed with a small meal containing fat than with a large meal containing little to no fat.

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**Q. What are DRI, RDA, AI, and UL?**

The Dietary Reference Intakes (DRIs) is a system of nutrition recommendations designed by the Institute of Medicine (a US institution now known as the Health and Medicine Division). RDA, AI, and UL are part of this system.

Contrary to what the name suggests, a Recommended Dietary Allowance (RDA) doesn’t represent an ideal amount; it represents the minimum you need in order to avoid deficiency-related health issues. More precisely, it represents an amount just large enough to meet the minimum requirements of 97.5% of healthy males and females over all ages — which implies that the RDA is too low for 2.5% of healthy people.

The Adequate Intake (AI) is like the RDA, except that the number is more uncertain.

The Tolerable Upper Intake Level (UL) is the maximum safe amount. More precisely, it is the maximum daily amount deemed to be safe for 97.5% of healthy males and females over all ages — which implies that the UL is too high for 2.5% of healthy people.

As a general rule, a healthy diet should include at least the RDA of each nutrient — but less than this nutrient’s UL. This rule has many exceptions, though. For instance, people who sweat more need more salt (i.e., sodium), whereas people who take metformin (a diabetes medicine) need more vitamin B12.

Moreover, the DRIs are based on the median weight of adults and children in the United States. Everything else being equal (notably age, sex, and percentage of body fat), you likely need a lesser amount of nutrients if you weigh less, and vice versa if you weigh more. The numbers, however, are not proportional — if only because the brains of two people of very different weights have very similar needs. So you can’t just double your RDIs for each nutrient if you weigh twice as much as the median adult of your age and sex (even if we overlook that people weighing the same can differ in many respects, notably body fat).

**Q. Why don’t you mention vitamin K3?**

K~~1~~ and K~~2~~ are the only natural forms of vitamin K, but there exist several synthetic forms, the best known of which is K~~3~~. However, whereas the natural forms of vitamin K are safe, even in high doses, K3 can interfere with glutathione, your body’s main antioxidant.

K3 was once used to treat vitamin K deficiency in infants, but it caused liver toxicity, jaundice, and hemolytic anemia. Nowadays, it is used only in animal feed, in small doses. In animals, vitamin K3 gets converted into K2 MK-4, which you can consume safely.

**Q. Can nitric oxide (NO) supplements be combined?**

Yes, they can. Rather than being mutually redundant, the three types of NO supplement in this guide are synergistic. Each has a different mechanism of action. The flavonoids in cocoa, grape seeds, or pine bark can increase the rate of NO production, whereas nitrates bring raw material your body can turn into NO without help from the nitric oxide synthase (NOS) enzyme. As for garlic, it enhances NO signaling, but its lowering action on blood pressure is mostly due to its enhancing hydrogen sulfide (H2S) signaling. 52

**Q. Can I get enough nitrates from fruit?**

In short, no. Even “nitrate-rich” fruits, such as melons and strawberries, pale in comparison to most vegetables. Compare, for instance, 100 g of beetroot (199.2 mg of nitrates) with 100 g of melon (32.5 mg), strawberries (17.2 mg), banana (7.6 mg), apple (2 mg), or orange (0.9 mg).

**Q. What can I do to help prevent my fish oils from oxidizing?**

Since fish oil is primarily polyunsaturated fat, it is prone to becoming rancid and oxidizing. Oxidation largely depends on exposure to heat, light, and oxygen. The addition of antioxidants to the final product can reduce the rate of oxidation during storage. Vitamin E is typically used, but there’s a lot of research on other antioxidants like carnosic acid suggesting they might be superior.[309]

Part of the responsibility for ensuring fish oil remains unoxidized is on the buyer. Exposure of fish oil to light, heat, and oxygen accelerates the oxidation of the oil, with the magnitude of damage depending on the length and degree of exposure. Once you buy the supplement, it is prudent to store it in a cool place away from light, such as the fridge.

If you buy oil in a bottle, the bottle should be tinted to prevent light from getting through and small enough that you can work through it in a month or two. After all, oxygen gets in the bottle every time you open it. Some fish oil bottles come with a pump, which can help reduce oxygen exposure. Buying capsules instead of bottles can also help prevent oxidation.

**Q. Wait, where’s calcium?**

While calcium supplementation may promote cardiovascular health and reduce blood pressure, it may also increase the risk of hypercalcemia (dangerously high levels of calcium in the blood), potentially contributing to heart disease, the leading cause of death among older adults in the United States. When paired with vitamin D, there is a possible increased risk of stroke.[310] The evidence on heart health is mixed and still developing; whether or not the potential benefits outweigh the potential harm is still to be determined.

**Q. If I have a heart condition, can I still have caffeine?**

In healthy adults, caffeine intake of up to 400 mg/day has not been linked to increases in cardiovascular disease risk.[278][311] However, if you have high blood pressure or pre-existing heart conditions (in other words, in people for whom stimulants in general are contraindicated), the long-term effects of regular caffeine intake are uncertain[278][312]. Low to moderate intake may be OK, but this should be assessed on a case-by-case basis in consultation with a physician.

**Q. How is hypertension (i.e., high blood pressure) defined?**

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Blood pressure is usually reported in two numbers. For example, a reading of 120/80 mmHg. The first number, systolic blood pressure, tells us how much pressure your blood is exerting against the arterial walls when your heart contracts. The second number, diastolic blood pressure, signifies how much pressure your blood is exerting when the heart is relaxed and being refilled with blood. Blood pressure measures are generally divided into the four categories seen below.

Blood pressure category cutoffs (mmHg)

| **CATEGORY** | **SYSTOLIC** | **DIASTOLIC** |
| --- | --- | --- |
| Normal blood pressure | <120 | <80 |
| Elevated blood pressure | 120–129 | <80 |
| Stage 1 hypertension | 130–139 | 80–89 |
| Stage 2 hypertension | ≥140 | ≥90 |

Adapted from Whelton et al. Hypertension. 2018.[313]

**Q. What are the effects of lifestyle interventions on blood pressure?**

Clinically, even a small 2 to 5 mmHg decrease in systolic blood pressure (SBP) can noticeably reduce cardiovascular disease and total mortality.[314] Hypertension (i.e., high blood pressure) can be handled using a multitude of approaches, which are often better in combination than they are in isolation. However, here are how individual treatments alone can affect your blood pressure.[315][316][317][318][319]

Effects of lifestyle interventions on systolic blood pressure\* (mmHg)

| **INTERVENTION** | **SBP**  **REDUCTION** | **CAVEAT** |
| --- | --- | --- |
| Protein intake | 2–3 | Depends on baseline protein intake. Minimum effective dose unknown. |
| Weight loss | 5–20 | About 1 mmHg for every 1 kg (2.2 lb) reduction in body weight.The effect eventually plateaus as body weight normalizes. |
| DASH diet | 8–14 | Depends on the baseline diet pattern. The DASH diet tested was rich in fruits and vegetables and low in fat and saturated fat. |
| Salt intake  reduction | 2–8 | Depends on baseline salt intake. Aim for at least a 1,000 mg (1 g) reduction. |
| Potassium intake increase | 4–5 | With an intake of 3,500–5,000 mg (3.5–5 g) per day, particularly from potassium rich foods. |
| Increased  physical activity | 4–9 | A mix of endurance and resistance may be more effective than either alone. |
| Alcohol intake  reduction | 2–4 | Depends on baseline alcohol intake. |

\* Greater improvements will be seen in those with higher starting systolic blood pressure

**Q. Is there a best type of exercise to reduce blood pressure?**

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As we mentioned above, increasing physical activity can reduce your systolic blood pressure by 4–9 mmHg. However, it’s not as clear if there’s a dose-response effect of exercise or what types of exercise might impact blood pressure the most. Luckly, a recent network meta-analysis aimed to answer these questions.[320]

Exercise becomes more effective for lowering blood pressure the higher the starting systolic pressure is — in other words, people with higher starting blood pressures tend to benefit more from exercise. You can also see from the figure below that a combination of resistance and endurance training looks to be more effective, although there’s no clear winner between isometric, endurance, and resistance training taken on their own.

**Effects of exercise on systolic blood pressure**

****Reference: Naci et al. Br J Sports Med. 2019.[320]

However, the authors of the paper caution that more research is needed to explore whether one type of exercise is indeed better than another due to the relative lack of research into this topic. There are also some other key takeaways from this research that aren’t apparent from the figure.

Due to reporting issues and lack of relevant data, the authors were not able to explore whether some frequencies or durations of exercise improved blood pressure more than others.

The authors didn’t see a clear relationship between exercise intensity and blood pressure reduction, mainly due to not having enough data. There is much more room for future research to explore the relationship between exercise intensity and blood pressure reduction.

There’s some concern about the generalizability of the exercise results to people with hypertension (i.e., high blood pressure), since most of the exercise trials involved people with normal or mildly elevated blood pressure. Future research focused on exercise’s effect on people with hypertension would be useful.

In short: all types of exercise seem to reduce systolic blood pressure, especially in people with 55

hypertension. However, how much exercise is best, whether intensity matters, and exactly what kinds of exercise have the biggest impact are still unclear.

**Q. Should I modify how I exercise based on my cardiovascular disease risk factors?**

Different types of cardiovascular disease (CVD risk) may require different amounts, types, or doses of exercise, and major guidelines don’t provide such tailored advice. Recently, a team of experts created a system called the EXercise Prescription in Everyday practice & Rehabilitative Training (EXPERT) tool to help guide clinicians to give patients tailored exercise advice based on their needs.

The team released a consensus statement that gives specific exercise recommendations for several cardiovascular risk states based on the evidence they considered.[321] Some of the team's recommendations are summarized below.

Each recommendation is accompanied by a grade denoting the level of the recommendation.

“A” means the recommendation is supported by high-quality systematic reviews or randomized controlled trials that are directly relevant for the population at hand.

“B” means high-quality observational evidence or inference from randomized trials supports the recommendation.

“C” means the recommendation is supported by well-conducted case-control or cohort studies with overall consistent results could be applicable to the target population.

“D” means the recommendation is supported by poorer-quality observational evidence, inference from higher-quality observational evidence, or expert opinion.

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**Exercise recommendations by CVD risk factors**

****Reference: Hansen et al. Sports Med. 2018.[321]

**Q. How does salt increase blood pressure?**

Sodium is a known regulator of blood pressure. Sodium concentrations are sensed by macula densa cells in the kidneys.[322] When the blood sodium concentration becomes too low, these cells activate the renin angiotensin-aldosterone system, as shown below. In this way, very low sodium may cause high blood pressure.[323]

More often, however, increased salt intake causes your body to hold onto more water, which increases blood pressure. This extra pressure places a strain on your cardiovascular system which can eventually lead to worse cardiovascular disease outcomes over time.

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**Q. How does baseline blood pressure modify the effects of salt reduction?**

Sodium restriction may reduce both systolic and diastolic blood pressure, primarily among people starting out with higher blood pressure. Although there can be small benefits among people with lower blood pressure, these effects are either not clinically relevant (and possibly non-existent). The effects of a reduction in salt intake of 2,300 milligrams (2.3 g) stratified by blood pressure are summarized below.

**Changes in blood pressure to salt reduction, by baseline status Q. Can red meat cause heart disease?**

There is some evidence that eating a lot of red meat or processed meat might increase the risk of cardiovascular diseases, but that evidence tends to be of lower certainty.[324][325][326] Yet, given the difficult nature of conducting long-term nutrition trials, we aren’t likely to get any truly high-quality evidence anytime soon. So, what are we to make of the studies we have, low-quality though they may be?

Remember that red and processed meat consumption is just a small part of the overall lifestyle factors that will influence your heart health. If you moderate your red meat intake, exercise regularly, eat your fruits and veggies, consume adequate fiber, don’t smoke, and drink alcohol only in moderation, red meat’s effect on your heart health isn’t something to worry too much about.

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Still, if you wish to be cautious, you can limit your intake to three servings per week (1 serving of meat = 3 oz = 85 grams). Prioritize limiting the kind of meat that has been cured, smoked, or highly processed.

**Q. Why take NAC to make glutathione? Why not take glutathione directly?**

Oral glutathione gets digested into its constituent amino acids: cysteine, glycine, and glutamic acid. Of those three, cysteine is the rate-limiting factor in endogenous glutathione production. Oral N-Acetylcysteine (NAC) is simply a more efficient (and cheaper) way of providing your body with cysteine. Multiple studies have reported greater increases in circulating glutathione from oral NAC than from (an equal dose of) oral glutathione.

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