Effective Health Care Program

Complementary and Alternative Medicine
**Dietary Supplements and Cardiovascular Drugs**

# Use Versus Nonuse of Dietary Supplements in Adults Taking Cardiovascular Drugs

## Research Focus for Clinicians

In response to a request from the public regarding the use of dietary supplements by patients currently undergoing pharmacologic cardiovascular treatment, a review was undertaken to evaluate the evidence regarding the benefits and harms of concomitant use of dietary supplements with cardiovascular drugs. The systematic review included 70 studies published through September 2011. The full report, listing all studies, is available at www.effectivehealthcare.ahrq.gov/dietary-supplements.cfm. This summary is provided to inform discussions with patients of options and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

## Background

Estimates suggest that approximately one-third to two-thirds of people suffering from heart failure or other forms of cardiovascular disease (CVD) use dietary supplements.[1] These supplements are available in pharmacies, grocery stores, and health food stores and on the Internet. They are often consumed by patients without the knowledge of their health care providers and under the impression that they are safe and beneficial. Such claims of benefit are often unsubstantiated, however. These products do not require U.S. Food and Drug Administration (FDA) approval nor are there any FDA regulations that require evidence of purity, quality, or composition before marketing. Use of dietary supplements for CVD occurs in the setting where, in addition to lifestyle and dietary recommendations, patients receive pharmaceuticals (6.9 prescription drugs on average from 5.9 different drug classes[2]) to prevent or treat CVD. Patients may be at risk for drug-supplement or supplement-supplement interactions.

On one hand, patients taking supplements may be placed at risk for potential adverse effects from the supplements themselves or from interactions with other pharmacologically active agents. On the other hand, adding a dietary supplement to conventional cardiovascular drugs may confer benefits. Although a substantial amount of research describes drug-drug interactions in various populations, the evidence for drug-supplement interactions is unclear, especially in CVD populations. The evidence for benefits and adverse effects in patients with CVD has not been summarized previously.

## Conclusion

Evidence for the use of dietary supplements in combination with cardiovascular drugs was insufficient to permit conclusions about clinical cardiovascular efficacy, effectiveness, and adverse effects (e.g., mortality, thrombotic events, and arrhythmia).

Evidence for most intermediate outcomes (e.g., lipid profile, blood pressure, international normalized ratio (INR), and bleeding and coagulation) was also insufficient or of low strength and suggested no effect. Where an effect on an intermediate outcome might be suggested, studies were often small, at risk of bias, and subject to the uncertainties associated with testing of agents of uncontrolled purity, quality, or composition.

Some findings with low strength of evidence, if acted on by a patient without consulting a physician, could lead to adverse effects.

Furthermore, the interactions of these agents with other noncardiovascular drugs that patients may be taking cannot be predicted from any of these studies. Comorbidities such as renal disease or liver disease that could affect the metabolism, actions, and safety of supplements were not studied.

Advertised claims for dietary supplements should be interpreted cautiously, and clinicians should ask their patients with CVD about their use of supplements, regardless of whether the supplement is to be taken to provide cardiovascular protection or for other purposes.

Details of the comparisons and findings are available online at www.effectivehealthcare.ahrq.gov/dietary-supplements.cfm.

## Clinical Bottom Line

**Clinical Cardiovascular Effectiveness/Efficacy Outcomes**

For all combinations of dietary supplements and cardiovascular drugs studied, evidence was inconclusive about the effects of concomitant use of specific dietary supplements (when compared with cardiovascular drugs alone) on clinical cardiovascular effectiveness/efficacy outcomes like mortality and specific cardiovascular or cerebrovascular conditions. ○○○

*(Continued on next page)*

**Strength of Evidence Scale**

| | | |
|---|---|---|
| High: | ●●● | High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate: | ●●○ | Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. |
| Low: | ●○○ | Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. |
| Insufficient: | ○○○ | Evidence is either unavailable or does not permit a conclusion. |

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## Clinical Bottom Line *(Continued)*

**Intermediate Cardiovascular Efficacy Outcomes**
***(Continued summary of the evidence review—not to be construed to represent clinical recommendations or guidelines)***

*Lipid Profile*

The concomitant use of coenzyme Q10 with fenofibrate provided no additional benefit for HDL-C. ●○○

The concomitant use of garlic with warfarin or nitrates improved HDL-C. ●○○

The concomitant use of omega-3 fatty acids with statins improved triglyceride levels. ●○○

The concomitant use of omega-3 fatty acids with calcium channel blockers + aspirin improved triglyceride levels. ●○○

The concomitant use of omega-3 fatty acids with calcium channel blockers + aspirin + dipyridamole improved triglyceride levels. However, for LDL-C, calcium channel blockers + aspirin + dipyridamole taken alone without omega-3 fatty acids was favored. ●○○

The concomitant use of vitamin E with nifedipine improved LDL-C and triglyceride levels. ●○○

Evidence was inconclusive regarding the effects of concomitant use of all other supplement-drug combinations on lipid profile. ○○○

*Blood Pressure*

The concomitant use of omega-3 fatty acids with statins improved systolic blood pressure but provided no additional benefit for diastolic blood pressure. ●○○

The concomitant use of omega-3 fatty acids with ACE inhibitors provided no additional benefit for either systolic or diastolic blood pressure. ●○○

Evidence was inconclusive regarding the effects of concomitant use of all other supplement-drug combinations on blood pressure. ○○○

*International Normalized Ratio*

According to only one small study (n = 70)* of patients who have unstable control of anticoagulation when receiving warfarin, the consistent and regular concomitant use of vitamin K may help improve the percentage of time the INR is in the target therapeutic range and decrease the variability of the INR. This finding may not be applicable to a larger, unselected warfarin-treated patient population. ●○○

***(Continued in next column)***

*International Normalized Ratio* ***(Continued)***

Evidence was inconclusive regarding the effects of concomitant use of all other supplement-drug combinations on INR. ○○○

*Bleeding and Coagulation Measures*

Evidence was inconclusive regarding the effects of concomitant use of all supplement-drug combinations on bleeding and coagulation measures. ○○○

**Clinical or Intermediate Harms Outcomes**

For all combinations of dietary supplements and cardiovascular drugs, evidence was inconclusive about the effects of concomitant use of specific dietary supplements (when compared with cardiovascular drugs alone) on clinical or intermediate harms outcomes like organ toxicity or serious adverse effects. ○○○

**Pharmacokinetic Outcomes**

For the concomitant use of *Echinacea* with warfarin, ginger with warfarin, and *Ginkgo biloba* with warfarin, there was no evidence of interaction for AUC, $C_{max}$, half-life, or clearance. ●○○

For the concomitant use of garlic with warfarin, there was no evidence of interaction for AUC, half-life, or clearance. ●○○

For the concomitant use of *Ginkgo biloba* with ticlopidine, there was no evidence of interaction for AUC, half-life, or $C_{max}$. ●○○

For the concomitant use of ginseng with warfarin, there was no evidence of interaction for $C_{max}$, half-life, or clearance. ●○○

For the concomitant use of omega-3 fatty acids with rosuvastatin or atorvastatin, there was no evidence of interaction for AUC or $C_{max}$. ●○○

Evidence was inconclusive regarding the effects of concomitant use of all other supplement-drug combinations on pharmacokinetic outcomes. ○○○

* Sconce E, Avery P, Wynne H, et al. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood. 2007 Mar 15;109(6): 2419-23. PMID: 17110451.

ACE = angiotensin-converting enzyme; AUC = area under the curve (to infinity or at steady-state); $C_{max}$ = maximum concentration; HDL-C = high-density lipoprotein cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol

## Supplement/Drug Combinations and Outcomes Studied

| Supplement/drug combinations with findings: | |
|---|---|
| **Combination** | **Outcomes studied** |
| coenzyme Q10/fenofibrate | LP |
| *Echinacea*/warfarin | PO |
| *Ginkgo biloba*/warfarin | PO |
| *Ginkgo biloba*/ticlopidine | PO |
| garlic/warfarin | LP, PO |
| garlic/nitrates | LP |
| ginger/warfarin | PO |
| ginseng/warfarin | PO |
| omega-3 fatty acids/ACE inhibitors | BP |
| omega-3 fatty acids/aspirin + calcium channel blockers | LP |
| omega-3 fatty acids/aspirin + calcium channel blockers + dipyridamole | LP |
| omega-3 fatty acids/atorvastatin | PO |
| omega-3 fatty acids/simvastatin | PO |
| omega-3 fatty acids/statins | BP, LP† |
| vitamin E/nifedipine | LP |
| vitamin K/anticoagulants | INR |
| **Supplement/drug combinations with inconclusive findings:** | |
| coenzyme Q10/ACE inhibitors | CCE/EO, CIHO |
| coenzyme Q10/fenofibrate | BP, CIHO, LP |
| coenzyme Q10/statins | CIHO, LP |
| *Echinacea*/warfarin | BP, CIHO, INR |
| *Ginkgo biloba*/antiplatelet agents | BCM, BP, CCE/EO, LP |
| *Ginkgo biloba*/aspirin | BP, CIHO, LP |
| *Ginkgo biloba*/aspirin + pentoxifylline | CIHO |
| *Ginkgo biloba*/cilostazol | BCM, BP, CIHO |
| *Ginkgo biloba*/clopidogrel | CIHO |
| *Ginkgo biloba*/digoxin | CIHO, PO |
| *Ginkgo biloba*/nitrates | CIHO |
| *Ginkgo biloba*/pentoxifylline | CIHO |
| *Ginkgo biloba*/ticlopidine | CIHO |
| *Ginkgo biloba*/warfarin | CIHO, INR |
| garlic/nitrates | LP, CIHO |
| garlic/statins | PO |
| garlic/statins + aspirin | CIHO, LP |
| garlic/warfarin | BP, CIHO, INR, LP, PO |

*(Continued in next column)*

| Supplement/drug combinations with inconclusive findings: *(Continued)* | |
|---|---|
| ginger/warfarin | INR |
| ginseng/warfarin | CIHO, INR |
| hawthorn/digoxin | CIHO, PO |
| magnesium/beta-blockers | BP, CCE/EO, CIHO |
| magnesium/hydrochlorothiazide | BP, CIHO, LP |
| niacin (<250 mg)/propranolol | CIHO, LP |
| omega-3 fatty acids/ACE inhibitors | LP |
| omega-3 fatty acids/aspirin | BP, CCE/EO, CIHO, LP |
| omega-3 fatty acids/aspirin + calcium channel blockers | LP |
| omega-3 fatty acids/aspirin + calcium channel blockers + dipyridamole | CIHO, LP |
| omega-3 fatty acids/aspirin + clopidogrel | CIHO |
| omega-3 fatty acids/atorvastatin | PO |
| omega-3 fatty acids/beta-blockers | BP |
| omega-3 fatty acids/calcium channel blockers | LP |
| omega-3 fatty acids/fenofibrate | CCE/EO, CIHO, LP |
| omega-3 fatty acids/irbesartan | CIHO |
| omega-3 fatty acids/niacin + aspirin | LP |
| omega-3 fatty acids/ramipril | CIHO |
| omega-3 fatty acids/ramipril + irbesartan | CIHO |
| omega-3 fatty acids/rosuvastatin | PO |
| omega-3 fatty acids/simvastatin | PO |
| omega-3 fatty acids/statins | CCE/EO, CIHO, LP†† |
| omega-3 fatty acids/warfarin | CCE/EO, CIHO, INR |
| vitamin E/antiplatelet agents | LP |
| vitamin E/aspirin | CCE/EO, CIHO |
| vitamin E/furosemide | BP, CIHO |
| vitamin E/gemfibrozil | BP, LP |
| vitamin E/nifedipine | BP, CIHO, LP |
| vitamin E/statins | LP |
| vitamin K/anticoagulants | CCE/EO, INR |
| vitamin K/warfarin | CIHO |

**Key**

BCM = bleeding and coagulation measures
BP = blood pressure
CCE/EO = clinical cardiovascular effectiveness/efficacy outcomes
CIHO = clinical or intermediate harms outcomes
INR = international normalized ratio
LP = lipid profile
PO = pharmacokinetic outcomes

† For triglycerides
†† For high-density lipoprotein cholesterol and low-density lipoprotein cholesterol

## Gaps in Knowledge

- Future research with dietary supplements should involve substances for which the identity of the agents can be clearly ascertained and the chemical composition well characterized and ideally standardized. If the active ingredients or biologic activity is not known, studies to characterize these variables, identify mechanisms of action, and describe safety should precede clinical efficacy studies.
- As the extant literature is largely based on a few small efficacy studies of limited internal validity that examined intermediate outcomes, future supplement-cardiovascular drug interaction trials should focus on meaningful clinical outcomes, should be appropriately powered and rigorously conducted and reported, and should provide precise measurements of both clinical effectiveness and harms outcomes.
- Most studies were conducted in speciality settings, excluded patients with comorbidities or uncontrolled comorbidities, and did not include ethnic and racial minorities. Future trials should be representative of the population taking cardiovascular drugs in terms of comorbidities, setting, and racial distribution. They should also collect data and undertake subgroup analyses for age, sex, race, comorbidities (e.g., liver or renal compromise), and genotypic polymorphisms of the cytochrome P450 enzyme.
- A substantial number of pharmacokinetic interaction studies did not report and analyze pharmacokinetic outcomes according to FDA guidance for bioequivalence studies.

## What To Discuss With Your Patients

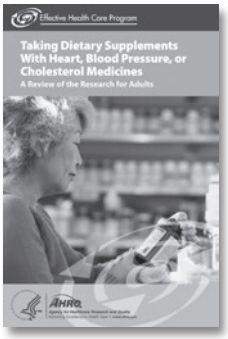
Given these findings, clinicians may wish to inquire about supplement use among their patients with cardiovascular disease. Topics of discussion include:

- The importance of informing their clinician about a decision to take a supplement
- The high uncertainty about the benefits or potential side effects of dietary supplements used in combination with cardiovascular drugs
- The importance of continuing to take prescribed cardiovascular medication(s) if the patient decides to take a dietary supplement
- The fact that dietary supplements do not require FDA approval before being advertised and sold, and that there may be uncertainty about the purity, quality, or composition of the supplements
- The potential but uncharacterized risks for interactions with prescribed medicines or with other supplements

## Resource for Patients

*Taking Dietary Supplements With Heart, Blood Pressure, or Cholesterol Medicines, A Review of the Research for Adults* is a free companion to this clinician research summary. It can help patients with cardiovascular disease who are considering taking dietary supplements in conjunction with their cardiovascular drugs talk with their health care professionals about their options. It provides information about:

- How much evidence is available concerning the cardiovascular benefits or harms of taking dietary supplements in conjunction with cardiovascular medications




- Warnings about the lack of regulation or standardization of supplement products sold in stores or on the Internet
- The importance of discussing the use of supplements with their doctor before adding them to cardiovascular medications, and questions to guide that discussion

## Ordering Information

For electronic copies of *Taking Dietary Supplements With Heart, Blood Pressure, or Cholesterol Medicines, A Review of the Research for Adults*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/dietary-supplements.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

## Source

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