Comparative Effectiveness Review
Number 51

Effective Health Care Program

Dietary Supplements in Adults Taking Cardiovascular Drugs

Executive Summary

Background

The American Heart Association estimates that more than 81 million American adults (one-third of all adults) have at least one form of cardiovascular disease (CVD).[1] CVD is broadly defined to include all the disorders of the arterial system, including the heart and coronary arteries, the arterial supply to the brain, and the peripheral arterial system. CVD manifests typically as hypertension, angina, myocardial infarction (MI), heart failure, stroke and transient ischemic attacks (TIAs), and intermittent claudication or blockage. While there has been progress in the control of CVD, it demands huge investments from the health care system, and represents great burdens and lost opportunities for individuals, families, and society overall.

In addition to lifestyle and dietary recommendations, frontline treatment for prevention and treatment of CVD is primarily pharmaceutical, with patients requiring, on average, 6.3 concomitant prescription drugs from, on average, 5.9 different drug classes for primary and secondary prophylaxis of the disease itself and management of associated comorbidities.[2-4]

Complementary and alternative medicine (CAM) refers to preventive and therapeutic modalities not generally considered to be part of conventional medicine,[5] including dietary supplements. CAM utilization has increased dramatically in North America over the past decades in both the general and CVD populations.[6,7]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • **www.ahrq.gov**

Effective Health Care

The National Health Interview Survey indicated that Americans spent a total of $34 billion out of pocket on CAM in 2007.[8] Estimates suggest that approximately one-third to two-thirds of people suffering from heart failure or other cardiovascular disease use dietary supplementation and are thus placed at risk for potential adverse events from interactions with other pharmacologically active agents and nonadherence associated with polypharmacy.[7,9-13] With compromised physiology due to aging, the elderly are most vulnerable to the adverse events of any drug interaction. On the other hand, addition of a dietary supplement to conventional cardiovascular drugs may confer benefit. Evidence of both benefits and harms of adding a supplement to cardiovascular drugs has been reported.[6,14]

Incorporation in clinical practice of knowledge regarding the impact of concomitant use of cardiovascular medications and dietary supplements requires access to reliable drug-supplement information, as well as physicians' commitment to documenting patients' supplement use.[15,16] While a substantial amount of research and data is available describing drug–drug interactions in various populations, the evidence for drug–supplement interactions or simply add-on supplement effect is unclear, especially in the CVD populations.

Objectives

The objective of this Comparative Effectiveness Review was to systematically synthesize and grade the strength of evidence of benefits and harms of adding a dietary supplement to cardiovascular drugs routinely prescribed in outpatient settings. A related objective included assessment of whether the altered outcomes of efficacy and/or effectiveness and harms are a result of a simple add-on effect of a dietary supplement or more complex interactions with the cardiovascular drug. Supplement–drug interactions were examined by investigating evidence of statistical and pharmacokinetic interactions.

These objectives were framed in the following Key Questions.

In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared with cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on:

Key Question 1. Clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction and stroke)?

a. Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?

b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

Key Question 2. Intermediate cardiovascular efficacy outcomes (e.g., lipids, blood pressure, electrocardiographic measurements, serum markers, bleeding, and coagulation times)?

a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?

b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?

Key Question 3. Clinical or intermediate harms outcomes (e.g., organ toxicity, serious adverse events, withdrawal due to adverse events)?

a. Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?

b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

Key Question 4. Pharmacokinetic outcomes (e.g., half life [$t_{1/2}$], area under the concentration curve [AUC]) of cardiovascular drugs of interest?

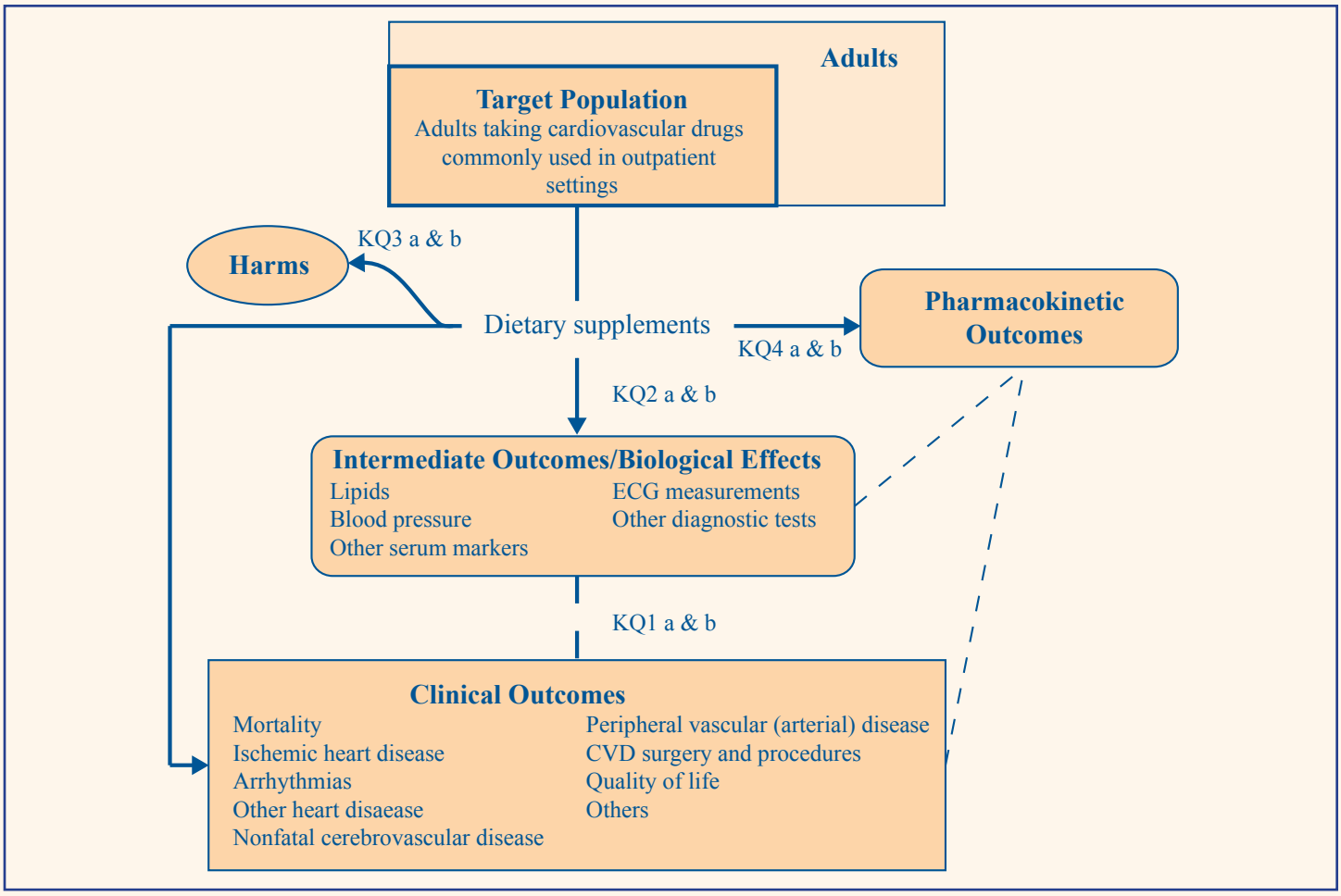
a. Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?

b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

Analytic Framework

The expectations behind using a dietary supplement with prescription cardiovascular drugs are improvement in the disease process (or its prevention) and reduction in harms related to cardiovascular drugs. These effects might come about through either an add-on effect of a supplement or its biological interaction with a cardiovascular drug. Benefits and harms are measured as outcomes that may be clinical outcomes, their proxy surrogates, or pharmacokinetic parameters. The analytic framework in Figure A depicts the causal pathways forming the basis of the Key Questions.

Figure A. Analytic framework of dietary supplement coadministration with routinely prescribed cardiovascular drugs



CVD = cardiovascular disease; ECG = electrocardiography; KQ = Key Question

Methods

Input From Stakeholders

Preliminary broad searches identified the necessity to focus this review, so we formulated the population, intervention, comparator, and outcome (PICO) analytic framework and Key Questions in consultation with the Key Informants during a topic refinement stage. The range of dietary supplements was narrowed to include only those most commonly taken along with cardiovascular drugs and for which there was no recent review. A fifth Key Question, regarding P450 isozyme activity and cellular drug transport mechanisms, was dropped. The Key Informants included clinicians (cardiologists, naturopathic doctors, clinical pharmacology specialist, and nutritionist), a patient/consumer advocate, and systematic review research methodologists. The public were invited to provide comments on the Key Questions. During the review process, we followed an a priori research protocol developed with the clinical and methodological input of a Technical Expert Panel (TEP) of specialist clinicians and methodologists. The protocol followed the Effective Health Care Program's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[17]

Data Sources and Searches

We searched the following electronic databases from inception to September 1, 2011: MEDLINE®, Embase, the Cochrane Library (CENTRAL, CDSR, DARE, and HTA), International Bibliographic Information on Dietary Supplements (IBIDS), and Allied and Complementary Medicine Database (AMED). We developed peer-reviewed search strategies (shown in Appendix A of the full report) using a broad range of controlled vocabulary to address the various synonyms associated with this topic, as well as to cover any evolutionary gaps associated with the introduction of certain vocabulary terms. We also searched trial registries (e.g., ClinicalTrials.gov, Current Controlled

Trials, Clinical Study Results, World Health Organization Clinical Trials), the Cambridge Scientific Abstracts Conference Papers Index, and Scopus.

Results were refined using filters for systematic reviews, randomized controlled trials (RCTs), non-RCTs and observational studies, and safety. A more specific strategy related solely to herb-drug interactions was run in the same databases using only a systematic review filter.

We also contacted TEP members and the Scientific Resource Center at the Agency for Healthcare Research and Quality.

Study Selection

Two reviewers screened titles, abstracts, and full-text reports, with conflicts resolved by consensus or third-party adjudication. A primary study was eligible if it:

- Was published in English or German.
- Examined a dietary supplement. A dietary supplement was defined as a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance, or a concentrate metabolite, constituent, or extract intended to increase the total dietary intake made for ingestion in pill, capsule, tablet, powder, or liquid form not represented for use as conventional food or as the sole item of a meal or diet).
- Compared the effect of adding a dietary supplement to cardiovascular medication(s) to the same cardiovascular medication(s) or to another dietary supplement (from the list above) added to the same cardiovascular medication(s).
- Evaluated use of a dietary supplement intended for ingestion as pill, capsule, tablet, powder, or liquid. The dietary supplements considered were coenzyme Q10, *Echinacea,* garlic, ginger, *Ginkgo biloba, Panax ginseng,* American ginseng, hawthorn, oral magnesium, niacin (no more than 250 mg/day), omega-3 fatty acids/fish oils, red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium, vitamin E, and vitamin K. This list was selected after extensive discussions with the TEP and reference to surveys of the general and cardiovascular populations in the Unites States.[7,18-23]
- Included cardiovascular drugs that were commonly used in outpatient settings (Table 1 of full report).
- Reported clinical or surrogate cardiovascular efficacy or harms, or pharmacokinetic outcomes, in any adult population.
- Was a randomized controlled trial, nonrandomized trial, or observational study with an independent concurrent or historical control group including at least five participants. For Key Question 4, studies employing participants as their own controls were also eligible. (This was a post hoc decision in light of the relevance of this design for study of pharmacokinetic interactions.)

Good-quality English language systematic reviews on the topic were also eligible. However, a systematic review could replace de novo synthesis of evidence only when the review was deemed to be current, obviating the need to update it.

Studies included after full-text screening were removed from data synthesis because of one or more of the following reasons:

- Cardiovascular drug(s) were not taken by at least 80 percent of participants in RCTs. Including such studies would have severely limited the applicability of evidence.
- The study reported effect estimates that did not reflect a comparison of supplement plus drug(s) versus drug(s) alone (or plus another supplement).
- No relevant outcome was reported in the study or the outcome data were not received from the authors of the studies. (Authors were contacted for data clarification and additional outcome data when data were recognized to have been recorded but not reported in the published study—for example, outcome data without a measure of dispersion.)
- The design of the study was lower in the hierarchy of evidence (i.e., nonrandomized experimental or observational study in the presence of higher quality RCT evidence) and did not meaningfully add to the evidence already included by being a longer term or pragmatic study reporting conclusive results.
- Studies included cardiovascular drugs not marketed in the United States.
- Administration dose and/or frequency of the dietary supplement was not quantified.

Data Extraction and Risk-of-Bias Assessment

One reviewer extracted relevant data from each study and a second reviewer independently verified data for a 10 percent random sample of studies. Extraction items included general study characteristics (e.g., year of publication, study design); population characteristics (e.g., inclusion/exclusion criteria, age, race, level

of activity, condition); intervention characteristics (e.g., dose, duration, details about comparators, level of care); and outcomes (i.e., clinical and surrogate outcomes of efficacy and harms, and pharmacokinetic outcomes) with their estimates. During the data extraction process, one reviewer with a clinical background rated study populations' 10-year coronary heart disease (CHD) risk according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines.[24]

We assessed study risk of bias according to outcome, using generic items for confounding and various types of bias (e.g., selection, performance, detection, and attrition bias) separately for each study design. Selected items from the McMaster Quality Assessment Scale of Harms were also incorporated into the risk-of-bias assessment for harm-related outcomes. Certain criteria were specific to particular study designs; for example, allocation generation and concealment applied only to RCTs.[25] For gradable outcomes, one reviewer rated the overall risk of bias for the study as low, moderate, or high risk, and a second reviewer independently verified the assessment. Outcomes were rated as high risk of bias if there was an apparent and major flaw in the study that would invalidate results. Appendix C in the full report provides the detailed individual study data and risk-of-bias ratings.

Grading the Strength of the Body of Evidence and Applicability

In principle, a body of evidence originating in randomized trials starts with a presumed high strength of evidence and is downgraded across the domains when there is important overall risk of bias for contributing studies, inconsistency in the direction of the intervention effect, indirectness of the outcome of interest (e.g., a surrogate outcome rather than a clinical health outcome), or imprecision in effect estimates of an extent that neither important benefit nor harm can be ruled out. For nonrandomized studies, the body of evidence starts with a presumed low strength of evidence but may be upgraded across certain domains. The strength of a body of evidence was graded based on the following four domains, per published guidance: overall risk of bias by outcome, consistency, directness, and precision.[26]

Gradable important outcomes for this review were identified a priori in consultation with the TEP (Table A). This was done because customarily only a subset of important outcomes that are more meaningful for decisionmaking concerning each specific Key Question are chosen.[26]

A methodologist and a content expert graded the strength of the body of evidence as "high," "moderate," "low," or "insufficient." From a larger list of outcomes of interest for each Key Question (see the Methods section of the full report).[26,27]

The strength of evidence was graded insufficient when there was no evidence for an outcome, when the direction of the estimates was inconsistent between studies without an identifiable cause, or when the body of evidence from the contributing study/studies was underpowered for the outcome of interest (imprecise estimate). When an effect estimate was associated with a confidence interval (CI) that was not only nonsignificant, but wide enough that the clinical action would differ if the upper versus the lower boundary of the CI represented the truth, we rated the effect as imprecise. This reflected our uncertainty regarding clinically important benefit or harm, or a clinically unimportant difference in effect estimates between the contrasting interventions.

Table A. A priori outcomes for grading the strength of evidence

Key Question	Outcomes
1	Mortality (all-cause and vascular death); myocardial ischemic events (fatal myocardial infarction, nonfatal myocardial infarction, unspecified myocardial infarction, and acute coronary syndromes); cerebrovascular events (hemorrhagic/ischemic/unspecified stroke); quality of life; hospitalization; arrhythmia; and clinical outcomes of peripheral arterial disease
2	Blood pressure (systolic and diastolic); lipid profile (low-density lipoprotein, high-density lipoprotein, and non-high-density lipoprotein cholesterol and triglycerides); international normalized ratio for coumarin derivatives; incidence of metabolic syndrome; and change in 10-year Framingham risk profile
3	Serious adverse events (composite outcome according to the Food and Drug Administration definition of serious adverse events);[27] withdrawal due to adverse events; clinical bleeding (intracranial, gastrointestinal, genitourinary, subretinal, etc.); renal dysfunction (e.g., proteinuria, elevated creatinine, need for transplant, glomerular filtration rate); hepatotoxicity (elevated enzymes or fulminant failure); and QT prolongation
4	Area under the plasma cardiovascular drug concentration-time curve (AUC), maximum drug concentration (C_{max}), drug half-life ($t_{1/2}$), and oral clearance

Following published guidance, we summarized the determinants of applicability of the body of evidence for outcomes with conclusive results.[28] Studies that evaluated representative patient populations in usual or routine care conditions and lasting long enough to meaningfully measure health outcomes of both benefits and harms were considered pragmatic or effectiveness studies. In contrast, studies examining intermediate efficacy outcomes in highly selected patients were considered efficacy studies.[29]

Data Synthesis and Analysis

All analyses compared the combination of dietary supplement plus cardiovascular drug with cardiovascular drug alone or plus placebo or plus another dietary supplement. Meta-analyses were carried out when there was clinical and methodological homogeneity. For pharmacokinetic outcomes, we followed the U.S. Food and Drug Administration (FDA) guidance for analysis and interpretation of drug interaction studies—that is, the zone of bioequivalence is recommended to be between the lower and upper bound of the 90 percent geometric mean ratio (GMR), with a CI between 0.8 and 1.25.[30]

We did not pool experimental and observational studies, but did pool parallel studies with valid crossover randomized trials. We did not consider precrossover data for synthesis except when it was judged that the treatment given to participants in a given crossover trial was not appropriate for the condition under consideration.[31,32] Similarly, we did not pool crossover trials that had not employed a sufficient washout period between the two treatment periods because of bias arising from carryover treatment effects. We did not meta-analyze observational studies because of the differences in adjustment for confounders and residual confounding.

Meta-analysis was considered when studies were randomized trials that included similar populations, compared the same type of dietary supplement versus comparator treatment, and reported the same outcome measures in the same statistical format (e.g., mean difference or GMR). Relative risk (RR) and post-treatment mean differences (MDs) were meta-analyzed using the DerSimonian and Laird random-effects model,[33] and Peto odds ratios were calculated when event rates were less than1 percent.[32]

For studies with zero events in some arms or sparse data overall, we pooled using the fixed-effects Mantel-Haenszel method without continuity correction.[34] Studies with zero events in both arms were excluded from meta-analysis.[32] Where applicable, we examined statistical heterogeneity by calculating the synergy index (detailed in the Methods section of the full report).[35] The synergy index estimates the supplement-drug statistical interaction when the effect observed with the combination is of a magnitude that is greater than or less than would be anticipated in an additive model, knowing the independent effects of the supplement and drug. An S-index (ratio of effects measured to additive calculation) greater than 1 describes a positive interaction (synergism), and an S-index less than 1 indicates a negative interaction (antagonism). Statistical heterogeneity was assessed using Cochran's Q ($\alpha = 0.10$) and the I^2 statistic.

Outcome results were considered to be inconclusive when the pooled estimate or the single contributing study estimate had confidence intervals wide enough to incorporate both clinically important benefit and harm (i.e., type II error suggesting underpowered studies unable to precisely conclude benefit, harm, or no difference between treatments). Results were also considered to be inconclusive when studies could not be pooled—for example, when similar outcomes were reported in different statistical formats in studies or study results pointed in opposite directions. When inconclusive results were associated with a gradable outcome, strength of evidence was deemed insufficient.

Results

Overview

The PRISMA flow diagram summarizes the number of records screened and included (Figure B).

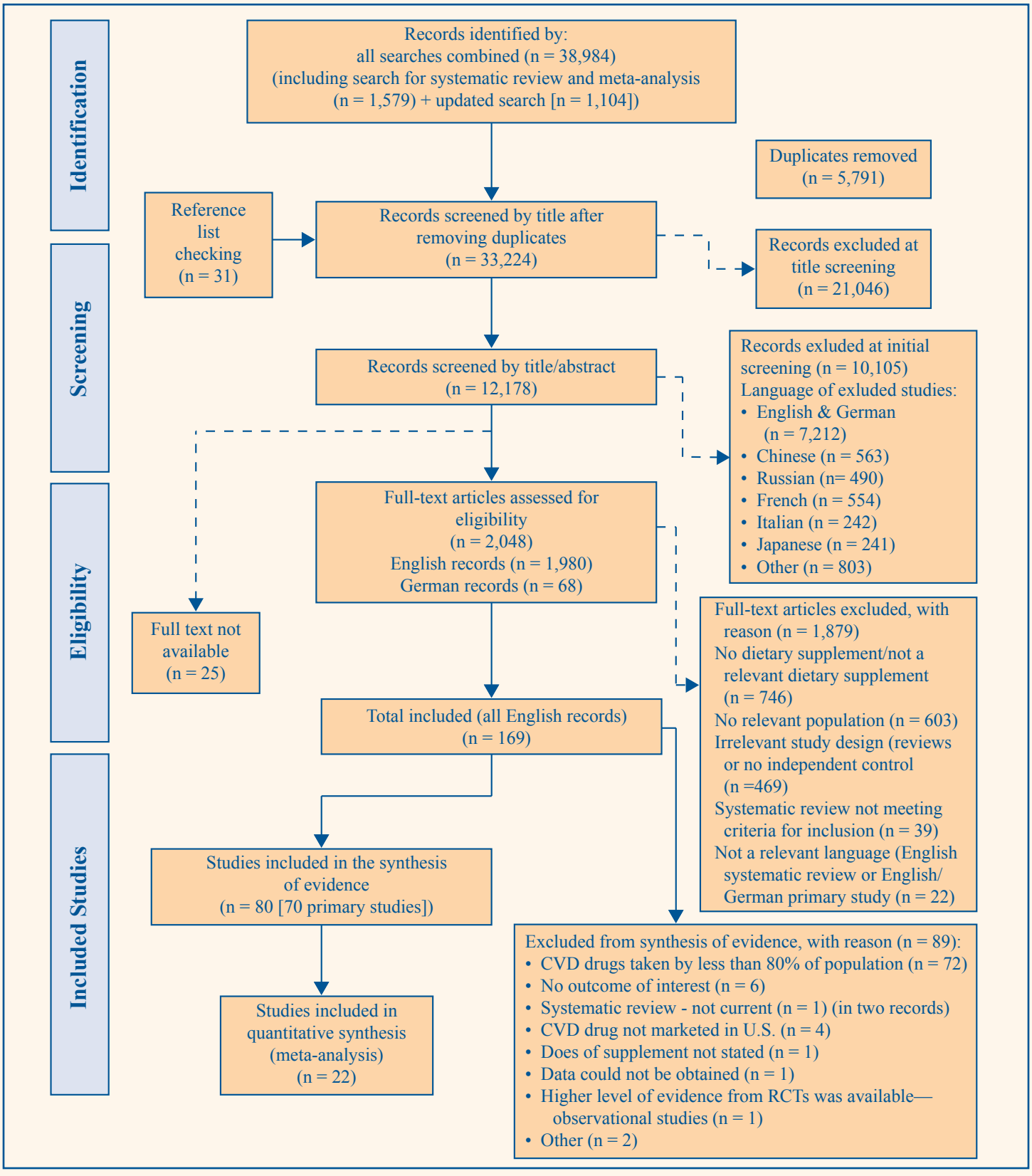
In total, 38,984 records were identified by searches of databases (including gray literature, reference list checking, and search for systematic reviews and meta-analyses) and screened for eligibility. Seventy unique English-language studies (in 80 published articles), including one of observational design, contributed evidence. No systematic reviews were found to be eligible for evidence synthesis. Additionally, we found no relevant unique German publications. Twenty-two studies contributed to meta-analyses in this review.

Table B shows the most relevant risk-of-bias criteria for the randomized and controlled clinical trials included (n = 69).

Key Question 1. Clinical cardiovascular effectiveness/efficacy of cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 1 is shown in Table C.

Figure B. PRISMA flow chart of study identification, screening, eligibility, and inclusion



CVD = cardiovascular disease; RCT = randomized controlled trial

Table B. Risk-of-bias criteria and conflict of interest for all RCTs and CCTs			
Item	Percent of Total Studies (n = 69)		
	Yes	No	Unclear
Adequate generation of allocation sequence	25	3	72
Allocation concealment	9	0	92
Comparability of groups	25	9	67
Blinding of allocated intervention	22	27	52
Freedom from potential for conflict of interest	29	28	43

CCT = controlled clinical trial; RCT= randomized controlled trial
Note: Percents may not add to 100 due to rounding.

Table C. Evidence for the clinical outcomes – Key Question 1	
Outcome	Dietary Supplement + Cardiovascular Drug(s)
Insufficient strength of evidence **Conclusion: Inconclusive** **Single underpowered studies for each combination precluded meaningful conclusions**	
All-cause mortality	Coenzyme Q10 (33 mg TID) + ACE inhibitors *Ginkgo biloba* (40 mg QID) + Antiplatelet agents Omega-3 fatty acids (4 g/day + Statins or aspirin or warfarin or fenofibrate Vitamin K (150 µg/day) + Coumarin derivative[a]
Quality of life	Coenzyme Q10 (100 mg/day) + ACE inhibitors
Myocardial infarction	Oral magnesium (365 mg/day) + Beta-blockers Omega-3 fatty acids (1.8 g eicosapentaenoic acid +1.2 g docosahexaenoic acid) + Aspirin + Calcium channel antagonists Vitamin K (100-150 µg/day) + Coumarin
Arrhythmia	Omega-3 fatty acids (4 g/day) + Statins
Stroke	Vitamin E (0.4 g/day) + Aspirin Vitamin K (150 µg/day) + Coumarin[b]
Ischemic stroke, hemorrhagic stroke, and TIA	Vitamin E (600 IU/day) + ASA (aspirin)

ACE = angiotensin-converting enzyme; QID = 4 times daily (every 6 hours); TIA = transient ischemic attack; TID = 3 times daily
Note: Evidence was "insufficient" for all outcomes, so applicability is not presented.
[a]Small trial reported 1 death
[b]Underpowered trial contributed evidence

Twenty-one randomized controlled trials contributed evidence for Key Question 1.[36-56] No data were available from observational studies. Generally, across all combinations of dietary supplements and cardiovascular drugs, the strength of evidence of the gradable outcomes of comparative efficacy or effectiveness was graded insufficient. Type II error could not be excluded due to the low statistical power of mostly short-term efficacy trials. In addition, strict inclusion criteria excluded patients with uncontrolled comorbidities and acute ischemic events.

Coenzyme Q10

Insufficient evidence was found for the effect of coenzyme Q10 coadministered with angiotensin-converting enzyme (ACE) inhibitors on all-cause mortality and quality of life in 30 mostly male patients with left ventricular dysfunction over a 3-month period.[54] Adherence to simvastatin with or without supplement coadministration was 98 percent during a 12-week pilot study in 22 patients with previous statin-related myalgia.[38]

Ginkgo biloba

With no deaths observed, insufficient evidence for mortality was found for *G. biloba* coadministered with aspirin and/or pentoxyphilline during a 4-week underpowered study in 33 South Asians with previous ischemic stroke.[48]

Magnesium

In a crossover trial of oral magnesium aspartate or placebo administered daily for 8 weeks to a selected group of 40 hypertensive patients with no comorbidities on therapeutic doses of beta-blockers, a single event of myocardial infarction was noted.[42]

Omega-3 Fatty Acids

Insufficient evidence from underpowered efficacy studies addressed the outcomes of mortality (in 50 healthy men)[36] and arrhythmia (in 122 highly selected dyslipidemic patients)[40] when omega-3 fatty acids were coadministered with statins. In three short-term efficacy trials of omega-3 fatty acid and statin coadministration, statin adherence as judged by pill count was found to be greater than 95 percent in both treatment groups.[37,44,53]

Insufficient evidence from single efficacy trials did not demonstrate a difference in the outcome of all-cause mortality when study cardiovascular drugs were aspirin (291 high-risk patients followed for 1 year with 9 deaths), warfarin (319 high-risk patients followed for 1 year with 5 deaths), and fenofibrate (unclear 10-year CHD risk in 167 participants with hypertriglyceridemia followed for 8 weeks with no deaths).[47,56]

Insufficient evidence addressed the outcome of acute myocardial infarction in a 6-month efficacy study of omega-3 fatty acids in addition to therapeutic doses of aspirin plus calcium channel antagonist following successful coronary angioplasty in 58 participants.[51]

Vitamin E

Insufficient evidence with sparse events of stroke and transient ischemic attack was provided by an efficacy trial of vitamin E plus aspirin versus aspirin alone in 100 highly selected patients with previous neurologic deficit.[49]

Vitamin K

Insufficient evidence was found for mortality and stroke. In one 6-month efficacy trial in 70 selected groups of patients with unstable international normalized ratios (INRs) anticoagulated with warfarin with coadministered vitamin K, no stroke and 1 death were observed.[41]

Other Supplement-Cardiovascular Drug Combinations and Outcomes

Three notable trials reported outcomes that were not a priori gradable outcomes.

One pragmatic trial in 19,934 women randomized to vitamin E plus aspirin versus aspirin alone for 10 years noted no significant differences for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR, 0.95; 95% CI, 0.79 to 1.13).[39] Although components of the composite outcome were gradable, it was not possible to discern if shifts in the incidence of stroke and heart attack might have been obscured in this composite outcome.

Inconsistent evidence on rates of restenosis following successful coronary angioplasty, best explained by differences in study population, design, and treatment, was found with omega 3 fatty acids added to conventional antiplatelet therapy and calcium channel antagonists.[51,52] When 82 highly selected male patients took omega-3 fatty acids daily along with therapeutic doses of aspirin, dipyridamole, and calcium channel antagonists, significantly lower rates of restenosis (at least 50 percent reduction in diameter) were observed compared with the cardiovascular drugs alone (RR, 0.40; 95% CI, 0.20 to 0.82); however, the mean percentage reduction in luminal diameter was not significantly different between the two groups.[52] No differences were noted in rates of restenosis when a similar but lower quality trial was conducted in 107 South Asians in India who were not taking dipyridamole.[51]

Underpowered studies addressed other outcomes that were not graded per the a priori protocol. These included exacerbation of congestive heart failure, number of patients undergoing cardiac procedures, graft occlusion, neurologic recovery score, coronary vasospasm, and number of angina attacks for various dietary supplement and cardiovascular drug combinations. Most studies were short-term efficacy trials.

No data were identified for hospitalization or peripheral arterial disease for any supplement-cardiovascular drug(s) combination.

No evidence on outcomes of clinical efficacy/effectiveness was found for *Echinacea,* garlic, ginger, ginseng, hawthorn, supplemental doses of niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, or vitamin D (with or without calcium) supplementation coadministered with a cardiovascular drug.

Key Question 1a. Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?

A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of preidentified subgroups or documentation of any dose-response effect.

Key Question 1b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

No study analyzed statistical interactions between a supplement and a cardiovascular drug in terms of clinical outcomes.

Key Question 2. Intermediate cardiovascular efficacy outcomes of cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 2 is shown in Table D.

Fifty-seven RCTs and two non-RCTs were included for this Key Question. No relevant observational study was identified. Study participants in most studies had mixed (low and/or moderate) or unclear CHD risk (27.1 percent and 37.3 percent, respectively).Study quality was variable. In the majority of RCTs, the generation of allocation sequence (78 percent) and allocation concealment (93 percent) were unclear. In about 20 percent of studies, participants, health care providers, or outcome assessors were blinded to treatment allocation. This information was not clear for 56 percent of the studies.

Table D. Evidence for the gradable intermediate efficacy outcomes – Key Question 2

Outcome	Dietary Supplement + Cardiovascular Drug(s)	Conclusion, Effect Estimate	Applicability
Low strength of evidence			
Lipid profile	Co-Q10 (200 mg/day) + Fenofibrates	No difference for HDL-C (1 study) MD,1.55 mg/dL (95% CI, -6.78 to 3.68)	Mean age: 53 years Mixed gender High CHD risk 12 weeks treatment
Lipid profile	Garlic (4 g/day) + Nitrates	In favor of combination for HDL-C (1 study) MD, 8.40 mg/dL (95% CI, 1.91 to 14.89)	Unknown age, gender High CHD risk 12 weeks treatment
Lipid profile	Garlic (4 g/day) + Warfarin	In favor of combination for HDL-C (1 study) MD, 4.50 mg/dL (95% CI, 0.19 to 8.81)	Mean age: 56 years Mixed gender High CHD risk 12 weeks treatment
Lipid profile	Omega-3 fatty acids (3.6 g/day omega-3 to 9.2 g/day fish oil) + Statins	In favor of combination: TG (2 studies pooled) MD, -74.95 mg/dL (95% CI, -95.80 to -54.10) No difference for: HDL-C (7 studies pooled) MD, 1.70 mg/dL (95% CI, -1.52 to 4.92) LDL-C (6 studies pooled) MD, -1.06 mg/dL (95% CI, -5.28 to 3.16) Achieving LDL-C and HDL-C targets (1 study) RR, 0.93 (95% CI, 0.84 to 1.03) and 1.00 (95% CI, 0.90 to 1.10), respectively	Mean age: 45-63 years Mixed or unclear CHD risk Mixed gender Up to 25 weeks treatment

Table D. Evidence for the gradable intermediate efficacy outcomes – Key Question 2 (continued)			
Outcome	**Dietary Supplement + Cardiovascular Drug(s)**	**Conclusion, Effect Estimate**	**Applicability**
Low strength of evidence (continued)			
Lipid profile	Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin	In favor of combination for TG (2 studies not pooled) -81.00 mg/dL (95% CI, -125.30 to -36.70) and -54.00 mg/dL (95% CI, -94.1 to -13.90)	Mean age: 57 years 85% males High CHD risk 4-6 weeks treatment
Lipid profile	Omega-3 fatty acids (3.2 g/day) + Calcium channel blockers + Aspirin + Dipyridamole	In favor of CV drug alone for LDL-C (1 study) 21.00 mg/dL (95% CI, 3.30 to 38.70) In favor of combination for TG (1 study) -81.0 mg/dL (95% CI, -125.30 to -36.70)	Mean age: 56 years 100% males High CHD risk Up to 12 weeks treatment
Lipid profile	Vitamin E (900 mg/day) + Nifedipine	In favor of combination for LDL C (1 study) MD, -39.83 mg/dL (95% CI, -71.29 to -8.37) In favor of combination for TG (1 study) MD, -23.91 mg/dL (95% CI, -35.89 to -11.93)	Elderly Mixed gender High CHD risk 12 weeks treatment
Blood pressure	Omega-3 fatty acids (2 g/day) + Statins	In favor of combination for SBP (1 study) MD, -8.50 mmHg (95% CI, -16.33 to -0.66) No difference for DBP (1 study) MD, 0.20 mmHg (95% CI, -4.76 to 5.16)	Mean age among groups: 44-53 years Mixed gender Mixed CHD risk 5 weeks treatment
Blood pressure	Omega-3 fatty acids (4 g/day fish oil) + Statins	Median reductions from baseline in SBP (1 study) (-5.00 vs. 0.30 mmHg, p = 0.008) and DBP (-3.30 vs. -1.80 mmHg, p = 0.045)	Mean age: 58 years Mixed gender Unclear CHD risk 6 weeks treatment
Blood pressure	Omega-3 fatty acids (3-5 g/day) + ACE inhibitors	No difference between groups for SBP (2 studies pooled): MD, -0.51 mm/Hg (95% CI, -10.59 to 9.57) or for DBP: MD, -1.75 mm/Hg (95% CI, -5.98 to 2.48)	Mean age: 40-55 years Mixed gender Unclear CHD risk 6-25 weeks treatment
INR	Vitamin K (150 µg /day) + Anticoagulants	In favor of combination (1 study) RR for % of time in therapeutic range, 9.0% (95% CI, 1.42 to 16.57) RR for n achieving stable INR, 2.56 (95% CI, 1.24 to 5.28)	Elderly (age range 58-85 years) Mixed gender Unclear CHD risk 25 weeks treatment

Table D. Evidence for the gradable intermediate efficacy outcomes – Key Question 2 (continued)	
Outcome	**Dietary Supplement + Cardiovascular Drug(s)**
Insufficient strength of evidence **Conclusion: Inconclusive (type II error or inconsistent direction of estimates)**	
Lipid profile	***All lipid(s):*** Coenzyme Q10 (100 mg/day) + Statins; Coenzyme Q10 (200 mg/day) + Fenofibrate; Garlic (4 g/day) + Warfarin; Garlic (4 mL/day) + Statins/Aspirin *Gingko biloba* (120 mg/day) + Antiplatelets Magnesium (365 mg/day) + Hydrochlorothiazide Omega-3 fatty acids (4 g/day) + Fenofibrate; Omega-3 fatty acids (3 g/day) + Calcium channel blockers; Omega-3 fatty acids (4 g/day) + Niacin/Aspirin; Omega-3 fatty acids (10 g/day) + Aspirin; Omega-3 fatty acids + Statins Vitamin E (0.6 g/day) + Gemfibrozil; Vitamin E (100 mg/day, 100 IU/day) + Statins ***Only specific lipid(s):*** TG: Niacin (250 mg/day) + Propranolol Garlic (4 g/day) + Nitrates Omega-3 fatty acids + ACE inhibitors Magnesium (4.5 g/day) + Hydrochlorothiazide Vitamin E (900 mg/day) + Antiplatelet agents **LDL-C:** Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin **HDL-C:** Vitamin E (900 mg/day) + Nifedipine Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin; Omega-3 fatty acids (3.2 g/day) + Calcium channel blockers + Aspirin + Dipyridamole
Blood pressure	Coenzyme Q10 (200 mg/day) + Fenofibrates (systolic blood pressure) *Echinacea* (5 g/day) + Warfarin Garlic (4 g/day) + Warfarin *Gingko biloba* (120 mg/day) + Aspirin; *G. biloba* (300 mg/day) + Antiplatelet thienopyridines; *G. biloba* (120 mg/day) + Cilostazol Magnesium (4.5 g/day) + Hydrochlorothiazide; Magnesium (3.65 g/day) + Beta-adrenergic antagonists Omega-3 fatty acids (10 g/day) + Aspirin; Omega-3 fatty acids (4 g/day) + Beta-blockers Vitamin E (600 mg/day) + Furosemide; Vitamin E (900 mg/day) + Nifedipine; Vitamin E (600 mg/d) + Gemfibrozil
INR	*Echinacea* (5 g/day) + Warfarin Garlic (4 g/day) + Warfarin Ginger (3.6 g/day) + Warfarin *Gingko biloba* (2 g/day) + Warfarin Ginseng (1.5-2 g/day) + Warfarin Omega-3 fatty acids (4 g/day) + Warfarin
QT prolongation	Vitamin E (400 IU/day) + Statins

CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein-cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein-cholesterol; MD = mean difference; RR = relative risk; SBP = systolic blood pressure; TG = triglycerides

The majority of evidence on intermediate outcomes was contributed by small underpowered RCTs whose statistically nonsignificant results with wide confidence intervals could rule out neither important benefits nor harms. Due to this imprecision, the strength of evidence for several gradable outcomes was rated insufficient (inconclusive results). When a significant effect was observed, we graded the strength of evidence to be low because of limitations in the internal validity of studies, surrogacy of outcomes, and generally poor to absent reproducibility among studies in the direction of effect estimates (Table D). None of the studies reported outcomes evaluating incidence of metabolic syndrome, incidence of hypotension, carotid-intima media thickness, or change in 10-year Framingham risk profile.

Coenzyme Q10

Evidence was available from four RCTs with unclear CHD risk (49 Asians with hypercholesterolemia[57]), mixed CHD risk (44 participants with statin-induced myalgia[38]), and high CHD risk (40 participants with diabetes and dyslipidemia[58] and 30 participants with ischemic or idiopathic dilated cardiomyopathy[54]). Overall, no significant differences (grade: insufficient; results inconclusive) were seen between the combination of coenzyme Q10 plus a cardiovascular drug versus drug alone in post-treatment levels of:

- C-reactive protein (statins)
- High-density lipoprotein-cholesterol (HDL-C) (statins or fenofibrate)
- Non-HDL-C (fenofibrate)
- Total cholesterol (statins or fenofibrate)
- Triglycerides (statins or fenofibrate)
- Ejection fraction (ACE inhibitors)
- Systolic blood pressure (SBP) (fenofibrates)

Lowgrade evidence was available from one trial indicating no significant difference in high density lipoprotein-cholesterol (HDL-C) for the combination of coenzyme Q10 plus fenofibrate versus fenofibrates alone.

Echinacea

In one small study in 12 healthy male participants (low CHD risk),[59] post-treatment levels of INR and platelet aggregation were not significantly different in the combination of *Echinacea* plus warfarin than with warfarin alone. The results were inconclusive.

Garlic

Four studies examined the effects of garlic in combination with warfarin (48 participants with unclear CHD risk[60] and 16 males with low CHD risk[61]), nitrates (60 participants with high CHD risk[62]), and statins plus aspirin (19 participants with high CHD risk[63]).

The effect of garlic plus warfarin versus warfarin alone on post-treatment lipid profile, blood pressure, INR, platelet aggregability, and platelet count was not significant (inconclusive; grade: insufficient)[60,61] except for significant improvement of HDL-C levels for garlic plus warfarin versus warfarin alone (grade: low).[60]

In participants with coronary artery disease (high CHD risk), the combination of garlic plus nitrates[62] significantly improved total cholesterol (MD, -28.20 mg/dL [95% CI, -48.30 to -8.10]) and HDL-C levels, but not triglyceride levels (MD, -10.30 mg/dL [95% CI, 27.60 to 7.00]).

The effects of garlic combined with statins plus aspirin[63] on lipid profile, C-reactive protein, platelet count, and Agaston calcium score were not significantly different from those of statins plus aspirin in participants with coronary artery disease (Framingham risk >20 percent).

Ginger

In one trial of 12 healthy male participants there was no significant difference in post-treatment INR (inconclusive; grade: insufficient) or platelet aggregability between participants taking the combination of ginger plus warfarin versus warfarin alone.[64]

Ginkgo biloba

Five RCTs investigated this supplement in combination with antiplatelet agents (acetylsalicylic acid,[65,66] clopidogrel,[67] or ticlopidine[68]), an anticoagulant (warfarin[64]), or a vasodilator (cilostazol[67]). For *G. biloba* plus antiplatelet agents (104 participants in total, mixed CHD risk),[65,66] the differences in clotting time, partial thromboplastin time, platelet count, lipid parameters, and blood pressure were not significant (results for lipids and blood pressure inconclusive; grade: insufficient).

The pooled results of two trials (24 participants with mixed CHD risk,[68] 10 participants with low CHD risk[67]) indicated no significant differences in platelet aggregation and bleeding time between the *G.biloba* plus antiplatelet combination versus antiplatelet-only groups. Similarly, *G. biloba* (200 mg of *G. biloba* leaf, 9.6 mg of ginkgo flavonglycosides, 2.4 mg of ginkgolides and bilobalide three times/day) plus warfarin did not result in significantly different post-treatment levels of platelet aggregability or INR (result for INR inconclusive; grade: insufficient) in 12 healthy males.[64] In one trial, however,[67] platelet aggregability (MD, 18.00 percent [95% CI, 1.92 to 34.08]) and bleeding time (MD, 1.02 minutes [95% CI, 0.10 to 1.94]) were significantly better in the *G. biloba* plus cilostazol combination group than the cilostazol-only group.

Ginseng

Three RCTs investigated various ginseng products in combination with warfarin.[69-71] The results from these studies for INR were conflicting (inconclusive; grade: insufficient). Two trials showed no significant difference (25 participants with high CHD risk,[69] 12 males with low

CHD risk[71]). One trial (20 participants with low CHD risk[70]) showed a significant difference, with lower peak INR and AUC of INR in the combination versus control group (MD, -0.19 [95% CI, -0.36 to -0.07] for peak INR and -0.43 [95% CI -1.00 to -0.09] for AUC of INR). The differences in prothrombin time,[69] platelet count,[69] or platelet aggregability[71] between the ginseng-warfarin combination and warfarin-only groups were not significant (results were inconclusive).

Hawthorn

One small trial[72] found no significant difference in an ECG measure (PR interval, which is measured from the beginning of the P wave to the beginning of the QRS complex) between participants receiving hawthorn plus digoxin and those receiving digoxin alone (results inconclusive) in 11 adults at low risk for CHD.

Magnesium

Three RCTs investigated oral magnesium in combination with hydrochlorothiazide[73,74] or beta-adrenergic antagonists[42] in participants with hypertension. In two trials, SBP and DBP (diastolic blood pressure) did not differ significantly between the magnesium hydrochlorothiazide combination versus hydrochlorothiazide-alone groups in the study with 18 participants with unclear CHD risk[73] or the study with 21 participants with low/moderate CHD risk[74] (inconclusive; grade: insufficient). Similarly, in another study,[42] neither SBP nor DBP was significantly different in 39 participants receiving the combination of magnesium plus beta-adrenergic antagonists versus those receiving beta-adrenergic antagonists alone. In one trial,[73] post-treatment total cholesterol and triglyceride levels were not significantly different between the magnesium-hydrochlorothiazide combination versus hydrochlorothiazide-alone groups (inconclusive; grade: insufficient).

Niacin (no more than 250 mg/day)

One RCT in 28 participants with hyperlipoproteinemia (unclear CHD risk)[75] investigated niacin in combination with propranolol. Post-treatment levels of triglycerides and total cholesterol were not significantly different between the group receiving niacin plus propranolol and the groups receiving propranolol alone (inconclusive; grade: insufficient). This study was judged to be at high risk of bias because groups were administered different dosages of propranolol (20 mg and 60 mg).

Omega-3 Fatty Acids

Twenty-four RCTs investigated the use of omega-3 fatty acids plus cardiovascular drugs (statins, ACE inhibitors, calcium channel blockers alone or with other cardiovascular drugs, fenofibrates, niacin plus aspirin, aspirin, beta-blockers, or an anticoagulation agent) versus cardiovascular drugs alone.

The effect on post-treatment triglyceride (TG) levels of adding the supplement to statins was modified according to baseline levels of triglycerides. Specifically, in participants with higher mean baseline levels of TG (greater than 200 mg/dL) there was a statistically significant pooled mean reduction in post-treatment TG levels in the combination arm (two trials, grade: low).[40,76] In contrast, the meta-analysis of four studies with participants with lower levels of TG at baseline (under 200 mg/dL) showed no significant difference between the groups (grade: insufficient). Pooled analyses for levels of HDL-C (seven trials), LDL-C (six trials), and total cholesterol (six trials) showed no significant differences (grade: low) in participants with mixed or unclear CHD risk. The mean SBP was significantly lowered in the supplement-statin combination group (grade: low) in 22 participants with hyperlipemia. Evidence was inconclusive for the outcomes of total cholesterol/HDL-C ratio, non-HDL-C, lipoprotein A, diastolic blood pressure, and bleeding time. Additionally, for nongradable outcomes such as C-reactive protein and blood coagulation parameters (prothrombin time (PT), activated partial thromboplastin time [aPTT], platelet aggregation), there were no significant differences between combination and control groups.

Trials of 43 elderly males undergoing angioplasty using omega-3 fatty acids-statins combinations reported post-treatment levels of non-HDL-C, total cholesterol/HDL-C ratio, and platelet count that were conflicting (opposite direction of effect estimates) and thus inconclusive (grade: insufficient).

In trials using omega-3 fatty acids-ACE inhibitors combination treatment, there were no changes in blood pressure (no difference; grade: low), but significantly more participants experienced at least 50 percent reduction in proteinuria in favor of the combination treatment (RR, 4.00 [95 percent CI, 1.40 to 11.30]).[77]

In one trial using omega-3 fatty acids-fenofibrate combination treatment in participants with high triglyceride levels,[56] the incidence of hypertension was not significantly different in the combination versus control group (RR, 0.98 [95% CI, 0.14 to 6.85]).

In one trial[50] using omega-3 fatty acids-calcium channel blockers combinations, there was no significant difference between the combination and control groups in post-treatment lipid profile (inconclusive; grade: insufficient). Two other trials using aspirin in addition to calcium channel blockers found significant differences in triglycerides (grade: low) in favor of the combination treatment.[51,52] These trials were not pooled because dipyridamole was an additional drug in one trial and not in another.

In one underpowered trial (14 participants with atherogenic dyslipidemia, unclear CHD risk[78]), post-treatment lipid profile did not differ significantly between the combination of omega-3 fatty acids plus niacin and aspirin versus niacin and aspirin (inconclusive; grade: insufficient). In one trial (11 participants with unclear CHD risk), treatment with 3 or 6 g/day omega-3 fatty acids plus warfarin versus warfarin resulted in no significant difference in post-treatment INR values between groups (no numeric data provided).

Vitamin E

Ten RCTs and one controlled clinical trial[79] examined the use of vitamin E with antiplatelet agents (aspirin or ticlopidine),[80] aspirin,[49] furosemide,[81] gemfibrozil,[79] nifedipine,[82] or statins.[46,83-87]

In one trial,[80] post-treatment total cholesterol and triglyceride levels were not significantly different between the groups receiving vitamin E-antiplatelet agent (aspirin or ticlopidine) combination versus aspirin or ticlopidine alone in 16 participants with carotid atherosclerosis (inconclusive; grade: insufficient). Platelet aggregation was significantly decreased with vitamin E supplementation plus aspirin compared with aspirin alone (MD, -1.70 per cm^2 [95% CI, -2.06 to -1.34]).[49]

The effect of vitamin E-furosemide combination on blood pressure was not significantly different from that of furosemide alone in 24 participants with essential hypertension (inconclusive; grade: insufficient).[81] The vitamin E-nifedipine combination significantly lowered total cholesterol (MD, -35.96 mg/dL [95% CI, -46.96 to -24.96]), LDL-C (grade: low), and triglycerides (grade: low), but not HDL-C (inconclusive, grade: insufficient) or SBP (inconclusive, grade: insufficient) in 30 elderly subjects at high risk of CHD.[82]

There was no significant difference in lipid profile across trials using vitamin E-gemfibrozil or vitamin E-statins combinations when compared with the cardiovascular drug alone (inconclusive; grade: insufficient). (See pooled analyses for HDL-C, LDL-C, total cholesterol, and triglycerides.) Likewise, there was no significant difference in blood pressure (inconclusive; grade: insufficient) for vitamin E-gemfibrozil combination, and no significant difference in C-reactive protein, prothrombin time, and platelet count for vitamin E-statins combinations compared with cardiovascular drug(s) alone.

Vitamin K

In one trial,[41] percentage of time INR was in therapeutic range was improved in the group receiving vitamin K-coumarin derivative (warfarin) combination compared with warfarin alone. In addition, number of participants achieving stable INR was higher in combination than with warfarin alone.

Overall evidence indicates that supplementation with vitamin K may improve the stability of anticoagulant therapy (grade: low).

Other Supplements

No evidence was identified for effects of red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs on intermediate outcomes.

Key Question 2a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?

Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.

Key Question 2b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular efficacy outcomes?

Two studies contributed to the evidence regarding statistical interaction between cardiovascular drugs and dietary supplements for this section.[44,78] One study assessed statistical interaction using general linear modeling.[44] No significant interactions were observed between the combination of omega-3 fatty acids and statins with regard to changes in lipid profile (HDL-C, LDL-C, total cholesterol, triglycerides, non-HDL-C) in 52 obese men with dyslipidemia and insulin resistance (moderate/moderately high risk for CHD).[44] Authors of another trial[78] conducted a formal assessment of statistical interaction using ANOVA (analysis of variance) and found that the decrease in triglyceride levels resulting

Table E. Evidence for the gradable harms outcomes – Key Question 3	
Outcome	**Dietary Supplement + Cardiovascular Drug(s)**
Insufficient strength of evidence **Conclusion: Inconclusive (type II error or inconsistent direction of estimates)**	
Serious adverse events	Coenzyme Q10 (100-200 mg/day) + Statins *Ginkgo biloba* (300 mg/day) + ASA; *G. biloba* + Warfarin Magnesium (365 mg/day) + Beta-adrenergic antagonists Omega-3 fatty acids (3-4 g/day) + Statins or fenofibrate
Withdrawal due to adverse events	Coenzyme Q10 (3-4 g/day) + Statins or fenofibrate *Echinacea* (5 g/day) + Warfarin *Ginkgo biloba* (40 mg/day) + ASA and/or pentoxiphylline; G. biloba (2 g/day) + Warfarin; *G. biloba* (240 mg/day) + Digoxin Ginseng (3 g/day) + Warfarin Magnesium (365 mg/day) + Hydrochlorothiazide; Magnesium (365 mg/day) + Beta-adrenergic antagonists Niacin (250 mg/day) + Beta-adrenergic antagonists Omega-3 fatty acids (4 g/day) + ASA; Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (3 g/day) + Ramipril and/or irbesartan; Omega-3 fatty acids (4 g/day) + ASA + Dipyridamole + Calcium channel blockers; Omega-3 fatty acids (4 g/day) + Fenofibrate; Omega-3 fatty acids (3 or 6 g/day) + Warfarin Vitamin E (400 IU/day) + ASA; Vitamin E (1350 IU/day) + Nifedipine
Bleeding (major, minor, and undefined)	Garlic (10 mL/day) + Warfarin *Ginkgo biloba* (300 mg/day) + ASA Ginseng (3 g/day) + Warfarin Omega-3 fatty acids (4 g/day) + ASA; Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (3 g/day) + Ramipril and/or irbesartan; Omega-3 fatty acids (4 g/day) + ASA + Dipyridamole + Calcium channel blockers; Omega-3 fatty acids (mean 3 g/day) + ASA + Clopidogrel; Omega-3 fatty acids (3 or 6 g/day) + Warfarin Vitamin E (400 IU/day) + ASA Vitamin K (5 mg/day) + Warfarin
Renal dysfunction (abnormal glomerular filtration rate, creatinine, blood urea nitrogen, serum potassium)	Coenzyme Q10 (100-200 mg/day) + ACE inhibitors; Coenzyme Q10 (100-200 mg/day) + Statins; Coenzyme Q10 (200 mg/day) + Fenofibrate *Ginkgo biloba* (300 mg/day) + ASA; *G. biloba* (80 mg/day)+ Ticlopidine Magnesium (365 mg/day) + Hydrochlorothiazide Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (4 g/day) + Fenofibrate Vitamin E (400 IU/day) + Statins; Vitamin E (1350 IU/day) + Nifedipine
Hepatotoxicity (abnormal liver enzymes)	Coenzyme Q10 (100-200 mg/day) + Statins; Coenzyme Q10 (100-200 mg/day) + ACE inhibitors Omega-3 fatty acids (4-9 g/day) + Statins Vitamin E (400 IU/day) + Statins
Corrected QT interval	Vitamin E (400 IU/day) + Statins

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid (aspirin); CV = cardiovascular

from the combination of omega-3 fatty acids plus niacin was more than twice the additive effect of either therapy alone in 29 participants with atherogenic dyslipidemia (unclear CHD risk).

Key Question 3. Clinical or intermediate harms with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 3 is shown in Table E.

A total of 58 studies contributed evidence for Key Question 3. One included study was a retrospective cohort study examining omega-3 fatty acids and antiplatelet agents; it had important limitations in design and reporting, as it was unclear regarding participant selection, confounding, and blinding of outcome assessors.[88] The rest of the studies were RCTs, mostly of moderate risk of bias for the gradable outcomes of harms (serious adverse events, withdrawal due to adverse events, renal dysfunction, hepatotoxicity, QT interval, and bleeding). Most of these studies recruited a small number of participants and were underpowered for the outcomes of harm.

Meta-analyses were possible for some omega-3 fatty acids studies. Other evidence could not be pooled because either there was a single study per outcome or zero events in both treatment arms.

For all combinations of dietary supplement and cardiovascular drug, the strength of evidence for all gradable outcomes was insufficient due to inconsistent effect estimates across studies suggesting conflicting findings with no obvious explanation or statistically nonsignificant estimates with wide confidence intervals (Table E). Most crossover trials incorporated an adequate washout period, so carryover effect was not a major concern.

Coenzyme Q10

Five short-term (up to 12 weeks duration) small RCTs that included participants with mixed (moderate and high risk)/unclear[38,57,89] or high[54,58] CHD risk examined coenzyme Q10 plus statins, fenofibrate, ACE inhibitors, or, in one study, vitamin E added to statins. No statistically significant differences were observed for total adverse events,[54,57] abnormalities in fasting blood glucose,[57,58] myoglobin,[57] creatine phosphokinase (CPK),[57,58,89] electrocardiogram (ECG),[58] or retinopathy.[58] However, the studies were underpowered to detect differences in these harms.

One RCT of 32 participants with statin-induced myopathic symptoms[89] found a significantly greater number of subjects with reduced myopathic pain (RR, 4.18 [95% CI, 1.50 to 11.46]) and lower pain severity scores on the Brief Pain Inventory (MD, -1.76 [95% CI, -2.93 to -0.58]) and pain interference score (MD, -1.43 [95% CI, -2.76 to -0.10]) in the combination group (coenzyme Q10 100 mg/day plus statins) versus vitamin E (400 IU/day) plus statin group. A small pilot RCT of 44 participants with self-reported myalgia unable to take adequate doses of statins[38] did not find a significant difference in myalgia, using a visual analog scale, or in number of participants tolerating simvastatin (RR, 1.23 [95% CI, 0.80 to 1.90]) in participants taking coenzyme Q10 plus statins versus statin-alone groups.

Echinacea

One small RCT of 12 healthy volunteers examined *Echinacea* plus a single dose of warfarin versus warfarin alone. No withdrawals due to adverse events or other adverse events were observed.[59]

Garlic

Four small short-term RCTs examined garlic in combination with warfarin, nitrates, or statins plus aspirin in healthy males[61] or those with cardiovascular conditions.[60,62,63] No significant between-group differences were observed across gradable and nongradable outcomes such as fasting blood glucose,[60,62,63] anemia,[60] and leukopenia.[63] Wide confidence intervals for differences in bleeding and fasting blood glucose precluded drawing any meaningful conclusions.

Ginkgo biloba

Seven small RCTs examined *G. biloba* plus warfarin, digoxin, aspirin, aspirin and/or pentoxiphylline, nitrates, cilostazol or clopidogrel, or ticlopidine.[48,64-68,90] The subjects either were healthy volunteers,[64,65,67,68,90] had experienced acute ischemic stroke,[48] or had peripheral arterial disease.[66] Two of these studies included only a single dose of cilostazol/clopidogrel[67] or ticlopidine,[68] so their results should be interpreted with caution. Across all cardiovascular medications, nonsignificant results were observed for gradable outcomes (i.e., withdrawal due to adverse events, bleeding, renal dysfunction, hepatotoxicity, and serious adverse events). Nonsignificant results were also found for all other harms, such as total adverse events,[66,67,90] upset stomach,[66] anemia,[65,66] abnormal white blood cell count,[65] gastrointestinal events,[48,90] diarrhea,[64] constipation,[64] hypoglycemia,[66] hyperglycemia,[66] leukopenia,[66] thrombocytopenia,[66]

and abnormal ECG.[66] These studies were underpowered to detect any differences in harms outcomes.

Ginseng

Three RCTs examined the effects of *Panax ginseng*,[69,71] American ginseng,[70] and Korean ginseng[71] plus warfarin versus warfarin alone. No statistically significant effects were observed in gradable outcomes (i.e., withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity) or nongradable outcomes such as prothrombin time, total adverse events, headache, dizziness, indigestion, INR above 3.5, diarrhea, constipation, hematocrit, and anemia.[69] These trials were all small and underpowered.

Hawthorn

One RCT examined hawthorn plus digoxin versus digoxin alone in eight healthy volunteers.[72] No statistically significant differences were observed in incidence of flatulence, nausea, insomnia, headache, and dizziness.

Magnesium

Two small RCTs in hypertensive subjects examined the effects of magnesium plus hydrochlorothiazide or beta-adrenergic antagonists.[42,73] No statistically significant differences were observed for withdrawal due to adverse events,[42,73] renal dysfunction,[42,73] serious adverse events,[42] diarrhea,[73] vomiting,[73] nausea,[73] adverse events,[73] hypercalcemia,[73] abnormal fasting blood glucose,[73] or abnormal ECG.[73]

Niacin (not more than 250 mg/day)

One RCT of 20 subjects with hyperlipoproteinemia investigated the effects of niacin plus propranolol versus propranolol alone.[75] No statistically significant differences were found in nausea and flushing or in hypotension. This study was at high risk of bias because groups received different dosages of propranolol (20 mg in combination group and 60 mg in monotherapy group).

Omega-3 Fatty Acids

Twenty-two studies (21 RCTs and 1 retrospective cohort study) examined omega-3 fatty acids plus statins,[36,37,40,53,91-97] aspirin,[47,52,78,98,99,99] aspirin and clopidogrel,[88] aspirin in combination with dipyridamole and calcium channel blockers,[52] warfarin,[47,55] ramipril and/or irbesartan,[77] or fenofibrate.[56] These studies were generally small and underpowered. They recruited healthy subjects, or subjects with CHD or risk factors for CHD.

For omega-3 fatty acids plus statins versus statins alone, meta-analyses yielded nonsignificant estimates for serious adverse events, withdrawal due to adverse events, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total adverse events, dyspepsia, headache, constipation, upper respiratory infection, and elevated creatine kinase (CK)/creatine phosphokinase (CPK). However, a significantly elevated fasting blood glucose in the omega-3 fatty acids plus statin group was observed in one RCT.[40] For omega-3 fatty acids in combination with other cardiovascular drugs, no significant differences were found in harms outcomes.

Vitamin E

Ten RCTs examined vitamin E plus aspirin,[39,49,100] nifedipine,[82] furosemide,[81] or statins.[46,83,84,86,87] No statistically significant differences were observed for total adverse events,[100] incidence of headache,[100] gastrointestinal discomfort,[100] incidence of cancer,[39] abnormalities in fasting blood glucose,[81,82] glycosylated hemoglobin,[87] leukopenia,[46] or anemia.[46] These studies recruited subjects who were healthy, or who had CHD or risk factors for CHD. Sample sizes were generally small, except for one study that recruited over 9,000 women.[39]

Vitamin K: One RCT of 6 months duration examined the effects of vitamin K plus warfarin versus warfarin alone.[41] No significant differences were found for bleeding[41] or withdrawal due to adverse events.[41] This study recruited 70 participants with indications for anticoagulant therapy.

Other Supplements

No evidence on clinical harms was identified for the effects of ginger, red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs.

Key Question 3a. Do the effect estimates of clinical or intermediate harms vary by age, ethnicity, gender, or health status?

Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.

Key Question 3b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

One RCT presented data that would allow examination of the interaction between vitamin E supplements and the cardiovascular medication aspirin. This RCT found no significant difference in the rates of adverse events (headache, gastrointestinal discomfort, and withdrawal due to adverse events) among treatment regimes.[100]

Table F. Strength of Evidence for the gradable pharmacokinetic outcomes – Key Question 4			
Outcome	**Dietary Supplement + Cardiovascular Drug(s)**	**Conclusion**	**Applicability**
Low Strength of Evidence			
AUC_{∞}, C_{max}, half-life, and clearance (S- and R-warfarin)	*Echinacea* (5 g/day) + Warfarin Ginger (3.6 g/day) + Warfarin *Ginkgo biloba* (25 mg single dose) + Warfarin	No clinically significant interactions	Healthy volunteer pharmacokinetic studies using single dose of 25 mg warfarin
AUC_{∞}, half-life, and clearance (S- and R-warfarin)	Garlic (4 g/day) + Warfarin	No clinically significant interactions	Healthy volunteer pharmacokinetic study using single dose of 25 mg warfarin
AUC_{∞}, half-life, and C_{max} (ticlopidine)	*Ginkgo biloba* (80-240 mg/day) + Ticlopidine	No clinically significant interactions	Healthy Korean males given single dose of 250 mg of ticlopidine
C_{max}, half-life, and clearance (S- and R-warfarin)	Ginseng (25 mg single dose) + Warfarin	No clinically significant interactions	Healthy volunteer pharmacokinetic study of American and Korean ginseng and either 3 doses of 5 mg warfarin over 3 days of week 1 and week 4 or a single dose of 25 mg warfarin
AUC_{ss}, C_{max} (statin)	Omega-3 fatty acids (4 g/day) + Rosuvastatin or atorvastatin	No clinically significant interactions	Healthy volunteer studies based on therapeutic doses of statins for 14 days

Outcome	**Dietary Supplement + Cardiovascular Drug(s)**
Insufficient Strength of Evidence **Conclusion: Inconclusive (potential for type II error or inconsistent direction of estimates)**	
C_{max} (S- and R-warfarin)	Garlic (4 g/day) + Warfarin
AUC_{∞}, C_{max}, half-life, and clearance (digoxin)	*Ginkgo biloba* (80-240 mg/day) + Digoxin
AUC_{∞} (warfarin)	Ginseng (3 g/day) + Warfarin
Half-life and clearance (rosuvastatin and atorvastatin and/or metabolites)	Omega-3 fatty acids (4 g/day) + Rosuvastatin or atorvastatin
AUC_{ss}, C_{max}, half-life, and clearance (beta-hydroxysimvastatin)	Omega-3 fatty acids (4 g/day)/ + Simvastatin; Garlic (3600 µg of allicin twice daily) + Statins
AUC_{∞}, C_{max}, half-life, and clearance (digoxin)	Hawthorn (900 mg/day) + Digoxin

AUC_{∞} = area under the curve to infinity; AUC_{ss} = area under the curve at steady-state; C_{max} = maximum concentration; CV = cardiovascular

Key Question 4. Pharmacokinetic outcomes with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 4 is shown in Table F.

Twelve randomized controlled trials contributed evidence on pharmacokinetic outcomes.[36,59,61,64,68,70-72,90,93,95,101] No data were available from observational studies. Generally, these studies were open-label crossover RCTs of moderate risk of bias for the gradable outcomes, including between 8 and 50 healthy volunteers. Six studies investigated cardiovascular drug kinetics following a single dose.[59,61,64,68,71,90] The clinical significance of the interaction was evaluated using the FDA guidance.[30] According to this guidance, the statistical significance

of interactions alone cannot determine the clinical significance of interactions. Interactions are deemed significant when the 90 percent confidence intervals of the geometric mean ratio (GMR) fall clearly outside of the default no-effect range of 0.80 to 1.25.

It must be noted that the evidence of pharmacokinetic interactions may not translate into altered clinical effectiveness or harms. Also, evidence originating in healthy young adults may not be applicable to older CVD patients taking cardiovascular drugs due to possible differences in abilities to absorb, metabolize, and excrete drugs.

Echinacea

Evidence of low strength demonstrated no clinically significant interactions between a mixture of 600 mg of *Echinacea* angustifolia root plus 675 mg of *E. purpurea* root given four times a day for a period of 2 weeks and a single dose of 25 mg warfarin. The 90 percent upper and lower bound of GMR for the individual warfarin pharmacokinetic parameters were within the 0.80 to 1.25 boundaries of bioequivalence (Table F).[59]

Garlic

Interactions of 7.4 mg/day of allicin pretreatment for 2 weeks with a single dose of 25 mg warfarin are unclear. Low-strength evidence suggested no clinically relevant interactions for some pharmacokinetic outcomes, while for other important outcomes the strength of evidence was graded as insufficient.[61] Evidence from one garlic-statin trial demonstrated insufficient evidence for pharmacokinetic interactions between the supplement (3,600 µg of allicin twice daily) and 20 mg single doses of both simvastatin and pravastatin.[101] Interactions and bioequivalence could not be clearly established.

Ginger

Evidence of low strength demonstrated no clinically significant interactions between 7-day pretreatment with ginger and a single 25 mg dose of warfarin.[64]

Ginkgo biloba

Evidence of low strength demonstrated no clinically significant interactions between 7-day pretreatment with *G. biloba* and a single 25 mg dose of warfarin.[64] Low-strength evidence revealed no clinically significant interactions between single doses of *G. biloba* and ticlopidine.[68] Insufficient evidence addressed interactions between 7-day pretreatment with *G. biloba* and single doses of digoxin. While pharmacokinetic outcomes showed statistically nonsignificant changes, data were not reported as GMRs, so meaningful conclusions could not be drawn.[90]

Ginseng

Panax ginseng (Korean ginseng) coadministered with warfarin demonstrated no clinically significant interactions based on evidence of low strength.[71] In contrast, interactions of American ginseng (*P. quinquefolius* 2 g/day from weeks 2 to 4) with warfarin were unclear. Low-strength evidence suggested no clinically relevant interactions for some pharmacokinetic outcomes, while for other important outcomes the strength of evidence was graded as insufficient.[70]

Hawthorn

In a trial of hawthorne (84.3 mg/day of oligomeric procyanidines) added to digoxin for 21 days versus digoxin alone for 10 days, no significant differences in pharmacokinetic outcomes were observed between groups. As analyses evaluated mean differences instead of GMRs, we could not exclude type II error and graded the strength of evidence as insufficient for clinically significant interactions.[72]

Omega-3 Fatty Acids

Three open-label randomized crossover studies in 24 to 50 healthy adult volunteers investigated interactions between omega-3 fatty acids and various statins.[36,93,95] Each study compared a statin (rosuvastatin, atorvastatin, or simvastatin) coadministered with 4 g/day of omega-3 fatty acids versus statin alone over a 14-day period. Insufficient evidence for interactions with simvastatin precluded meaningful conclusions about interactions because pharmacokinetic outcomes were analyzed as differences in arithmetic means, yielding nonsignificant results with potential for type II error.[95] Interactions with rosuvastatin or atorvastatin were unclear because for some of the pharmacokinetic outcomes there was low-strength evidence suggesting no clinically relevant interactions, while for other important pharmacokinetic outcomes the strength of evidence was graded as insufficient.[36,93]

Other Supplements

No studies were found examining pharmacokinetic interactions between a cardiovascular drug and coenzyme Q10, magnesium, niacin (no more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, or vitamin K.

Key Question 4a. Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?

A paucity of evidence for supplement-drug combinations precluded exploration of heterogeneity in terms of preidentified subgroups such as age and gender.

Key Question 4b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

Statistical interaction data were not reported in any pharmacokinetic study.

Discussion

Patients with cardiovascular disease commonly take dietary supplements along with prescription drugs, but this review uncovered a paucity of high-quality research into benefits and interactions of drugs coadministered with some of the most common supplements. No trials were identified for most potential combinations, while those that were found were generally underpowered efficacy trials of short duration in highly selected populations.

Clinical outcomes were reported in a sparse collection of inconclusive trials; therefore, evidence on important gradable clinical outcomes was rated insufficient. Findings of note include inconsistent evidence of decrease in rates of coronary artery restenosis following successful angioplasty with coadministration of omega-3 fatty acids in two trials with aspirin and other cardiovascular drugs. Also, evidence from a well-powered pragmatic trial in women showed no benefit of adding vitamin E to daily aspirin on the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death; evidence on individual vascular events was not available.

For most intermediate outcomes of efficacy, such as lipid profile, blood pressure, and INR, we found either insufficient evidence or evidence of low strength demonstrating no effect; however, evidence indicated that omega-3 fatty acids (2 to 4 g/day) likely do not interfere with the efficacy of statin therapy or calcium channel blockers in the presence of antiplatelet agents, but may provide independent benefit in resolving hypertriglyceridemia. There is evidence of low strength that supplemental vitamin K (0.1 to 0.15 mg/day) may help to stabilize INR when given with warfarin. Also, garlic (4 to 10 g/day) may not interact negatively with nitrates and warfarin, and may confer independent benefit in improving HDL-C and total cholesterol. However, our confidence in the validity and reproducibility of these benefits on intermediate outcomes is low.

Safety of intake of dietary supplements concomitant with prescription cardiovascular medications is largely unclear due to insufficient evidence. Evidence regarding benefit of coenzyme Q10 in reducing myalgia in participants with statin-induced myopathic pain is based on two small RCTs and is inconclusive. One study found benefit of supplementation of coenzyme Q10 versus vitamin E added to statins, while another pilot study reported no significant differences between groups using simvastatin with or without coenzyme Q10 in myalgia and tolerance for statin therapy.

Evidence of low strength demonstrated no clinically significant pharmacokinetic interactions when *Echinacea*, ginger, or *Ginkgo biloba* were coadministered with warfarin or when *G. biloba* was coadministered with ticlopidine. Insufficient or conflicting evidence addressed most other supplement–drug pharmacokinetic interactions.

Without an adequate evidence base from the literature, variability in effects across clinically important subgroups (e.g., age, ethnicity, gender, and health status) could not be assessed.

Limitations of our systematic review process include our restriction of the number of dietary supplements of interest to 16 of the most commonly used; this was necessary given limitations of resources and review time. Up to 30 percent of included studies were assessed to have potential for financial conflict of interest, and approximately 45 percent did not report funding information. Given the uncertainties involved in interpreting asymmetry tests for publication bias in most reviews, especially in the presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.[102,103] In fact, a recent recommendation is that tests for funnel plot asymmetry should be used only in a minority of meta-analyses that include at least 10 studies of unequal sizes per analysis without substantial heterogeneity in their effect sizes.[104] We did not adopt other means of evaluating publication bias and selective outcome reporting, such as comparing publications with study protocol, because of time and resource limitations. Seemingly, another limitation could be the exclusion of indirect evidence of drug interactions derived from surrogate measures, such as alterations in probe drug metabolism, that highlight effects on enzymes involved in drug metabolism. As such evidence traditionally originates in healthy volunteers, the applicability of such evidence would have been as much of a concern as for

the pharmacokinetic outcomes we examined, whose applicability was restricted to healthy volunteers with uncompromised drug metabolism. In order to make causal inferences possible for translation into practice, we also excluded combinations of multiple dietary supplements with cardiovascular drugs. For example, a given combination of multivitamins coadministered with a cardiovascular drug or drugs would be limited both in causal inference of supplement-drug(s) interactions and in applicability to the specific doses and combinations of vitamins employed as intervention in the study. Finally, we considered potential benefits, harm, or bioequivalence independently for pharmacokinetic outcomes, according to the FDA guidance.[30] In the absence of guidance regarding intermediate outcomes, we did not draw conclusions on the two sides of clinical decisionmaking, such as "unknown benefit but harm is unlikely" and "unknown harm but benefit is unlikely."

Available evidence poorly addresses the safety and effectiveness of coadministration of dietary supplements with cardiovascular drugs. Given the steady increase in the use of dietary supplements for self-care and the identified gaps in research, we make the following recommendations for future research.

1. First and foremost, 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 of these substances is not known, then studies to characterize these variables, identify mechanisms of action, and describe safety should precede clinical efficacy studies. According to the 2011–15 strategic plan of the National Center for Complementary and Alternative Medicine (NCCAM), clinical trials of dietary supplements will not be supported without documentation of biology and mechanism of action.[105]
2. As extant literature is largely based on few small-size efficacy studies of limited internal validity examining intermediate outcomes, future supplement–cardiovascular drug interaction trials should focus on meaningful clinical outcomes, be appropriately powered and rigorously conducted and reported, and provide precise measurements of both clinical effectiveness and harms outcomes.
3. Most studies were conducted in specialty settings, excluded patients with comorbidities or uncontrolled comorbidities, and did not include ethnic and racial minorities; prospective 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 analysis for age, gender, race, comorbidities (e.g., liver or renal compromise), and genotypic polymorphisms of the cytochrome P450 enzyme.
4. A substantial number of pharmacokinetic interaction studies did not report and analyze pharmacokinetic outcomes according to FDA guidance for bioequivalence studies.[30] Future experiments of drug interactions must evaluate pharmacokinetic outcomes as geometric mean ratios with predefined margins of bioequivalence. Future studies of drug interactions must report pharmacokinetic outcomes as geometric mean ratios. This would allow statistically allow statistically significant as well as nonsignificant outcomes to be interpreted in terms of clinical significance, using predefined margins of bioequivalence.
5. Given the dearth of studies examining interactions between specific supplements and cardiovascular drugs, future clinical trials and observational studies that explore the effect of cardiovascular drugs should additionally assess the use of dietary supplements and include this in the reporting of results. One way to facilitate this would be to consider inclusion of inquiry about dietary supplement use and other CAM care in reporting guidelines such as CONSORT (CONsolidated Standards of Reporting Trials).
6. Phase I trials of cardiovascular drugs should include older populations and, if possible, a pharmacokinetic assessment that includes dietary supplement usage.
7. As subgroups were underrepresented in existing studies, future studies investigating supplement–drug interactions should examine vulnerable subgroups such as the elderly, those with compromised renal and liver functions, and patients with multiple comorbidities.
8. When possible, comparative effectiveness studies should include a statistical analysis for supplement-drug interactions, and the trials should be powered accordingly.
9. Until well-powered experimental studies are conducted to examine dietary supplement–drug coadministration, evidence from well-conducted prospective observational studies should be sought. Observational studies compliant with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines should be powered appropriately to address predefined endpoints of both efficacy and safety in a naturalistic setting, where the population sampled is

reflective of the population for which these data would be meaningful.[106]

10. Given the difficulty and resource-intensive nature of clinical trials, other sources of data should be considered to derive information regarding drug–dietary supplement interactions. Possibilities include synthesis of reports of adverse events made to both FDA and the Pharmacovigilance program at Health Canada. In addition, electronic health record linkages between databases of dietary supplement use and cardiovascular drug prescription may also add to the sparse evidence on supplement-cardiovascular drug interaction that currently exists.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circ Cardiovasc Qual Outcomes. 2010 Feb 23;121(7):e46-e215. PMID: 20019324.
2. Brautbar A, Ballantyne CM. Pharmacological strategies for lowering LDL cholesterol: statins and beyond. Nat Rev Cardiol. 2011 May;8(5):253-65. PMID: 21321561.
3. Mills EJ, Rachlis B, Wu P, et al. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008 Nov 25;52(22):1769-81. PMID: 19022156.
4. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. Arch Intern Med. 2011 May 9;171(9):814-22. PMID: 21555659.
5. National Center for Complementary and Alternative Medicine. What is Complementary and Alternative Medicine? http://nccam.nih.gov/health/whatiscam/. Accessed June 20, 2011.
6. Miller KL, Liebowitz RS, Newby LK. Complementary and alternative medicine in cardiovascular disease: a review of biologically based approaches. Am Heart J. 2004;147(3):401-11.
7. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. Am J Cardiol. 2006 Sep 1;98(5):673-80. PMID: 16923460.
8. Nahin RL, Barnes PM, Stussman BJ, et al. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Natl Health Stat Report. 2009 Jul 30;(18):1-14. PMID: 19771719.
9. Zick SM, Blume A, Aaronson KD. The prevalence and pattern of complementary and alternative supplement use in individuals with chronic heart failure. J Card Fail. 2005 Oct;11(8):586-9. PMID: 16230260.
10. Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. J Am Coll Cardiol. 2010 Feb 9;55(6):515-25. PMID: 20152556.
11. Mashour NH, Lin GI, Frishman WH. Herbal medicine for the treatment of cardiovascular disease: clinical considerations. Arch Intern Med. 1998 Nov 9;158(20):2225-34. PMID: 9818802.
12. Maraldi C, Lattanzio F, Onder G, et al. Variability in the prescription of cardiovascular medications in older patients: correlates and potential explanations. Drugs Aging. 2009 Dec;26(Suppl 1):41-51. PMID: 20136168.
13. Garner JB. Problems of nonadherence in cardiology and proposals to improve outcomes. Am J Cardiol. 2010 May 15;105(10):1495-501. PMID: 20451702.
14. Ulbricht C, Chao W, Costa D, et al. Clinical evidence of herb-drug interactions: a systematic review by the Natural Standard Research Collaboration. Curr Drug Metab. 2008 Dec;9(10):1063-120. PMID: 19075623.
15. Voelker R. Cardiac patients' herbal supplement use deserves more careful investigation. JAMA. 2010 Mar 3;303(9):824. PMID: 20197523.
16. Qato DM, Alexander GC, Conti RM, et al. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA. 2008 Dec 24;300(24):2867-78. PMID: 19109115.
17. Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. [Version 1.0.] Rockville, MD. Draft posted Oct. 2007. http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf. Accessed July 14, 2011.
18. Pharand C, Ackman ML, Jackevicius CA, et al. Use of OTC and herbal products in patients with cardiovascular disease. Ann Pharmacother. 2003 Jun;37(6):899-904. PMID: 12773082.
19. Gohar F, Greenfield SM, Gareth BD, et al. Self-care and adherence to medication: a survey in the hypertension outpatient clinic. BMC Complementary and Alternative Medicine. 2008 Feb 8; 8(1). Article Number 4.
20. Balluz LS, Kieszak SM, Philen RM, et al. Vitamin and mineral supplement use in the United States: results from the third National Health and Nutrition Examination Survey. Arch Fam Med. 2000;9(3):258-62.
21. Schellhorn B, Doring A, Stieber J. [Use of vitamin and mineral supplements: Results from the survey 1994/95 of the WHO MONICA Project Augsburg] [German]. Z Ernahrungswiss. 1998;37(2):198-206.
22. Nahin RL, Pecha M, Welmerink DB, et al. Concomitant use of prescription drugs and dietary supplements in ambulatory elderly people. J Am Geriatr Soc. 2009 Jul;57(7):1197-205. PMID: 19515113.
23. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. Natl Health Stat Report. 2008 Dec 10;(12):1-23. PMID: 19361005.
24. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circ Cardiovasc Qual Outcomes. 2004 Jul 13;110(2):227-39. PMID: 15249516.

25. Santaguida P, Raina P. McMaster Quality Assessment Scale of Harms (McHarm) for Primary Studies: Manual for Use of the McHarm. http://hiru.mcmaster.ca/epc/mcharm.pdf. Accessed December 22, 2010.

26. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

27. U.S. Food and Drug Administration. What Is a Serious Adverse Event? www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm. Accessed August 7, 2011.

28. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1198-207. PMID: 21463926.

29. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. J Clin Epidemiol. 2006 Oct;59(10):1040-8. PMID: 16980143.

30. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Generic Drugs. Approved Drug Products With Therapeutic Equivalence Evaluations. 31st ed., Rockville (MD): U.S. Department of Health and Human Services; 2011.

31. Elbourne DR, Altman DG, Higgins JP, et al. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol. 2002 Feb;31(1):140-9. PMID: 11914310.

32. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1187-97. PMID: 21477993.

33. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.

34. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007 Jan 15;26(1):53-77. PMID: 16596572.

35. Takkouche B, Etminan M, Caamano F, et al. Interaction between aspirin and ACE inhibitors: resolving discrepancies using a meta-analysis. Drug Saf. 2002;25(5):373-8. PMID: 12020174.

36. Di Spirito M, Morelli G, Doyle RT, et al. Effect of omega-3-acid ethyl esters on steady-state plasma pharmacokinetics of atorvastatin in healthy adults. Expert Opin Pharmacother. 2008 Dec;9(17):2939-45. PMID: 19006470.

37. Maki KC, McKenney JM, Reeves MS, et al. Effects of adding prescription omega-3 acid ethyl esters to simvastatin (20 mg/day) on lipids and lipoprotein particles in men and women with mixed dyslipidemia. [Erratum appears in Am J Cardiol. 2008 Nov 15;102(10):1425.] Am J Cardiol 2008 Aug 15;102(4):429-33. PMID: 18678300.

38. Young JM, Florkowski CM, Molyneux SL, et al. Effect of coenzyme Q(10) supplementation on simvastatin-induced myalgia. Am J Cardiol. 2007 Nov 1;100(9):1400-3. PMID: 17950797.

39. Glynn RJ, Ridker PM, Goldhaber SZ, et al. Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: report from the Women's Health Study. Circ Cardiovasc Qual Outcomes. 2007 Sep 25;116(13):1497-503. PMID: 17846285.

40. Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007 Jul;29(7):1354-67. PMID: 17825687.

41. 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.

42. Wirell MP, Wester PO, Stegmayr BG. Nutritional dose of magnesium in hypertensive patients on beta blockers lowers systolic blood pressure: a double-blind, cross-over study. J Intern Med. 1994 Aug;236(2):189-95. PMID: 7913949.

43. Miyamoto S, Kawano H, Takazoe K, et al. Vitamin E improves fibrinolytic activity in patients with coronary spastic angina. Thromb Res. 2004;113(6):345-51. PMID: 15226088.

44. Chan DC, Watts GF, Mori TA, et al. Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. Eur J Clin Invest. 2002 Jun;32(6):429-36. PMID: 12059988.

45. Motoyama T, Kawano H, Kugiyama K, et al. Vitamin E administration improves impairment of endothelium-dependent vasodilation in patients with coronary spastic angina. J Am Coll Cardiol. 1998 Nov 15;32(6):1672-9. PMID: 9822095.

46. Napoli C, Leccese M, Palumbo G, et al. Effects of vitamin E and HMG-CoA reductase inhibition on cholesteryl ester transfer protein and lecithin-cholesterol acyltransferase in hypercholesterolemia. Coron Artery Dis. 1998;9(5):257-64. PMID: 9710685.

47. Eritsland J, Arnesen H, Gronseth K, et al. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol. 1996 Jan 1;77(1):31-6. PMID: 8540453.

48. Garg RK, Nag D, Agrawal A. A double blind placebo controlled trial of ginkgo biloba extract in acute cerebral ischaemia. J Assoc Physicians India. 1995 Nov;43(11):760-3. PMID: 8773035.

49. Steiner M, Glantz M, Lekos A. Vitamin E plus aspirin compared with aspirin alone in patients with transient ischemic attacks. Am J Clin Nutr. 1995 Dec;62(6 Suppl):1381S-4S. PMID: 7495235.

50. Yamamoto H, Yoshimura H, Noma M, et al. Improvement of coronary vasomotion with eicosapentaenoic acid does not inhibit acetylcholine-induced coronary vasospasm in patients with variant angina. [Erratum appears in Jpn Circ J. 1995 Nov;59(11):773-4.] Jpn Circ J. 1995 Sep;59(9):608-16. PMID: 7500544.

51. Kaul U, Sanghvi S, Bahl VK, et al. Fish oil supplements for prevention of restenosis after coronary angioplasty. Int J Cardiol. 1992 Apr;35(1):87-93. PMID: 1563884.

52. Dehmer GJ, Popma JJ, van den Berg EK, et al. Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids. N Engl J Med. 1988 Sep 22;319(12):733-40. PMID: 2842680.

53. Liu M, Wallmon A, Wallin R, et al. Effects of stable fish oil and simvastatin on plasma lipoproteins in patients with hyperlipidemia. Nutr Res. 2003;23(8):1027-34.

54. Watson PS, Scalia GM, Galbraith A, et al. Lack of effect of coenzyme Q on left ventricular function in patients with congestive heart failure. J Am Coll Cardiol. 1999;33(6):1549-52.

55. Bender NK, Kraynak MA, Chiquette E, et al. Effects of marine fish oils on the anticoagulation status of patients receiving chronic warfarin therapy. J Thromb Thrombolysis. 1998;5(3):257-61.

56. Roth EM, Bays HE, Forker AD, et al. Prescription omega-3 fatty acid as an adjunct to fenofibrate therapy in hypertriglyceridemic subjects. J Cardiovasc Pharmacol. 2009 Sep;54(3):196-203. PMID: 19597368.

57. Mabuchi H, Nohara A, Kobayashi J, et al. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis. 2007 Dec;195(2):e182-e189. PMID: 17681347.

58. Playford DA, Watts GF, Croft KD, et al. Combined effect of coenzyme Q10 and fenofibrate on forearm microcirculatory function in type 2 diabetes. Atherosclerosis. 2003 May;168(1):169-79. PMID: 12732401.

59. Abdul MI, Jiang X, Williams KM, et al. Pharmacokinetic and pharmacodynamic interactions of echinacea and policosanol with warfarin in healthy subjects. Br J Clin Pharmacol. 2010 May;69(5):508-15. PMID: 20573086.

60. Macan H, Uykimpang R, Alconcel M, et al. Aged garlic extract may be safe for patients on warfarin therapy. J Nutr. 2006 Mar;136(3 Suppl):793S-5S. PMID: 16484565.

61. Mohammed Abdul MI, Jiang X, Williams KM, et al. Pharmacodynamic interaction of warfarin with cranberry but not with garlic in healthy subjects. Br J Pharmacol. 2008 Aug;154(8):1691-700. PMID: 18516070.

62. Bordia A, Verma SK, Srivastava KC. Effect of garlic (Allium sativum) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids. 1998 Apr;58(4):257-63. PMID: 9654398.

63. Budoff MJ, Takasu J, Flores FR, et al. Inhibiting progression of coronary calcification using Aged Garlic Extract in patients receiving statin therapy: a preliminary study. Prev Med. 2004 Nov;39(5):985-91. PMID: 15475033.

64. Jiang X, Williams KM, Liauw WS, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol. 2005 Apr;59(4):425-32. PMID: 15801937.

65. Wolf HR. Does Ginkgo biloba special extract EGb 761 provide additional effects on coagulation and bleeding when added to acetylsalicylic acid 500 mg daily? Drugs in R & D. 2006;7(3):163-72. PMID: 16752942.

66. Gardner CD, Zehnder JL, Rigby AJ, et al. Effect of Ginkgo biloba (EGb 761) and aspirin on platelet aggregation and platelet function analysis among older adults at risk of cardiovascular disease: a randomized clinical trial. Blood Coagul Fibrinolysis. 2007 Dec;18(8):787-93. PMID: 17982321.

67. Aruna D, Naidu MU. Pharmacodynamic interaction studies of Ginkgo biloba with cilostazol and clopidogrel in healthy human subjects. Br J Clin Pharmacol. 2007 Mar;63(3):333-8. PMID: 17010102.

68. Kim BH, Kim KP, Lim KS, et al. Influence of Ginkgo biloba extract on the pharmacodynamic effects and pharmacokinetic properties of ticlopidine: an open-label, randomized, two-period, two-treatment, two-sequence, single-dose crossover study in healthy Korean male volunteers. Clin Ther. 2010 Feb;32(2):380-90. PMID: 20206795.

69. Lee SH, Ahn YM, Ahn SY, et al. Interaction between warfarin and Panax ginseng in ischemic stroke patients. J Altern Complement Med. 2008 Jul;14(6):715-21. PMID: 18637764.

70. Yuan CS, Wei G, Dey L, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. Ann Intern Med. 2004 Jul 6;141(1):23-7. PMID: 15238367.

71. Jiang X, Williams KM, Liauw WS, et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects.[Erratum appears in Br J Clin Pharmacol. 2004 Jul;58(1):102]. Br J Clin Pharmacol. 2004 May;57(5):592-9. PMID: 15089812.

72. Tankanow R, Tamer HR, Streetman DS, et al. Interaction study between digoxin and a preparation of hawthorn (Crataegus oxyacantha). J Clin Pharmacol. 2003 Jun;43(6):637-42. PMID: 12817526.

73. Paolisso G, Di Maro G, Cozzolino D, et al. Chronic magnesium administration enhances oxidative glucose metabolism in thiazide treated hypertensive patients. Am J Hypertens. 1992 Oct;5(10):681-6. PMID: 1418829.

74. Reyes AJ, Leary WP, Acosta-Barrios TN, et al. Magnesium supplementation in hypertension treated with hydrochlorothiazide. Curr Ther Res Clin Exp. 1984;36(2):332-40.

75. Avogaro P, Capri C, Cazzolato G, et al. Effects of the combination of nicotinic acid and propranolol in very low doses on blood lipids in man. Atherosclerosis. 1974 Sep;20(2):395-400. PMID: 4369975.

76. Nordøy A, Bonaa KH, Sandset PM, et al. Effect of omega-3 fatty acids and simvastatin on hemostatic risk factors and postprandial hyperlipemia in patients with combined hyperlipemia. Arterioscler Thromb Vasc Biol. 2000 Jan;20(1):259-65. PMID: 10634827.

77. Ferraro PM, Ferraccioli GF, Gambaro G, et al. Combined treatment with renin-angiotensin system blockers and polyunsaturated fatty acids in proteinuric IgA nephropathy: a randomized controlled trial. Nephrol Dial Transplant. 2009 Jan;24(1):156-60. PMID: 18685141.

78. Isley WL, Miles JM, Harris WS. Pilot study of combined therapy with omega-3 fatty acids and niacin in atherogenic dyslipidemia. J Clin Lipidol. 2007;1(3):211-7.

79. Sutken E, Inal M, Ozdemir F. Effects of vitamin E and gemfibrozil on lipid profiles, lipid peroxidation and antioxidant status in the elderly and young hyperlipidemic subjects. Saudi Med J. 2006 Apr;27(4):453-9. PMID: 16598319.

80. Micheletta F, Natoli S, Misuraca M, et al. Vitamin E supplementation in patients with carotid atherosclerosis: reversal of altered oxidative stress status in plasma but not in plaque. Arterioscler Thromb Vasc Biol. 2004 Jan;24(1):136-40. PMID: 14592846.

81. Barbagallo M, Dominguez LJ, Tagliamonte MR, et al. Effects of vitamin E and glutathione on glucose metabolism: role of magnesium. Hypertension. 1999 Oct;34(4 Pt 2):1002-6. PMID: 10523398.

82. Paolisso G, Gambardella A, Giugliano D, et al. Chronic intake of pharmacological doses of vitamin E might be useful in the therapy of elderly patients with coronary heart disease. Am J Clin Nutr. 1995 Apr;61(4):848-52. PMID: 7702030.

83. McDowell IF, Brennan GM, McEneny J, et al. The effect of probucol and vitamin E treatment on the oxidation of low-density lipoprotein and forearm vascular responses in humans. Eur J Clin Invest. 1994 Nov;24(11):759-65. PMID: 7890014.

84. Duffy SJ, O'Brien RC, New G, et al. Effect of anti-oxidant treatment and cholesterol lowering on resting arterial tone, metabolic vasodilation and endothelial function in the human forearm: a randomized, placebo-controlled study. Clin Exp Pharmacol Physiol. 2001 May;28(5-6):409-18. PMID: 11380515.

85. Desideri G, Croce G, Tucci M, et al. Effects of bezafibrate and simvastatin on endothelial activation and lipid peroxidation in hypercholesterolemia: evidence of different vascular protection by different lipid-lowering treatments. J Clin Endocrinol Metab. 2003 Nov;88(11):5341-7. PMID: 14602771.

86. De Caterina R, Cipollone F, Filardo FP, et al. Low-density lipoprotein level reduction by the 3-hydroxy-3-methylglutaryl coenzyme-A inhibitor simvastatin is accompanied by a related reduction of F2-isoprostane formation in hypercholesterolemic subjects: no further effect of vitamin E. Circ Cardiovasc Qual Outcomes. 2002 Nov 12;106(20):2543-9. PMID: 12427649.

87. Manuel YK, Vinckx M, Vertommen J, et al. Impact of Vitamin E supplementation on lipoprotein peroxidation and composition in Type 1 diabetic patients treated with Atorvastatin. Atherosclerosis. 2004 Aug;175(2):369-76. PMID: 15262194.

88. Watson PD, Joy PS, Nkonde C, et al. Comparison of bleeding complications with omega-3 fatty acids + aspirin + clopidogrel--versus--aspirin + clopidogrel in patients with cardiovascular disease. Am J Cardiol. 2009 Oct 15;104(8):1052-4. PMID: 19801023.

89. Caso G, Kelly P, McNurlan MA, et al. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. Am J Cardiol. 2007 May 15;99(10):1409-12. PMID: 17493470.

90. Mauro VF, Mauro LS, Kleshinski JF, et al. Impact of ginkgo biloba on the pharmacokinetics of digoxin. Am J Ther. 2003 Jul;10(4):247-51. PMID: 12845387.

91. Neil HA, Ceglarek U, Thiery J, et al. Impact of atorvastatin and omega-3 ethyl esters 90 on plasma plant sterol concentrations and cholesterol synthesis in type 2 diabetes: a randomised placebo controlled factorial trial. Atherosclerosis. 2010 Dec;213(2):512-7. PMID: 21036355.

92. Nordøy A, Svensson B, Hansen JB. Atorvastatin and omega-3 fatty acids protect against activation of the coagulation system in patients with combined hyperlipemia. J Thromb Haemost. 2003;1(4):690-7.

93. Gosai P, Liu J, Doyle RT, et al. Effect of omega-3-acid ethyl esters on the steady-state plasma pharmacokinetics of rosuvastatin in healthy adults. Expert Opin Pharmacother. 2008 Dec;9(17):2947-53. PMID: 19006471.

94. Bays HE, McKenney J, Maki KC, et al. Effects of prescription omega-3-acid ethyl esters on non-high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. Mayo Clin Proc. 2010 Feb;85(2):122-8. PMID: 20118387.

95. McKenney JM, Swearingen D, Di SM, et al. Study of the pharmacokinetic interaction between simvastatin and prescription omega-3-acid ethyl esters. J Clin Pharmacol. 2006 Jul;46(7):785-91. PMID: 16809804.

96. Balestrieri GP, Maffi V, Sleiman I, et al. Fish oil supplementation in patients with heterozygous familial hypercholesterolemia. Recenti Prog Med. 1996 Mar;87(3):102-5. PMID: 8650428.

97. Hansen JB, Lyngmo V, Svensson B, et al. Inhibition of exercise-induced shortening of bleeding time by fish oil in familial hypercholesterolemia (type IIa). Arterioscler Thromb. 1993 Jan;13(1):98-104. PMID: 8422345.

98. Svaneborg N, Kristensen SD, Hansen LM, et al. The acute and short-time effect of supplementation with the combination of n-3 fatty acids and acetylsalicylic acid on platelet function and plasma lipids. Thromb Res. 2002 Feb 15;105(4):311-6. PMID: 12031825.

99. Mueller BA, Talbert RL, Tegeler CH, et al. The bleeding time effects of a single dose of aspirin in subjects receiving omega-3 fatty acid dietary supplementation. J Clin Pharmacol. 1991 Feb;31(2):185-90. PMID: 2010565.

100. D'Arcangues C, Piaggio G, Brache V, et al. Effectiveness and acceptability of vitamin E and low-dose aspirin, alone or in combination, on Norplant-induced prolonged bleeding. Contraception. 2004 Dec;70(6):451-62. PMID: 15541406.

101. Hajda J, Rentsch KM, Gubler C, et al. Garlic extract induces intestinal P-glycoprotein, but exhibits no effect on intestinal and hepatic CYP3A4 in humans. Eur J Pharm Sci. 2010 Dec 23;41(5):729-35. PMID: 20933082.

102. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ. 2007 Apr 10;176(8):1091-6. PMID: 17420491.

103. Peters JL, Sutton AJ, Jones DR, et al. Assessing publication bias in meta-analyses in the presence of between-study heterogeneity. J Royal Stat Soc. Series A (Statistics in Society). 2010;173(3):575-91.

104. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. PMID: 21784880.

105. National Institutes of Health. Exploring the Science of Complementary and Alternative Medicine. National Center for Complementary and Alternative Medicine. Third Strategic Plan 2011-2015. U.S. Department of Health and Human Services; 2011.

106. Von EE, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007 Oct 20;370(9596):1453-7. PMID: 18064739.

Full Report

This executive summary is part of the following document: Seely D, Kanji S, Yazdi F, Tetzlaff J, Singh K, Tsertsvadze A, Sears ME, Tricco A, Ooi TC, Turek M, Tsouros S, Skidmore B, Daniel R, Ansari MT. Dietary Supplements in Adults Taking Cardiovascular Drugs. Comparative Effectiveness Review No. 51. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. HHSA 290-2007-10059-I.) AHRQ Publication No. 12-EHC021-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

For More Copies

For more copies of Dietary Supplements in Adults Taking Cardiovascular Drugs: Comparative Effectiveness Review Executive Summary No. 51 (AHRQ Pub. No. 12-EHC021-1), please call the AHRQ Publications Clearinghouse at 1-800-358-9295 or email ahrqpubs@ahrq.gov.

AHRQ Pub. No. 12-EHC021-1
April 2012