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Draft Comparative Effectiveness Review

Number xx

Dietary Supplements in Adults taking Cardiovascular Drugs

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Structured Abstract

Background: A substantial proportion of patients with cardiovascular diseases use some form of complementary and alternative medicine that includes dietary supplements. This places them at risk for potential adverse events from supplement-drug interactions and nonadherence associated with polypharmacy. Further, addition of a dietary supplement to conventional cardiovascular drugs may confer benefit.

Objectives: To examine the benefits, harms, and effects on cardiovascular drug pharmacokinetics, of co-administration of dietary supplements with cardiovascular drugs. Subgroup variability and evidence of statistical interactions between supplement and drug was also sought. Supplements were selected according to probability of co-administration with drugs**.**

Data Sources: MEDLINE, EMBASE, the Cochrane Library, International Bibliographic Information on Dietary Supplements (IBIDS), and Allied and Complementary Medicine Database (AMED) were searched from inception to October 2010. We also reviewed grey literature.

Study Selection: We followed *a priori* defined protocol. Two reviewers included English and German language records of experimental and observational studies.

Data Extraction: One reviewer extracted data into a standardized electronic form, assessed study risk of bias, graded the strength of evidence and reported its applicability. For the gradable outcomes, the overall study risk of bias and their strength of evidence were independently verified. A random ten percent subset of data were also verified by another reviewer.

Data Synthesis: 66 randomized controlled trials, 2 controlled clinical trials and 1 observational study contributed evidence. All analyses compared a supplement plus drug with the drug alone. With few small studies per supplement, evidence was *insufficient* for all gradable clinical efficacy and harms outcomes such as mortality, thrombotic events, serious adverse events, etc. One pragmatic trial showed no benefit from co-administering vitamin E with aspirin on the composite cardiovascular outcome. Evidence for most intermediate outcomes of efficacy was insufficient or of low strength suggesting no effect. Findings of note were incremental benefit of omega-3 fatty acid supplementation in improving triglyceridemia; INR stabilizing effect of vitamin K when added to warfarin therapy; garlic's potential benefit in improving HDL cholesterol, and reduction in myalgia by addition of coenzyme Q10 to statin therapy. Clinically non-significant or otherwise inconclusive changes were noted for pharmacokinetic outcomes.

Limitations: The evidence base was principally under-powered, short term studies in selected populations, generally with moderate risk of bias.

Conclusions: The evidence base consists of a small number of biased underpowered studies precluding meaningful conclusions across most supplement-drug combinations. Evidence of low strength points to benefit of omega-3 fatty acids, vitamin K, coenzyme Q10, and garlic co-administration on specific intermediate outcomes. Safety concerns, however, persist.

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Executive Summary

Background

The American Heart Association estimates that more than 81 million American adults (one-third of all American 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, manifesting for example, as hypertension, angina, myocardial infarction (MI), heart failure, stroke and transient ischemic attacks (TIA), 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, front line 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 (DS). CAM utilization has increased dramatically in North America over the past decades in both the general and CVD populations.[6,7]

The National Health Interview Survey (NHIS) indicated that a total of $34 billion in annual out-of-pocket expenditures was spent on CAM in 2007.[8] Estimates suggest that approximately one-third to nearly two-thirds of people suffering from heart failure or other cardiovascular disease use some form of CAM that includes DS, 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 ageing, the elderly are most vulnerable to adverse events of any drug interaction. On the other hand, addition of a DS to conventional cardiovascular drugs may confer benefit. Evidence of both benefit and harms of adding a DS to cardiovascular (CV) drugs have been reported.[6,14]

Incorporation in clinical practice of knowledge regarding the impact of concomitant use of CVD medications and DSs requires access to reliable drug-supplement information, as well as a commitment to documentation by clinicians.[15,16]While much more research and data are 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 benefit and harms of adding a dietary supplement to cardiovascular drugs routinely prescribed in the 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 dietary supplements or their complex interactions with cardiovascular drug. DS-drug interactions were examined by investigating evidence of statistical and pharmacokinetic interactions. These objectives were framed in the following Key Questions (KQ):

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:

KQ 1

-clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction [MI] 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?

KQ 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?

KQ 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?

KQ 4

-pharmacokinetic outcomes (e.g., $t_{1/2}$, area under the concentration curve [AUC]) of cardiovascular drugs of interest?

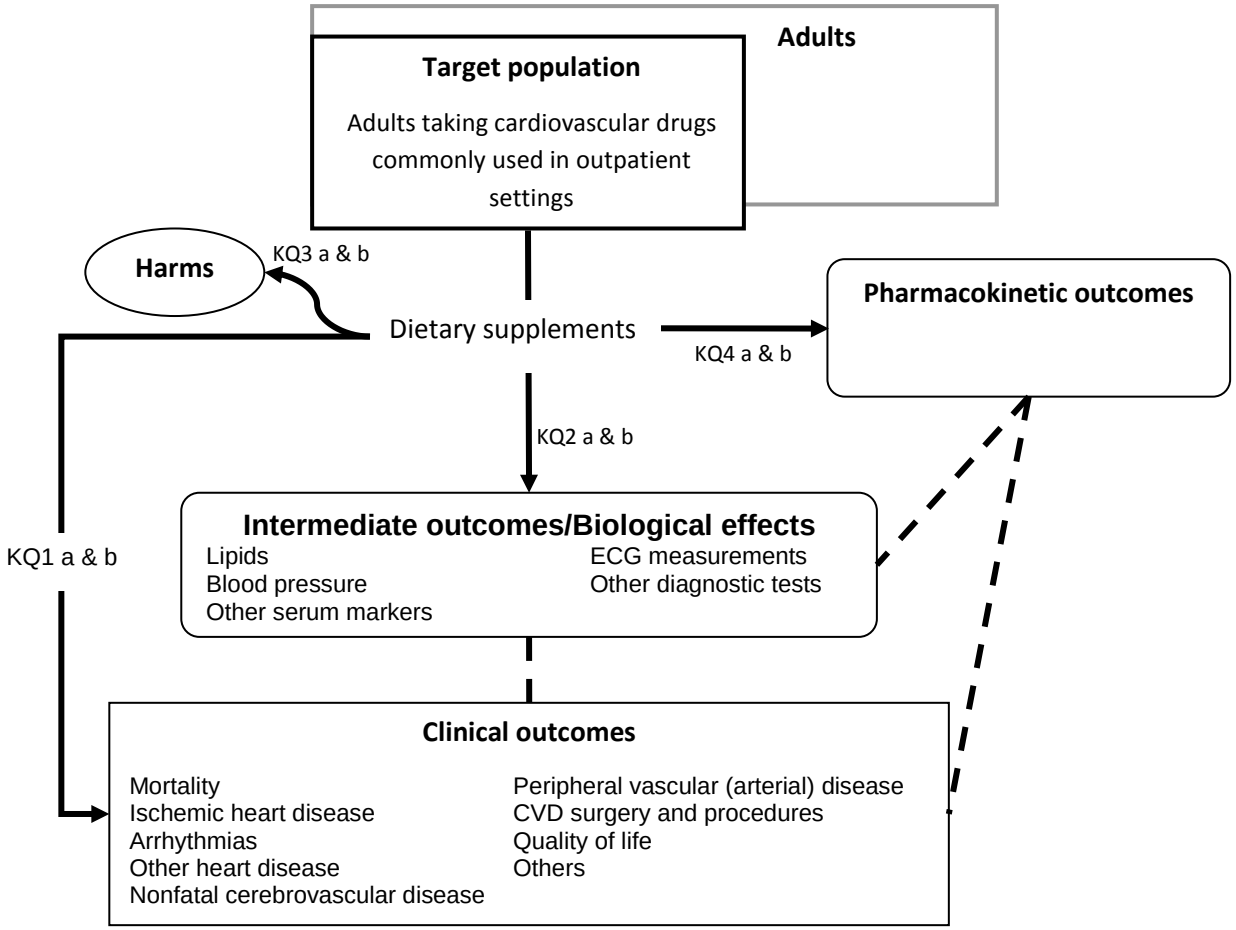
a) Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?

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

Analytic Framework

The expectation behind coadministration of a dietary supplement with prescription CV drugs is 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 DS, or biologic interaction of it with a CV drug. Outcomes with which these effects are measured may be clinical, their proxy surrogates or pharmacokinetic. The analytic framework below depicts the causal pathways forming the basis of the key questions (Figure ES-1).

Figure ES 1.Analytical framework of dietary supplement coadministration with routinely prescribed cardiovascular drugs



Abbreviations: CVD = cardiovascular disease; ECG = electrocardiography; KQ = Key Question.

Methods

Input From Stakeholders

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 Key Informants included clinicians (e.g., cardiologists, naturopathic doctors, clinical pharmacology specialist, and nutritionist), a consumer advocate, and systematic review research methodologists. The public was 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 of specialist clinicians and/or methodologists (TEP). The protocol followed Effective Healthcare Program's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[17]

Data Sources and Searches

We developed peer-reviewed search strategies (Appendix A) and searched the following electronic databases from inception to October 26, 2010: 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 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. Additional references were identified by scanning bibliographies of relevant systematic reviews, clinical trials. We also contacted Technical Expert Panel (TEP) members and the Scientific Resource Centre (AHRQ).

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 and:

- examined a dietary supplement coadministered with a cardiovascular drug(s) against the drug alone or coadministered with another supplement and reported clinical or surrogate cardiovascular efficacy and harms or pharmacokinetic outcomes in any adult population
- evaluated use of a dietary supplement intended for ingestion as pill, capsule, tablet, powder or liquid form and was either coenzyme Q10, *Echinacea*, garlic, ginger, *Gingko biloba*, *Panax ginseng* and American ginseng, hawthorne, oral magnesium, niacin (at most 250 mg/day), omega-3 fatty acids/fishoils, red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium, vitamin E, or vitamin K
- was a comparative experimental and observational study with an independent (concurrent or historical) control group including at least five participants. For KQ 4, studies employing participants as their own control were also eligible (a *post hoc* decision).

We restricted to those cardiovascular drugs that were commonly used in the outpatient settings (Table 1 in Introduction within main body of report). Because of the unmanageable scope of the review, we restricted to the list of dietary supplements outlined above after extensive discussions with the TEP and referring to surveys of the general and cardiovascular populations in the Unites States.[7,18-23]Good quality English language systematic reviews on topic were also eligible. However, a systematic review was to replace denovo synthesis of evidence only when it 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) that were not all taken by 100 percent or the majority (at least 80 percent) of participants in randomized controlled trials – including such studies would have severely limited applicability of evidence.
- the non-randomized controlled trial or observational study reported effect estimates that were not reflective of a supplement plus drug(s) versus drug(s) alone (or plus another supplement) comparison.
- no relevant outcome was reported in the study or outcomes data were not obtained from authors

- the design of the study was lower in the hierarchy of evidence, and did not meaningfully add (for example, by not being a longer-term pragmatic study) to the already included evidence from a higher study design category
- studies included CV drugs not marketed in the US
- 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 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.[25] Certain criteria were specific to particular study designs (e.g., allocation generation and concealment applied only to RCTs). For gradable outcomes, we rated (as low, moderate or high risk) the overall risk of bias for the study and another 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. Methodological quality (good, fair, or poor) of included systematic reviews was assessed across 11 domains using the AMSTAR tool.[26] Appendix C provides the detailed individual study data and risk of bias ratings.

Grading the Strength of the Body of Evidence and Applicability

The strength of a body of evidence was graded based on the following four domains per previously published guidance: overall risk of bias by outcome, consistency, directness, and precision.[27]A methodologist and a content expert graded the strength of the body of evidence as "High," "Moderate," "Low," or "Insufficient." Gradable important outcomes were identified *a priori* for each key question (Table ES-1).

Table ES 1. *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 normalised 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),[28] 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.

Strength of evidence was graded insufficient when there was no evidence for an outcome, when direction of estimates were inconsistent between studies without an identifiable cause, or when the confidence interval was wide or imprecise enough to incorporate both the possibility of clinically meaningful benefit as well as harms. In other words, it is possible that there is some true benefit or harm of supplement in combination with a CV drug as opposed to the drug alone.

We followed previously published guidance, and summarized the determinants of applicability of the body of evidence for outcomes with conclusive results.[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 or unexplained statistical heterogeneity. For pharmacokinetic outcomes, we followed the Food and Drug Administration (FDA) guidance for analysis and interpretation of drug interaction studies – i.e. the zone of bioequivalence is recommended to be between the lower and upper bound of the 90 percent geometric mean ratio (GMR) confidence interval (CI) of 0.8 and 1.25.[30]

We did not pool experimental and observational studies together, but did pool parallel with valid crossover randomized trials.

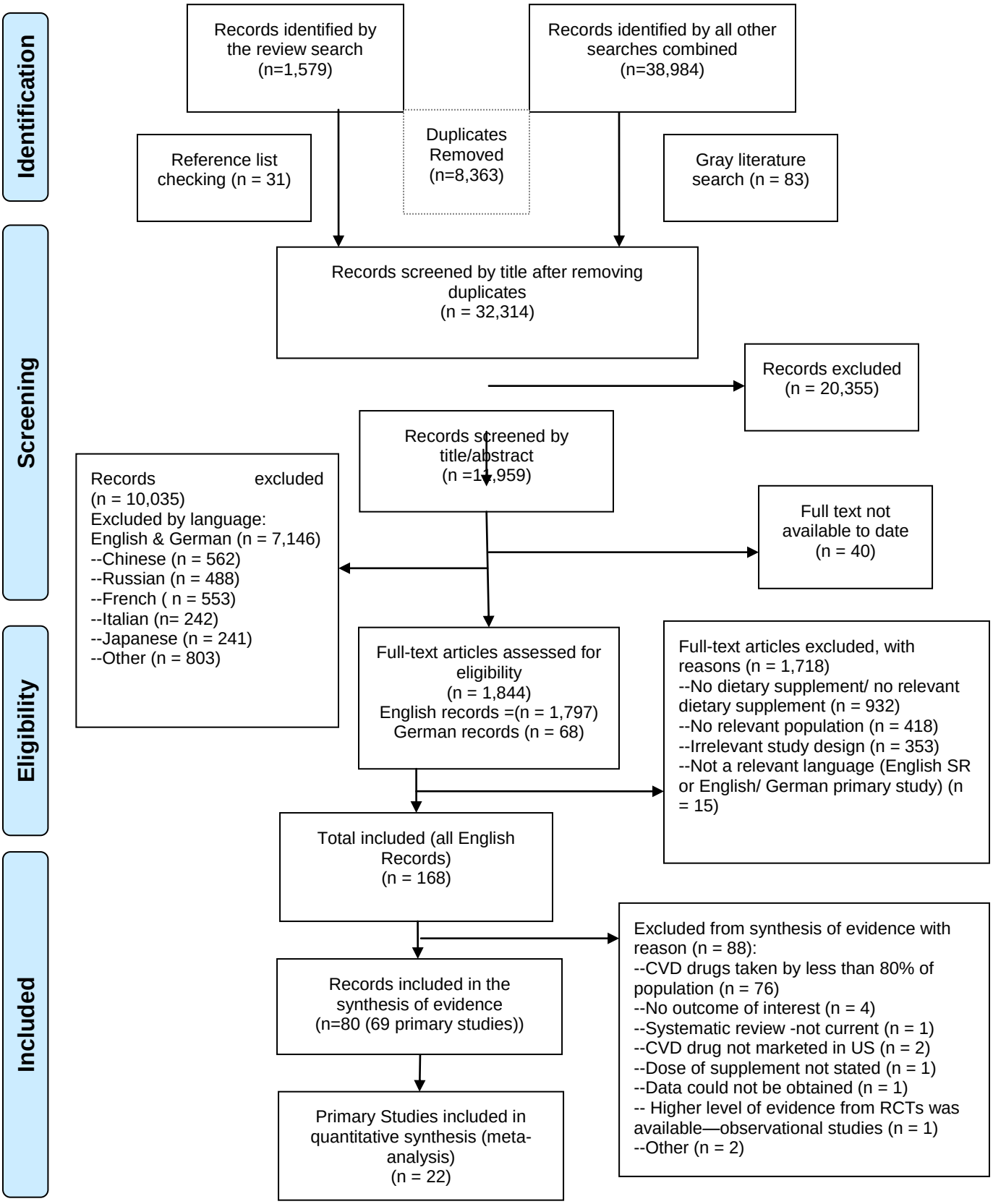
Relative risk (RR) and mean differences were meta-analyzed using the DerSimonian and Laird random-effects model,[31]and Peto odds ratios were calculated when event rates were less than1 percent.[32] For studies with zero events in some arms or sparse data overall, we pooled using the fixed effects Mantel-Haenszel method without continuity correction.[33] Studies with zero events in both arms were excluded from meta-analysis.[32]Where applicable, we examined statistical heterogeneity by calculating synergy index.[34] Statistical heterogeneity was assessed using Cochran's Q (α=0.10) and the I^2 statistic.

Results

Overview

The PRISMA flow diagram shows the number of records screened and included (Figure ES-2).

Figure ES 2. PRISMA flow chart of study identification, screening, eligibility and inclusion



In total, 32,314 records were identified by searches of databases and screened for eligibility. Sixty nine unique English language studies, including one observational design, contributed evidence. We found no relevant unique German publications.

Table ES-2 shows the most relevant risk of bias criteria for the included randomized or controlled clinical trials (n=68).

Table ES 2. Risk of bias criteria and conflict of interest

All RCTs and CCTs	% of total studies (N=68)		
Items	**Yes**	**No**	**Unclear**
Adequate generation of allocation sequence	25.0	1.5	73.5
Allocation concealment	7.4	0.0	92.6
Comparability of groups	25.0	8.8	66.2
Blinding of allocated intervention	19.1	26.5	54.4
Freedom from potential for conflict of interest	26.5	27.9	45.6

KQ1. Clinical cardiovascular effectiveness/efficacy of cardiovascular drug(s) plus supplement versus drug plus placebo, no supplement, or another supplement?

TableES 3. Evidence for the gradable KQ 1 outcomes with data*

Item	Supplement/Drug	Conclusion
Insufficient strength of evidence		
All-cause mortality	Coenzyme Q10/ACE inhibitors *Ginkgo biloba*/antiplatelet agents Omega-3 fatty acids/statins or aspirin or warfarin or fenofibrate; Vitamin K/coumarin derivative	Single underpowered studies per combination precluded meaningful conclusions. For vitamin K/coumarin, two small trials reported three deaths
Quality of life	Coenzyme Q10/ACE inhibitors	Single underpowered study precluded meaningful conclusions
Myocardial infarction	Oral magnesium/beta-blockers Omega-3 fatty acids/aspirin+calcium channel antagonists	Single underpowered studies per combination precluded meaningful conclusions
Arrhythmia	omega-3 fatty acids/statins	Single underpowered study precluded meaningful conclusions
Stroke	Vitamin E/aspirin; vitamin K/coumarin	Single underpowered studies per combination precluded meaningful conclusions for vitamin E/aspirin combination. For vitamin K/coumarin, two underpowered trials contributed evidence
Ischemic stroke, hemorrhagic stroke and TIA	Vitamin E/aspirin	Single underpowered study precluded meaningful conclusions.

Note: *evidence was “insufficient” for all outcomes, so applicability is not presented

Twenty-two randomized controlled trials contributed evidence.[35-56] No data was available from observational studies. With no data, strength of evidence was graded insufficient for the outcomes of hospitalization and peripheral arterial disease across all supplement-cardiovascular drug(s) combinations. No evidence on outcomes of clinical efficacy/effectiveness was found for *Echinacea*, garlic, ginger, ginseng, hawthorne, supplemental doses of niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, and vitamin D (with or without calcium) supplementation coadministered with a cardiovascular drug. A paucity of studies of supplement-drug combinations for which data was available precluded exploration of heterogeneity in terms of pre-identified subgroups. No study analyzed statistical interaction between a supplement and a cardiovascular drug on clinical outcomes.

Generally, across all combinations of dietary supplement and cardiovascular drugs, the strength of evidence of the gradable outcomes of comparative efficacy or effectiveness was graded insufficient because type II error could not be excluded due to low statistical power of mostly short-term efficacy trials with strict inclusion criteria excluding patients with uncontrolled comorbidities and acute ischemic events. Specifically, 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 mostly male patients with left ventricular dysfunction presenting at a specialty center;[54] ***Ginkgo biloba* plus aspirin and/or pentoxyphilline** on all-cause mortality in South Asians with previous stroke;[48] **oral magnesium and β-blockers** on myocardial infarction in hypertensives with no comorbidities;[42] **omega-3 fatty acids/fish oils plus statins** on all-cause mortality in healthy individuals and arrhythmia in highly selected dyslipidemic patients;[35,40] **omega-3 fatty acids/fish oils plus aspirin, warfarin or fenofibrate** on all-cause mortality in patients with unclear to high 10 year CHD risk;[47,56] **omega-3 fatty acids/fish oils plus aspirin and calcium channel antagonist** on acute myocardial infarction in high risk patients;[51] **vitamin E plus aspirin** on stroke and transient ischemic attacks in 100 highly selected patients with previous neurologic deficit;[49] and **vitamin K plus coumarin derivatives** on all-cause mortality, stroke and myocardial infarction in selected groups of patients anticoagulated for a period of 9 months to a year (Table ES-3).[39,41]

No differences in adherence (assessed by pill counting) to statins were noted with co-administration of **coenzyme Q10, omega-3 fatty acids, and vitamin E with statins**. Adherence rates were consistently greater than 90 percent in both drug plus supplement and drug alone groups in patients with self-reported myalgia, highly selected patients with dyslipidemia, and dyslipidemic patients with normal triglyceride.[36,44,46,53,57] No meta-analysis could be undertaken because adherence data by treatment groups were not reported. Conflicting evidence supporting benefit of **omega-3 fatty acids added to conventional antiplatelet therapy and calcium channel antagonists** on rates of restenosis following successful coronary angioplasty may be explained by differences in study population, design, and treatment.[51,52] When 3.2 grams eicosapentaenoic acid was taken daily along with therapeutic doses of aspirin, dipyridamole, and calcium channel antagonists by 82 highly selected male patients, significantly lower rates of restenosis (at least 50 percent reduction in diameter) were observed compared with CV drug alone (RR 0.40, 95 percent CI, 0.20, 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.[51] The differences in rates of restenosis could be explained by differences in study populations, and trial details. In the Indian trial dipyridamole was not among the CV drugs, and selection bias arose because followup angiography was only in only symptomatic patients, .

Underpowered studies addressed all other outcomes such as 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, except one pragmatic trial on 19934 women randomized to 600 IU of **vitamin E plus 100 mg/day of aspirin versus aspirin** alone for 10 years. In this trial, no significant differences were noted for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (relative risk [RR] 0.95 [95 percent confidence interval (CI) 0.79, 1.13]).[38]

KQ2. Intermediate cardiovascular efficacy outcomes of cardiovascular drug plus supplement versus drug plus placebo, no supplement, or another supplement?

Table ES 4. Evidence for the gradable KQ 2 outcomes with data

Gradable outcomes	Dietary supplement / CV drug(s)	Conclusion	Applicability
Low strength of evidence			
Lipid profile	Garlic/Nitrates	In favor of combination for HDL-C and TC (1 study)	Participants at high CHD risk treated for 12 wks (gender and age unknown)
Lipid profile	Omega-3-fish oil/Statins	No difference for: HDL-C (6 studies pooled); LDL-C (5 studies pooled); and achieving their thresholds (1 study)	Mean age: 45-63 y, mixed gender with Mixed CHD risk treated for up to 25 wks
Lipid profile	Omega-3-fish oil/Calcium Channel Blockers/ Aspirin	No difference for HDL-C (1 study) In favor of combination for TG (1 study)	Mean age: 57 y, 85% males with high CHD risk treated for up to 6 wks
Lipid profile	Omega-3-fish oil/Calcium Channel Blockers/ Aspirin/ Dipyridamole	No difference for HDL-C (1 study) In favor of CV drug alone for LDL-C (1 study) In favor of combination for TG (1 study)	Mean age: 56 y 100% males with high CHD risk Up to 12 wks treatment
Lipid profile	Vitamin E/Nifedipine	In favor of combination for LDL-C (1 study), TC (1 study) and TG (1 study)	Elderly, mixed gender High CHD risk 12 wks treatment
Blood pressure	Omega-3-fish oil/Statins	In favor of combination for SBP (1 study) No difference for DBP (1 study)	Mean age: 45-63 y, mixed gender with mixed CHD risk treated for up to 25 wks
Blood pressure	Omega-3-fish oil/Statins	No difference (1 study)	Mean age: 45-58 y Mixed gender Unclear CHD risk Up to 25 wks treatment
Proportion of participants with improved INR	Vitamin K/ Anticoagulants	In favor of combination (2 studies)	Elderly (58-86 y) mixed gender unclear or high CHD risk 25 wks treatment

Insufficient strength of evidence	Conclusion ***Inconclusive*** **(type II error or inconsistent direction of estimates)**
Lipid profile	Coenzyme Q10/Statins; Coenzyme Q10/Fenofibrate; Garlic/Warfarin; Garlic/Statins/Aspirin; *Gingko biloba*/Aspirin; Magnesium/ Hydrochlorothiazide; Omega-3-fish oil/Fenofibrates; Omega-3-fish oil/Calcium Channel Blockers; Omega-3-fish oil/Niacin/Aspirin; Omega-3-fish oil/Aspirin; Vitamin E/Gemfibrozil; Vitamin E/Statins **Only specific lipid(s)** TG Niacin/Propranolol; Garlic/Nitrates; Omega-3-fish oil/ACE inhibitors; Magnesium/Hydrochlorothiazide; Magnesium/Beta-Adrenergic Antagonists; Vitamin E/ Antiplatelet Agents LDL-C and TC Omega-3-fish oil/Calcium Channel Blockers/Aspirin (LDL-C and TC) TC Omega-3-fish oil/ Calcium Channel Blockers/Aspirin/ Dipyridamole HDL-C Vitamin E/Nifedipine
Blood pressure	Garlic/Warfarin; *G. biloba*/Aspirin*; G. biloba*/Antiplatelet thienopyridines; *G. biloba*/Cilostazol; Magnesium/ Hydrochlorothiazide; Magnesium/Beta-Adrenergic Antagonists; Omega-3-fish oil/Aspirin; Omega-3-fish oil/Beta-Blockers; Vitamin E/Furosemide; Vitamin E/ Nifedipine; Vitamin E/Gemfibrozil
INR	Echinacea/Warfarin; Garlic/Warfarin; Ginger/Warfarin*; G. biloba*/Warfarin; Ginseng/Warfarin; Omega-3-fish oil/ Warfarin
INR (% time below/above therapeutic range)	Vitamin K/Anticoagulants
QT prolongation	Vitamin E/Statins

Fifty-seven RCTs and two non-RCTs were included and reviewed for this key question.[58,59] No relevant observational study was identified. For 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, healthcare providers, or outcome assessors were blinded to treatment allocation. This information was not clear for about 56 percent of the studies. The dietary supplements used in these studies were co-enzyme Q10 (5 studies), *Echinacea* (1 study), garlic (4 studies), ginger (1 study), *Ginkgo biloba* (5 studies), ginseng (3 studies), hawthorne (1 study), magnesium (3 studies), niacin (1 study), omega-3 fatty acids/fish oil (23 studies), vitamin E (11 studies), and vitamin K (2 studies). The following CV drugs or drug classes were used across the studies: statins, calcium channel blockers, niacin, angiotensin-converting enzyme (ACE) inhibitors, aspirin, thienopyridine antiplatelets, beta-blockers, anticoagulants, fenofibrates, cilostazol, diuretics, or nitrates. Study participants in most studies had mixed (low and/or moderate) or unclear CHD risk (27.1 percent and 37.3 percent respectively).

The majority of evidence for KQ2 was contributed by small and underpowered RCTs for which statistically non-significant results could not rule out important benefit or harms due to imprecise confidence intervals. Due to this imprecision, the strength of evidence for several gradable outcomes was rated insufficient. When we observed significant effect, we graded the strength of evidence to be low because of limitations in the internal validity of studies, surrogacy

of outcomes, and mostly poor to absent reproducibility in the direction of effect estimates (see Table C). 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: Overall, evidence from 5 RCTs,[37,54,60-62] indicated no significant differences between the combination of coenzyme Q10 and a CV drug versus CV drug alone groups in post-treatment levels of C-reactive protein (CV drug was statins), HDL-C (statins or fenofibrate), non-HDL-C (fenofibrate), LDL-C (statins or fenofibrate), total cholesterol (statins or fenofibrate), triglycerides (statins or fenofibrate), ejection fraction (ACE inhibitors), or systolic blood pressure (ACE inhibitors). The results were inconclusive (grade: insufficient).

***Echinacea*:** In one small study,[63] post-treatment levels of International Normalized Ratio (INR) and platelet aggregation were not significantly different in the combination of *Echinacea* and warfarin compared to warfarin alone. The results were inconclusive (grade: insufficient).

Garlic: Four studies examined the effects of this supplement in combination with warfarin,[64,65] nitrates,[58] and statins plus aspirin.[66] The effect of garlic and warfarin combination (versus warfarin alone) on post-treatment lipid profile, blood pressure, INR, platelet aggregability, and platelet count was not significant (inconclusive; grade: insufficient).[64,65] In participants with CHD, the combination of garlic and nitrates[58] significantly improved total cholesterol (mean MD -28.20 mg/dL [95 percent CI -48.30, -8.10]) and HDL-C levels (MD 8.50 mg/dL [95 percent CI 1.91, 14.89]), but not triglyceride levels (MD -10.30 mg/dL [95 percent CI -27.60, 7.00]). The effects of garlic combined with statins and aspirin[66] on lipid profile (inconclusive; grade: insufficient), CRP, platelet count, and Agaston calcium score was not significantly different from those of statins and aspirin.

Ginger: In one trial of healthy participants, there was no significant difference in post-treatment INR (inconclusive; grade: insufficient), or platelet aggregability between the combination of ginger and warfarin versus warfarin alone.[67]

Gingko biloba: Five RCTs investigated this supplement in combination with antiplatelet agents (acetylsalicylic acid,[68,69] clopidogrel,[70] and ticlopidine[71]), anticoagulant (warfarin),[67] or with vasodilator (cilostazol).[70] For the combination of *Gingko* plus antiplatelet agents, 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[70,71] indicated no significant differences in platelet aggregation and bleeding time between the *Gingko*-antiplatelet combination versus antiplatelet only groups. Similarly the *Ginkgo*-warfarin combination did not result in significantly different post-treatment levels of platelet aggregability or INR (result for INR inconclusive; grade: insufficient). In one trial,[70] platelet aggregability (mean difference [MD] 18.00 percent [95 percent CI 1.92, 34.08]) and bleeding time (mean difference 1.02 minutes, 95 percent CI 0.10, 1.94) were significantly improved in the *Ginkgo*-cilostazol combination group versus cilostazol only group.

Ginseng: Three RCTs investigated this supplement in combination with warfarin.[72-74] The results from these studies for INR were conflicting (inconclusive; grade: insufficient), showing either no significant difference[72,74] or significant difference with lower peak INR and AUC of INR in the combination versus control group (MD -0.19 [95 percent CI -0.36, -0.07] for peak INR and -0.43 [95 percent CI -1.00, -0.09] for AUC of INR).[73] The differences in prothrombin time,[72] platelet count,[72] or platelet aggregability[74] between the ginseng-warfarin combination and warfarin only groups were not significant (results were inconclusive).

Hawthorne: One small trial[75] found no significant difference in PR interval between participants receiving hawthorne-digoxin combination and digoxin alone (results inconclusive).

Magnesium: Three RCTs investigated magnesium in combination with hydroclorothiazide [76,77] or beta-adrenergic antagonists.[42] For two trials, systolic and diastolic blood pressure (SBP and DBP) did not differ significantly between the magnesium-hydroclorothiazide combination versus hydroclorothiazide alone groups (inconclusive; grade: insufficient). The pooled estimates of mean difference for SBP and DBP were -4.54 mmHg (95 percent CI -13.25, 4.16) and -3.37 mmHg (95 percent CI -11.55, 4.81) respectively.[76,77] Similarly, in another study,[42] both SBP and DBP were not significantly different in participants receiving the combination of magnesium and beta-adrenergic antagonists versus those receiving beta-adrenergic antagonists alone. In one trial,[76] post-treatment total cholesterol and triglyceride levels were not significantly different between the magnesium-hydroclorothiazide combination versus hydroclorothiazide alone groups (inconclusive; grade: insufficient).

Niacin (less than or equal to 250 mg/day): One RCT (high risk of bias)[78] investigated this supplement in combination with propranolol in which post-treatment levels of triglycerides and total cholesterol were not significantly different between the two groups receiving treatment with niacin-propranolol combination and 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/fish oil: Twenty-three RCTs investigated the use of omega-3 fatty acids/fish oil with CV drugs (statins, ACE inhibitors, calcium channel blockers alone or with other CV drugs, fenofibrtates, niacin plus aspirin, aspirin, beta-blockers, or anticoagulation agent). In 12 RCTs, post-treatment levels of C-reactive protein, HDL-C, LDL-C, total cholesterol, triglycerides, lipoprotein A, DBP, blood coagulation parameters (PT, aPTT, platelet aggregation), and bleeding time did not differ significantly between the combination of omega-3 fatty acids/fish oil and statins versus statins alone. Pooled analyses for levels of HDL-C (6 trials), LDL-C (5 trials), total cholesterol (5 trials), and triglyceride (4 trials) also showed no significant differences (no difference for HDL-C and LDL-C; grade: low). The mean SBP was significantly lowered in the supplement-statin combination group (grade: low; -8.50mmHg [95 percent CI -16.33, -0.66]). The results from trials using omega-3 fatty acids/fish oil-statins combinations regarding post-treatment levels of non-HDL-C, total cholesterol/HDL-C ratio, and platelet count were conflicting (opposite direction of effect estimates), 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, 11.30]).[79] In one trial using omega-3 fatty acids/fenofibrate combination treatment,[56] the incidence of hypertension was not significantly different in the combination versus control group (RR=0.98 [95 percent CI 0.14, 6.85]). In one trial,[50] using omega-3 fatty acids/fish oil-calcium channel blockers combination, 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 (-81.00 mg/dL [95 percent CI -125.30, -36.70][52] and -54.00 mg/dL [95 percent CI -94.10, -13.90][51]). These trials were not pooled because dipyridamole was an additional drug in one trial and not in another. In one small trial,[80] post-treatment lipid profile did not differ significantly between the

combination of omega-3 fatty acids/fish oil with niacin plus aspirin versus niacin plus aspirin (inconclusive; grade: insufficient).

Vitamin E: Ten RCTs and one CCT [59] examined the use of vitamin E with antiplatelet agents (aspirin or ticlopidine),[81] aspirin,[49] furosemide,[82], gemfibrozil,[59] nifedipine[83] or statins.[46,84-88] In one trial,[81] 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 (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 percent CI -2.06, -1.34]).[49] The effect of vitamin E-furosemide combination on blood pressure was not significantly different from that of furosemide alone (inconclusive; grade: insufficient).[82] The vitamin E-nifedipine combination significantly lowered total cholesterol (MD -35.96 mg/dL [95 percent CI -46.96, -24.96]), LDL-C (MD 39.83 mg/dL [95 percent CI -71.29, -8.37]), and triglycerides (MD -23.91 mg/dL [95 percent CI -35.89, -11.93]), but not HDL-C or SBP in elderly subjects at high risk of CHD.[83] There was no significant difference in lipid profile across trials using vitamin E-gemfibrozil or vitamin E-statins (see pooled analyses for HDL-C, LDL-C, total cholesterol, and triglycerides) combinations when compared with CV drug alone (inconclusive; grade: insufficient). Likewise, there was no significant difference in blood pressure (inconclusive; grade: insufficient) for vitamin E-gemfibrozil combination, as well in C-reactive protein, prothrombin time, and platelet count for vitamin E-statins combination compared with CV drug(s) alone.

Vitamin K: One meta-analysis of two trials showed a significantly improved percentage of time for INR being in therapeutic range in favor of the vitamin K-coumarin derivatives combination (warfarin[41] or phenprocoumon[39]) over coumarine derivatives alone (MD 5.58 percent [95 percent CI 1.02, 10.14]). Number of participants achieving stable INR was higher in combination with warfarin (RR 2.56 [95 percent CI 1.24, 5.28])

Overall evidence indicates that supplementation with vitamin K (0.1 to 0.15 mg/day) may improve the stability of anticoagulant therapy (grade: low).

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

No studies or very few studies for each supplement-drug combination of interest precluded exploration of heterogeneity in the effect estimates across pre-identified subgroups.

b) Is there measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular efficacy outcomes?

Two studies used general linear modeling with ANOVA, and reported statistical interaction between the combination of supplement (omega-3 fatty acids/fish oil) and cardiovascular drugs (statins[44] or niacin plus aspirin[80]) on the outcomes relevant to Key Question 2. The results from these trials were conflicting, one indicating significant interaction between omega-3 fatty acids/fish oil and niacin (plus aspirin) with regards to triglyceride levels[80] and the other no significant interaction between omega-3 fatty acids/fish oil and statins with regards to changes in lipid profile (HDL-C, LDL-C, total cholesterol, triglycerides, non-HDL-C).[44] The trial that found statistical interaction consisted of male and female participants with atherogenic dyslipidemia,[80] and the trial that did not observe a significant interaction was conducted in obese men.[44]

KQ3. Clinical or intermediate harms with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement?

Table ES 5. Strength of evidence for the gradable KQ 3 outcomes with data

Gradable Outcome	Dietary Supplement/CV Drug	Strength of evidence	Conclusion
Serious adverse events	Coenzyme-Q10/Statins *Ginkgo biloba*/ASA *G. biloba*/ Warfarin Magnesium/ Beta-Adrenergic Antagonists Omega-3 Fatty Acids (Fish Oils)/Statins Omega-3 Fatty Acids (Fish oils)/Fenofibrate	Insufficient	Inconclusive
Withdrawal due to adverse events	Coenzyme-Q10/Statins Coenzyme-Q10/ Fenofibrate *Echinacea*/ Warfarin *Ginkgo biloba*/ASA and/or pentoxiphylline *Ginkgo biloba*/Warfarin *Ginkgo biloba*/Digoxin Ginseng/ Warfarin Magnesium /Hydrochlorthiazide Magnesium/Beta-Adrenergic Antagonists Niacin/ Beta-Adrenergic Antagonists Omega-3 Fatty Acids (Fish Oils)/ASA Omega-3 Fatty Acids (Fish Oils)/Statins Omega-3 Fatty Acids (Fish Oils)/Ramipril and/or Irbesartan Omega-3 Fatty Acids (Fish Oils)/ASA + Dipyridamole + Calcium Channel Blockers Omega-3 Fatty Acids (Fish Oils)/Fenofibrate Omega-3 Fatty Acids (Fish Oils)/Warfarin Vitamin E/ASA Vitamin E/Nifedipine	Insufficient	Inconclusive
Bleeding (major, minor, and undefined)	Garlic/ Warfarin *Ginkgo biloba* / ASA Ginseng/Warfarin Omega-3 Fatty Acids (Fish Oils)/ASA Omega-3 Fatty Acids (Fish Oils)/ Statins Omega-3 Fatty Acids (Fish Oils)/Ramipril and/or Irbesartan Omega-3 Fatty Acids (Fish Oils)/ASA + Dipyridamole + Calcium Channel Blockers Omega-3 Fatty Acids (Fish Oils)/ ASA + Clopidogrel Omega-3 Fatty Acids (Fish Oils)/Warfarin Vitamin E/ ASA Vitamin K/ Phenprocoumon; Vitamin K/Warfarin		
Renal dysfunction (abnormal glomerular filtration rate, creatinine, blood urea nitrogen, serum potassium)	Coenzyme-Q10/ ACE inhibitors Coenzyme-Q10/Statins Coenzyme-Q10/Fenofibrate *Ginkgo biloba* /ASA *Ginkgo biloba* /Ticlopidine Magnesium/Hydrochlorothiazide Omega-3 Fatty Acids (Fish Oils)/ Statins Omega-3 Fatty Acids (Fish Oils)/ Fenofibrate Vitamin E/Statins Vitamin E/Nifedipine	Insufficient	Inconclusive
Hepatotoxicity (abnormal liver	Coenzyme-Q10/ Statins	Insufficient	Inconclusive

enzymes)	Coenzyme-Q10/ACE inhibitors Omega-3 Fatty Acids (Fish Oils)/ Statins Vitamin E/ Statins		
Corrected QT interval	Vitamin E/ Statins	Insufficient	Inconclusive

A total of 57 studies contributed evidence for KQ3.[35,36,38,40,44,46,47,49,51-53,55,56,79,80,82-85,87-95, 37,39,41,42,48,54,58,60-72,74-78,96-100] One of the included studies was a retrospective cohort study examining omega-3 fatty acids/fish oils and antiplatelet agents with important limitations in design as it was unclear regarding participant selection, confounding, and blinding of outcome assessors.[100] The rest of the studies were randomized controlled trials 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 sample size and were likely underpowered.

Meta-analyses were possible for the omega-3 fatty acids/fish oil studies. Other evidence could not be pooled because either there was a single study per outcome, or zero events in both treatment arms. Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across pre-identified subgroups.

For all combinations of dietary supplement and CV drug, the strength of evidence for all gradable outcomes was insufficient because of inconsistent effect estimates across studies suggesting conflicting findings with no obvious explanation, or statistically non-significant estimates with wide confidence intervals (Table ES-5). Most crossover trials incorporated an adequate wash-out 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/unclear[37,61,62] or high [54,60] CHD risk examined coenzyme Q10 plus statins, fenofibrate, or ACE inhibitors. No statistically significant differences were observed for total adverse events,[54,61] abnormalities in fasting blood glucose,[60,61] myoglobin,[61] CPK,[60-62] electrocardiogram (ECG),[60] or retinopathy.[60] However, the studies were likely underpowered to detect differences in these harms.

For the coenzyme Q10-statin combination, the evidence for myopathic pain and myalgia was conflicting in two studies.[37,62] One RCT[62] found a significantly greater number of subjects with reduced myopathic pain (RR 4.18 [95 percent CI 1.50, 11.46]) and lower pain severity scores on Brief Pain Inventory (MD -1.76 [95 percent CI -2.93, -0.58]) and pain interference score (MD -1.43 [95 percent CI -2.76, -0.10]) in the combination versus statin alone group. In contrast, a second RCT[37] did not find a significant difference in myalgia, using the visual analogue scale (VAS). The latter study was likely underpowered.

***Echinacea*:** One small RCT of 12 healthy volunteers examined *Echinacea* plus a single dose of warfarin versus warfarin alone. No withdrawals due to adverse or other adverse events were observed.[63]

Garlic: Four small short-term RCTs examined garlic plus warfarin, nitrates, or statins plus aspirin in healthy males,[65] or those with cardiovascular conditions.[58,64,66] No significant between-group differences were observed across gradable and non-gradable outcomes such as fasting blood glucose,[58,64,66] anemia,[64] and leukopenia.[66] The wide confidence intervals for differences in bleeding and fasting blood glucose precluded drawing any meaningful conclusions.

***Gingko biloba*:** Seven small RCTs examined *Ginkgo biloba* plus warfarin, digoxin, aspirin, aspirin and/or pentoxiphylline, nitrates, cilostazol or clopidogrel, or ticlopidine.[48,67-71,99] The subjects were either healthy volunteers,[67,68,70,71,99] had had acute ischemic stroke,[48] or had peripheral arterial disease.[69] Two of these studies included only a single dose of

cilostazol/clopidogrel[70] or ticlopidine[71] so their results should be interpreted with caution. Across all cardiovascular medications, non-significant 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,[69,70,99] upset stomach,[69] anemia,[68,69] white blood cell count,[68] gastrointestinal events,[48,99] diarrhea,[67] constipation,[67] hypoglycemia,[69] hyperglycemia,[69] leukopenia,[69] thrombocytopenia,[69] and abnormal ECG.[69] These studies were likely underpowered to detect any differences in harms outcomes.

Ginseng: Three RCTs examined the effects of *Panax ginseng,*[72] American ginseng,[73] and Korean ginseng 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) and non-gradable outcomes such as prothrombin time, total adverse events, headache, dizziness, indigestion, international normalized ratio (INR) above 3.5, diarrhea, constipation, hematocrit, and anemia.[72] These trials were all small and underpowered.

Hawthorne: One RCT examined hawthorne plus digoxin versus digoxin alone in 8 healthy volunteers.[75] 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 hydrocholorthiazide or beta-adrenergic antagonists.[42,76] No statistically significant differences were observed for withdrawal due to adverse events,[42,76] renal dysfunction,[42,76] serious adverse events[42], diarrhea,[76] vomiting,[76] nausea,[76] adverse events,[76] hyperkalcemia,[76] fasting blood glucose,[76] and abnormal ECG.[76]

Niacin (less than or equal to 250mg/day): One RCT in 20 subjects with hyperlipoproteinemia investigated the effects of niacin plus propranolol versus propranolol alone.[78] No statistically significant differences were found in nausea and flushing, or 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/fish oil: Twenty-two studies (21 RCTs, and one retrospective cohort study) examined omega-3 fatty acids/fish oils plus statins,[35,36,40,53,91-96] aspirin,[47,52,80,90,90,97] aspirin and clopidogrel,[100] aspirin in combination with dipyridamole and calcium channel blockers,[52] warfarin,[47,55] rampril and/or irbesartan,[79] or fenofibrate,[56]. These studies were generally small and 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 AST and ALT, total adverse events, dyspepsia, headache, constipation, upper respiratory infection, and elevated CK/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,[38,49,89] nifedipine, [83] furosemide,[82] or statins[46,84,85,87,88]. No statistically significant differences were observed for total adverse events,[89] incidence of headache,[89] gastrointestinal discomfort,[89] incidence of cancer,[38] abnormalities in fasting blood glucose,[82,83] glycosylated hemoglobin,[88] leukopenia,[46] and anemia.[46] These studies recruited subjects who were healthy, or who had CHD, or risk factors for CHD. Sample sizes were generally small, although one study recruited over 9,000 women.[38]

Vitamin K: Two RCTs of 6 month duration examined the effects of vitamin K plus anticoagulants (phenprocoumon or warfarin) versus anticoagulants alone.[39,41] No significant differences were found for bleeding[39,41] or withdrawal due to adverse events[41]. These studies recruited 70[41] and 200[39] subjects with indications for anticoagulant therapy.

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

Assessment of statistical interaction between a dietary supplement and a CV drug could be undertaken for only one RCT[89] that examined the combination of vitamin E and aspirin. We calculated a synergy index (S-index) for relevant dichotomous outcomes. We found a positive interaction (i.e., synergism) between vitamin E and aspirin for withdrawal due to adverse events (S-index=1.11), indicating a greater number of withdrawals from combination treatment compared with vitamin E or aspirin alone. In the same study, we also found negative interactions (i.e., antagonism) for incidence of headache (S-index=-1.53) and gastrointestinal discomfort (S-index=-0.33), indicating a reduced incidence of these outcomes with combination treatment compared with vitamin E or aspirin alone.

KQ4. Pharmacokinetic outcomes with cardiovascular drug(s) plus supplement versus drug plus placebo, no supplement, or another supplement?

TableES 6. Strength of evidence for the gradable KQ 4 outcomes with data

Item	Supplement/Drug	Strength of evidence	Conclusion	Applicability of evidence
AUC_{∞}, C_{max} , half-life, and clearance for S- and R-warfarin	Echinacea/warfarin; Ginger/warfarin; *Gingko biloba*/warfarin	Low	No clinically significant interactions	Healthy volunteer pharmacokinetic studies using single dose of 25 mg warfarin
AUC_{∞}, half-life, and clearance for S- and R-warfarin; C_{max} S- and R-warfarin	Garlic/warfarin	Low; Insufficient	No clinically significant interactions; Clinically significant interactions could not be ruled out. GMR [90 percent CI] S-warfarin 1.06 [0.77, 1.47]; R-warfarin 1.02 [0.8, 1.4]	Healthy volunteer pharmacokinetic study using single dose of 25 mg warfarin
Ticlopidine AUC_{∞}, half-life and C_{max}	*Gingko biloba*/ ticlopidine	Low	No clinically significant interactions	Healthy Korean males given single dose of 250 mg of ticlopidine
Digoxin AUC_{∞}, Cmax , half-life, and clearance	*Gingko biloba*/digoxin	Insufficient	Inconclusive results because type II error could not be excluded - data were not reported as GMR	NA
Cmax , half-life, and clearance for S- and R-warfarin; Warfarin AUC_{∞}	Ginseng/warfarin	Low; Insufficient	No clinically significant interactions; The evidence of ginseng and warfarin interaction is unclear because with American ginseng, statistically significant reduction in AUC of warfarin was noted, but clinical significance is unclear. Korean ginseng demonstrated no clinically significant interactions	Healthy volunteer pharmacokinetic study of American and Korean ginseng and either three doses of 5 mg warfarin over 3 days of week 1 and week 4, or a single dose of 25 mg warfarin

Item	Supplement/Drug	Strength of evidence	Conclusion	Applicability of evidence
Statin AUC_{ss}, Cmax; Half-life and clearance of rosuvastatin and atorvastatin (and/or metabolites	Omega-3 fatty acids/rosuvastatin or atorvastatin	Low; Insufficient	No clinically significant interactions; Inconclusive results because type II error could not be excluded – data for $t_{1/2}$ and clearance were not reported as GMR	Healthy volunteer studies based on therapeutic doses of statins for 14 days
beta-hydroxysimvastatin AUC_{ss}, C_{max} , half-life, and clearance	Omega-3 fatty acids/Simvastatin	Insufficient	Inconclusive results because type II error could not be excluded – data were not reported as GMR	NA
Digoxin AUC_{∞}, Cmax , half-life, and clearance	Hawthorne/digoxin	Insufficient	Inconclusive results because type II error could not be excluded -- data were not reported as GMR	NA

Abbreviations: AUC = area under the curve (to infinity or at steady-state); C_{max} = maximum concentration.

Eleven randomized controlled trials contributed evidence on pharmacokinetic outcomes.[35,63,65,67,71,73-75,95,96,99] No data was available from observational studies. Generally, these studies were open-label, crossover RCTs, of moderate risk of bias for the gradable outcomes, including between eight and 50 healthy volunteers. Six studies investigated cardiovascular drug kinetics following a single dose.[63,65,67,71,74,99]. Clinical significance of interaction was evaluated using the United States Food and Drug Administration (FDA) guidance.[30] According to the guidance, statistically significant interactions alone cannot determine clinical significance of interactions unless the 90 percent confidence intervals of the geometric mean ratios fall well within the default no effect boundary of 0.80 to 1.25.

No studies were found examining pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (at most 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, or vitamin K, and a cardiovascular drug. A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of pre-identified subgroups such as age and gender. Statistical interaction data was not reported in any pharmacokinetic study.

No clinically significant pharmacokinetic interactions were noted when ***Echinacea*, ginger, *Ginkgo biloba* were coadministered with warfarin, or** when ***Ginkgo biloba* was coadministered with ticlopidine**; the 90 percent upper and lower bound of GMR ratio for the individual pharmacokinetic parameters were within the 0.80 to 1.25 boundaries of bioequivalence.[63,67] The strength of evidence for these findings regarding surrogate outcomes based on single pharmacokinetic studies, with moderate risk of bias was graded as low. For **garlic and warfarin**,[65] ***Ginkgo biloba* and digoxin**,[99], **omega-3 fatty acids and simvastatin**,[96] and **hawthorne and digoxin,** evidence was graded insufficient precluding meaningful conclusions about interactions, because pharmacokinetic outcomes were analyzed as differences in arithmetic means yielding nonsignificant results, or the geometric mean ratios crossed the upper and/or the lower bound of the 90 percent margins of bioequivalence.[75] Interactions between **ginseng and warfarin**, and **omega-3 fatty acids and rosuvastatin or atorvastatin** are unclear because for some of the pharmacokinetic outcomes there was low strength of evidence

suggesting no clinically relevant interactions, while for other important pharmacokinetic outcomes the strength of evidence was graded as insufficient (Table ES-6).[35,73,74,95]. 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.

Discussion

Mostly underpowered, short duration, efficacy trials in highly selected populations contributed sparse evidence on clinical outcomes. As such, the 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 and aspirin. 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, we found insufficient evidence or evidence of low strength suggesting 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 presence of antiplatelet agents, but may provide independent benefit in resolving hypertriglyceridemia. There is also some evidence that supplemental vitamin K (0.1 to 0.15 mg/day) may help to stabilize INR when given with warfarin. Also, garlic (4-10 grams/day) may not interact negatively with nitrates and warfarin and may confer independent benefit in improving HDL 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. Nevertheless, there is some evidence that coenzyme Q10 (100 to 200mg per day) taken in combination with statins, while not interfering with efficacy, might provide benefit for statin induced myalgia.

No clinically significant pharmacokinetic interactions were noted when *Echinacea*, ginger, or *Ginkgo biloba* were coadministered with warfarin and when *Ginkgo biloba* was coadministered with ticlopidine. Insufficient or conflicting evidence addressed most other supplement-drug pharmacokinetic interactions.

Ultimately this limited information makes it impossible to translate our findings into clear advice and tools for clinical decision-making. Without an adequate evidence-base from the literature, variability in effects across clinically important subgroups (e.g. age, ethnicity, gender or health status) could not be assessed.

Limitations of our systematic review process included restricting the number of dietary supplements of interest to 16 of the most commonly used; this was necessary given limitations of resources and review time. Another limitation was 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, applicability of such evidence would have been as much of a concern as for pharmacokinetic outcomes we examined as well providing less direct evidence of interaction. In order to make causal inferences possible for translation into practice, we also excluded combinations of multiple dietary supplements with cardiovascular drugs.

As we have identified that available evidence poorly addresses the safety and effectiveness of coadministration of dietary supplements with cardiovascular drugs, we have the following recommendations for future research:

1) Future trials should focus on meaningful clinical outcomes, be appropriately powered and rigorously conducted and reported, and provide precise measurements of both clinical outcomes and harms outcomes;

2) Trials should be representative of the population taking cardiovascular drugs in terms of comorbidities, setting, and racial distribution. They should also consider subgroup analysis for age, gender, race, comorbidities (e.g. liver or renal compromise), and genotypic polymorphisms of the cytochrome P450 enzyme;

3) Pharmacokinetic studies should follow Food and Drug Administration guidance for conduct and reporting so comparison between trials can be carried out more effectively;

4) Pharmacokinetic studies should present interpretation of statistically significant outcomes in terms of clinical significance;

5) Clinical trials and observational studies that explore the effect of cardiovascular drugs should assess the use of dietary supplements, and include this in the reporting of results;

6) Phase I trials of cardiovascular drugs should include older populations, and if possible a pharmacokinetic assessment that includes dietary supplement usage

7) Future studies should examine vulnerable subgroups such as the elderly, those with compromised renal and liver functions, and patients with multiple comorbidities;

8) Where possible, comparative effectiveness studies should include a statistical analysis for interactions, and the trials should be powered accordingly; and

9) Until well powered experimental studies are conducted to examine dietary supplement-drug coadministration, evidence from well-conducted prospective observational studies should be sought. Electronic health record linkages between databases of dietary supplement use and cardiovascular drug prescription may also add to the equipoise that has been so insufficiently addressed.

Introduction

Vascular disease is a preventable condition that is the leading contributor to mortality in the US [101], and second place in Canada after cancer.[102] Vascular disease includes peripheral vascular disease evident in hypertension; cardiovascular disease such as angina pectoris, myocardial infarction and heart failure; and cerebrovascular disease such as transient ischemic attack (TIA) and stroke.

The American Heart Association estimates that more than 81 million American adults (one-third of all American adults) have at least one form of cardiovascular disease, broadly defined to include all vascular disease.[1] 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, front line treatment for prevention and treatment of cardiovascular disease 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] The prescription drugs considered in this review are summarized in Table 1.

Table 1. Cardiovascular drugs of interest

Cardiovascular Drug Category	Drug Class	Drugs of Interest	
Beta adrenergic antagonists		acebutalol betaxolol bisoprolol carvedilol labetalol metoprolol	nadolol nebivolol pindolol propranolol sotalol timolol
Calcium channel antagonists	Dihydropyridine	amlodipine felodipine isradipine nicardipine	nifedipine nimodipine nisoldipine
	Non-Dihydropyridine	diltiazem	verapamil
Renin-angiotensin-aldosterone system antagonists	Angiotensin-converting enzyme inhibitors (ACE inhibitors)	benazepril captopril enalapril fosinopril lisinopril	moexipril perindopril quinapril ramipril trandolapril
	Angiotensin II receptor blockers (ARBs)	candesartan eprosartan irbesartan losartan	olmesartan telmisartan valsartan
	Renin inhibitors	aliskiren	
	Aldosterone receptor antagonist	eplerenone spironolactone	
Vasodilators	Central vasodilators	clonidine guanabenz	guanfacine methyldopa
	Direct vasodilators	diazoxide hydralazine	minoxidil
	Nitrates	isosorbide dinitrate	
		nitroglycerin	
	Phosphodiesterase inhibitors	sildenafil tadalafil	vardenafil cilostazol
	Prostacycline	alprostadil epoprostenol	iloprost treprostinil

Cardiovascular Drug Category	Drug Class	Drugs of Interest	
	Endothelin antagonist	bosentan	ambrisentan
	Miscellaneous vasodilators	papaverine isoxsuprine	rauwolfia alkaloids
Alpha adrenergic blockers		doxazosin prazosin	terazosin
Antiarrhythmic drugs	Class 1a	disopyramide procainamide	quinidine
	Class 1b	mexilitine	
	Class 1c	encainide flecainide	propafenone
	Class III	amiodarone dofetilide	dronedarone
Inotropic agents		digoxin	
Antilipemic agents	Bile acid sequestrants	colestipol colesevelam	cholestyramine resin
	Cholesterol absorption inhibitor	ezetimibe	
	Fibric acid Derivatives	fenofibrate	gemfibrozil
	HMG-CoA reductase Inhibitors	atorvastatin fluvastatin lovastatin	pravastatin rosuvastatin simvastatin
	Miscellaneous	niacin>250 mg/day*	
Anticoagulants	Coumarin derivatives	warfarin	
	Heparins	dalteparin enoxaparin	heparin tinzaparin
Antiplatelet agents		acetylsalicylic acid (ASA)	clopidogrel ticlopidine
Diuretics	Loop diuretics	bumetanide ethacrynic acid	furosemide torsemide
	potassium-sparing (K-sparing)	amilioride	triamterene
	Thiazide	chlorothiazide hydrochlorothiazide methyclothiazide	bendroflumethazide polythiazide
	Thiazide-like	chlorthalidone indapamide	metolazone

Note: * Niacin at higher doses was considered to be a cardiovascular drug.

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 cardiovascular disease populations.[6,7] The National Health Interview Survey (NHIS) indicated that a total of $34 billion in annual out-of-pocket expenditures was spent on CAM in 2007.[8] Of this amount, 44 percent was spent on non-vitamin, non-mineral DS.[8] Estimates suggest that approximately one-third to nearly two-thirds of people suffering from heart failure or other cardiovascular disease use some form of CAM that includes DS, and are thus placed at risk for potential adverse events from interactions among pharmacologically active agents.[7,9-11] The dietary supplements considered in this review are summarized in Table 2.

Table 2. Dietary supplements

Supplement category	Supplement
Vitamins and minerals	Niacin (restricted to doses ≤ 250 mg/d)*
	Vitamin A (beta carotene)†
	Vitamin D†
	Vitamin E
	Vitamin K
	Magnesium
Herbs or other botanicals	American ginseng (*Panax quinquefolius)*
	Asian ginseng *(Panax ginseng)*
	Echinacea (*Echinacea purpurea*)
	Garlic supplements (*Allium sativum*)
	Ginger supplements (*Zingiber officinale*)
	Gingko (*Ginkgo biloba*)
Refined dietary substances, to increase the total dietary intake (e.g., enzymes or tissues from organs or glands)	Omega-3 fatty acids / Fish oils
	Coenzyme Q10
	Red yeast rice extract
	Resveratrol
	Hawthorne

Notes: * Niacin at higher doses was considered to be a cardiovascular drug.
† The following vitamin analog forms are considered pharmaceutical drugs and were therefore excluded:
Analogs of vitamin A [bexarotene, fenretinide; 13-cis-retinoic acid (isotretinoin, Accutane); 9 –cis retinoic acid (Alitretinoin); and all trans retinoic acid (ATRA) (tretinoin)]; and
Analogues of vitamin D [Calcitriol; dihydrotachysterol (DHT); alfacalcidiol (1α-(OH)D3); calcipotriol; tacalcitol; 19-nor-1,25(OH)2D2 (19-norD2), oxacalcitriol (OCT), 22-oxa-1,25(OH)2D3; paricalcitol; doxercalciferol; 1α-hydroxyvitamin D2 (1α-(OH)D2); falecalcitriol]

Long term use of medications poses significant challenges with respect to both adherence, and potential for drug interactions. Risks for both non-adherence and interactions inevitably increase with the number of medications and supplements taken, and this is of greatest concern in the elderly.[12,13] In addition to concerns of polypharmacy, the elderly also experience physiological changes that make them more susceptible to interactions, as a consequence of alterations in metabolism and excretion, affecting both pharmacodynamics and pharmacokinetics.[103,104]

Understanding the potential for drug-supplement interactions and consequences of such interactions is essential for clinicians and patients when prescribing medications, or advising or deciding to add dietary supplements to current medication and supplement regimes. The increasing morbidity that occurs within older populations suffering from CVD, in conjunction with greater potential for drug interactions, makes this subgroup particularly important to explore. The use of some dietary supplements may complement standard care or may have a detrimental effect on either the pharmacodynamics or pharmacokinetics of standard care. People at risk of or suffering from cardiovascular disease often take dietary supplements alongside prescribed drugs. Given the uncertainty and potential for harm, we need to understand better the risks and benefits, or lack thereof associated with concomitant usage.

Dietary supplements can affect clinically relevant outcomes directly. For example, key factors within coagulation pathways are affected by garlic, fish oil, fenugreek, saw palmetto, gingko biloba and danshen, which all have been shown to inhibit blood coagulation.[10,105-107] When coupled with common anticoagulants like aspirin, warfarin, or ticlopidine, increased bleeding is a serious potential risk. Conversely other supplements, even a seemingly innocuous

one like green tea extract, contain vitamin K that may counteract the anticoagulant effects of certain drugs and thus limit their effectiveness.[108]

An example whereby the addition of a dietary supplement may confer benefit comes from combining coenzyme Q10 with statin therapy. Amongst other actions, coenzyme Q10 has been shown to lower cholesterol, specifically low-density lipoprotein cholesterol,[6] and while not proven, it is plausible that coenzyme Q10 reduces myalgia associated with statin therapy.[109,110] On the other hand, drug-dietary supplement interactions can negatively impact clinical and surrogate outcomes. St. John's wort for example, taken often for the treatment of depression, is a potent inducer of the CYP3A4 enzyme.[111] This enzyme is involved in the oxidative metabolism of many synthetic drugs,[106,107,112-115] including cardiac glycosides, β-adrenergic blockers, calcium channel blockers, statins, angiotensin receptor antagonists, and anticoagulants.[10,106,108] Inducing the metabolism of any of these drugs through this popular herbal product could reduce their effectiveness and potentially result in serious clinical consequences. Conversely, if prescription medication dosage is adjusted in the context of regular ingestion of a CYP3A4 enzyme inhibitor, then supplement cessation may result in excessive drug levels with other serious clinical consequences.

Incorporation in clinical practice of knowledge regarding the impact of concomitant use of cardiovascular disease medications and dietary supplements requires access to reliable drug-supplement information, as well as a commitment to documentation by clinicians.[15,16]

As a consequence of U.S. drug regulatory policy, much more research and data are available describing drug-drug interactions than drug-supplement interactions, and there is a clear need to synthesize information on drug-supplement interactions. A current, comprehensive systematic review of interactions between dietary supplements and drugs specifically in patients taking prescription medications for cardiovascular disease is clearly needed. Recently published systematic reviews addressing aspects related to this topic are not comprehensive, or focus on different populations of interest.[107,113,115] This synthesis evaluates literature that addresses meaningful clinical outcomes, as well as important surrogate or intermediate outcomes, in the context of patients concurrently taking prescription drugs and dietary supplements for prevention and treatment of CVD.

The key questions examined in this review are as follows:

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

1. clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction [MI] 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?
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?

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?

4. pharmacokinetic outcomes (e.g., T1/2, 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?

Methods

The methods for this Comparative Effectiveness Review follow the methods suggested in the *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*, Version 1.0 published by the Agency for Healthcare Research and Quality (AHRQ).[17] Unless stated otherwise, all methods and analyses were determined a priori and documented in a research protocol that was publicly posted by AHRQ for comments. Screening of literature and inclusion/exclusion of studies were tracked and presented according to the PRISMA methodology.[116]

Topic Development and Refinement

This evidence report addresses several key questions regarding the effects of concomitant use of specific dietary supplements and cardiovascular drugs compared with cardiovascular drugs alone or with different dietary supplements. The original topic nomination was for a comparative effectiveness review (CER) of the risks and benefits for elderly patients taking cardiovascular medication concomitantly with herbal supplements. Discussions were held with *Key Informants* representing the Food and Drug Administration (FDA), the National Center for Complementary and Alternative Medicine (NCCAM), and several other institutions on scope of the topic, research questions to be asked, and methodology of evidence synthesis to be adopted. The panel included clinicians (e.g., cardiologists, naturopathic doctors, a clinical pharmacology specialist, and a nutritionist), a consumer advocate, and systematic review research methodologists.
As preliminary searching indicated scarce data in the elderly subgroup, it was decided with the Key Informants to broaden the review topic to the benefits and risks of dietary supplement use in adults taking drugs for prevention and treatment of cardiovascular disease (CVD). Subgroups of interest were added to a preliminary list of demographic and clinical categories that included those with renal dysfunction and genetic polymorphisms in CYP2D6, 2C9, and 2C19. Drug-functional food and drug-conventional food interactions were considered but it was decided that should be evaluated as a separate research project. Five research key questions were finalized in the topic refinement process regarding the comparative efficacy, effectiveness, harms and pharmacokinetics of a dietary supplement coadministered with a cardiovascular drug. Subquestions sought to investigate subgroup effects and evidence of specific drug-supplement statistical interaction. An indirect question enquired about evidence based on human studies that some of the most commonly used dietary supplements cause alterations in cytochrome P450 isozyme activity and in cellular drug transport mechanisms.

All dietary supplements, according to the Dietary Supplement Health and Education Act of 1994 (DSHEA) definition, were of investigational interest. The dietary supplement was defined as one of the following substances:

- a vitamin,
- a mineral,
- an herb or other botanical,
- an amino acid,
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands), or
- a concentrate, metabolite, constituent or extract.

Furthermore, it must also conform to the following criterion:

- intended for ingestion in pill, capsule, tablet, powder or liquid form not represented for use as a conventional food or as the sole item of a meal or diet

AHRQ Effective Health Care Program posted the proposed Key Questions for public comment on their Web site from August 16 through September 13, 2010. In response, the following five general comments were received: 1) the review scope should be restricted to the most common dietary supplements and cardiovascular drugs; 2) the review should focus on patient-oriented outcomes; 3) the review should examine issues related to quality, dose and purity of the dietary supplements of interest; 4) the review should distinguish between regular and occasional users of dietary supplements; 5) the review should distinguish between nutrient and non-nutrient supplements. The Evidence-based Practice Center (EPC), with input from Key Informants and the Technical Expert Panel (TEP), reviewed and refined the Key Questions to ensure that the questions were specific and explicit about what information is being reviewed.

Protocol and Project Scope Amendment

The review according to the originally submitted protocol was proven to require resources beyond those allocated to the EPC centre. The search of included data bases yielded more than 32,000 records; beyond expectations founded on targeted search during topic refinement. A random 10 percent title, abstract and full text screening was conducted to estimate the final size of the review and the projected number of included studies was beyond review resources. Several phone and e-mail discussions were held with the TEP members and the Task Order Officer. Finally, three modifications were made as an amendment to the research protocol:

- restrict to dietary supplements commonly used in adults and elderly taking cardiovascular medication for which current evidence on possible drug-supplement interaction is lacking.
- eliminate the indirect question enquiring about alterations in cytochrome P450 isozyme activity and in cellular drug transport mechanisms.
- restrict to German only as the eligible foreign report language of inclusion.

With input from the TEP, and surveys of the general and cardiovascular populations in the Unites States,[7,18-23] the revised list of dietary supplements was arrived at as follows:

A. Dietary supplements commonly perceived to provide cardiovascular benefit, with a high probability of being used simultaneously with cardiovascular drugs: coenzyme Q10; garlic; ginger; *Gingko biloba*; ginseng; multivitamins; vitamin A or beta carotene; vitamin D; vitamin E; omega-3 fatty acids or fish oils; niacin; and magnesium.

B. Other dietary supplements commonly used by the population using cardiovascular drugs, for which there is some reason to believe there may be an interaction with cardiovascular drugs: *Echinacea*; St. John's wort; red yeast rice; resveretrol; hawthorne; and vitamin K.

C. Supplements falling into categories A or B may be omitted from the list if there is already well understood interaction and a review would be redundant. On this basis, it was proposed that these be excluded: St. Johns wort; therapeutic doses of niacin (greater than 250 mg/day); and magnesium as infusion or injection.

Language restriction was based on the fact that during the screening of the 10 percent random sample of a total of 32, 000 records, most commonly identified foreign languages were German (24 percent), Russian (16 percent), and Chinese (44 percent), comprising 84 percent of reports in language other than English. Other languages included Norwegian (4 percent) and Italian, Polish, Swedish, Dutch and French (2 percent each). Because of uncertain applicability of Russian and Chinese language studies, the only foreign language considered to be eligible was

German. The list of relevant dietary supplements, rationale for the above-mentioned project scope amendments, and other details, are presented in the Table 3 below.

Table 3. Protocol amendments

Item	Amendment	Section of the protocol report affected
Revision to the list of dietary supplements	Include only: Coenzyme Q10 Echinacea Garlic Ginger Gingko biloba Ginseng Hawthorne Magnesium (oral) Niacin (≤ 250 mg/d) omega-3 fatty acids/fishoils Red yeast rice extract Resveratrol Vitamin A Vitamin D ± calcium Vitamins E and K	Definition of intervention Method: Table 1 (intervention KQ 1-4)
Language of publication	Restriction to English and German for experimental and observational studies	Methods: criteria for inclusion; Table 1: report characteristics
Restriction of key questions	Elimination of Key Question 5	Key Question 5 Analytic framework Methods: criteria for inclusion, Table 1: grading the evidence

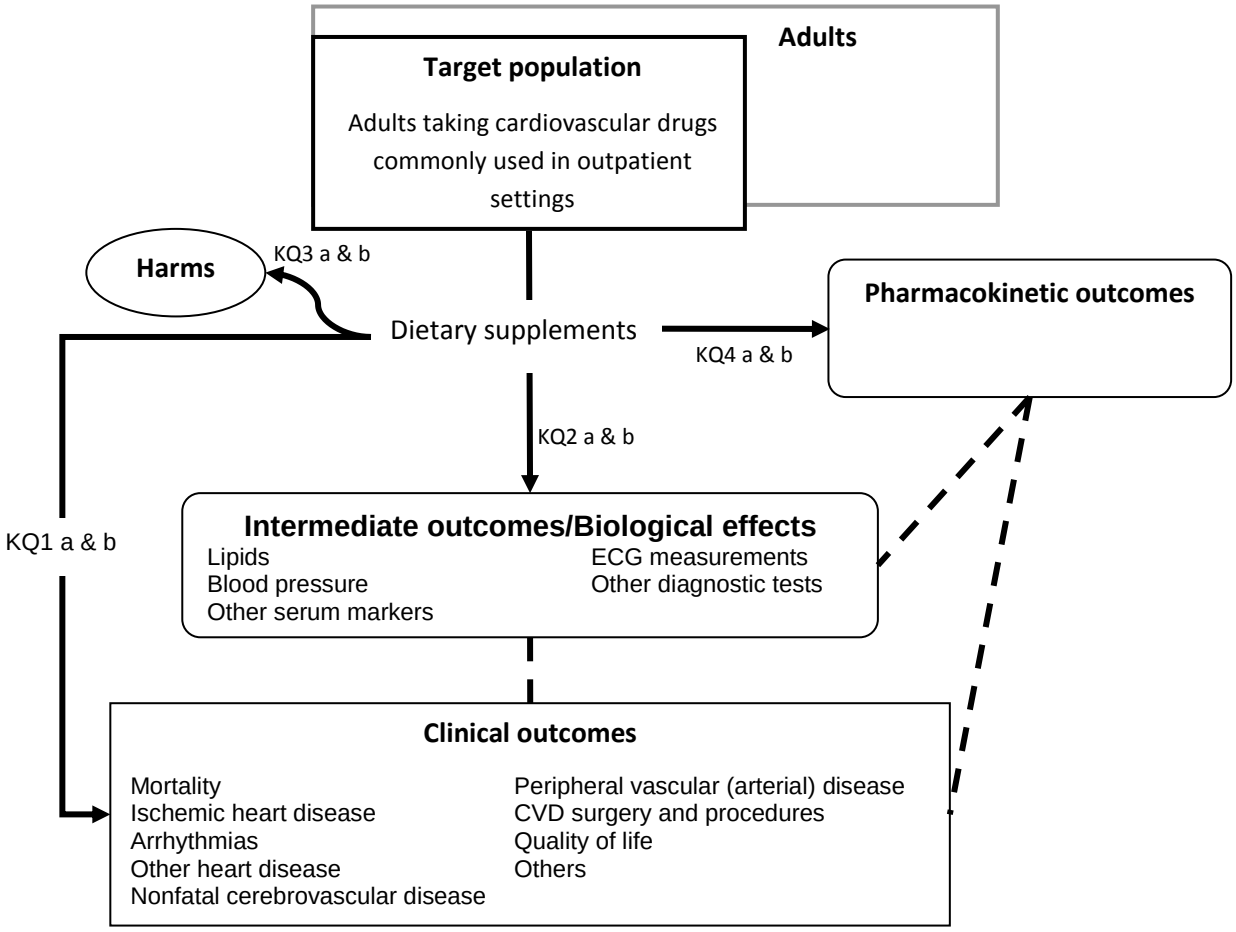
Development of the Analytic Framework

The analytic framework depicts the causal pathways forming the basis of the key questions (Figure 1). The framework outlines the conceptual basis or expectations for adding a dietary supplement to prescribed cardiovascular drugs. Expectations include improvement in efficacy and reduction in harms related to cardiovascular drugs. Outcomes that represent these changes may be clinical, surrogate (proxy for clinical), or pharmacokinetic. Altered outcomes may be a result of an add-on effect of the dietary supplement and/or supplement-drug interaction. Drug interactions may be seen as biologic (i.e. pharmacodynamic or pharmacokinetic interactions reflected in altered clinical and surrogate outcomes of benefit and harms) or statistical.[117]Statistical interactions measure biologic interactions in terms of a product term added to a linear model. The key questions posed therefore examine whether outcomes of benefit and harms alter with the addition of a dietary supplement. In addition, they examine pharmacokinetic and statistical interactions.

In the context of the population of interest, the key questions are indicated along the corresponding arrows connecting treatment and outcomes of interest. The framework includes 7 sections. The first section represents the adult population, within which the target population is included. The remaining 6 sections are: 1) target population (adults taking cardiovascular drugs commonly used in the outpatient setting); 2) treatment (dietary supplements); 3) intermediate outcomes/biological effects (lipid levels, blood pressure, electrocardiogram measurements, other serum markers, and diagnostic tests); 4) clinical outcomes (mortality, ischemic heart disease, arrhythmias, cerebrovascular disease, peripheral arterial disease, cardiovascular disease surgery

and procedures, and quality of life); 5) harms (allergic reactions, significant bleeding, and neurological and gastrointestinal adverse events); and 6) pharmacokinetic outcomes (measures of drug absorption, distribution, metabolism, and excretion).

Figure 1. Analytic framework



Abbreviations: CVD = cardiovascular disease; ECG = electrocardiography; KQ = Key Question.

Literature Search Strategy

An experienced medical information specialist developed and tested the electronic search strategies by using a combination of controlled vocabulary and free text in consultation with the team. An independent information specialist peer-reviewed the search strategies according to the PRESS checklist.[118]

To identify primary study reports (see Appendix A), we searched the following electronic databases from inception to October 26, 2010: MEDLINE, EMBASE, the Cochrane Library (CENTRAL, Cochrane Database of Systematic Reviews, DARE, HTA), International Bibliographic Information on Dietary Supplements (IBIDS), and Allied and Complementary Medicine Database (AMED). We used controlled vocabulary (e.g., "Dietary Supplements ," "Drugs, Chinese Herbal," "Phytotherapy," etc.) and keywords (e.g., nutritional supplements, garlic, ginger, etc.) in combination with controlled vocabulary and keywords related to cardiovascular agents.

To identify systematic reviews addressing research questions similar to the key questions outlined for this review, we used a slightly modified strategy from that indicated above, by including a systematic review filter (for MEDLINE and EMBASE) and limiting the search of the Cochrane Library to the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database (see Appendix Y). The identification of relevant systematic reviews addressing any one of the key questions would serve the purpose of replacing a *de novo* process involving primary synthesis with existing systematic reviews.

We restricted our searches to human studies without imposing any language or date restrictions. We attempted to identify unpublished literature (including abstracts and conference proceedings) through searches of trial registries (e.g., ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, World Health Organization Clinical Trials), the Cambridge Scientific Abstracts (CSA) Conference Papers Index, and Scopus. Additional references were identified by scanning bibliographies of relevant systematic reviews and clinical trials. We also contacted Technical Expert Panel (TEP) members.

Through the Scientific Resource Center, we contacted the industry for scientific information packets (SIPs) on drug-supplement interaction and requested for (Appendix B for list of drug manufacturers contacted):

- a current product label
- randomized controlled trials, published or unpublished
- observational studies, published or unpublished

All identified citations were downloaded into a Reference Manager 12[119] database for duplicate removal and early analysis. The unique references were then uploaded into DistillerSR,[120] a review management Web application.

Study Selection

Process Description

The reviewers involved in initial screening attended a screening training session and pilot tested the screening forms. Titles were screened by one reviewer; all exclusions were independently screened by a second reviewer. A similar process of screening was followed to

screen abstracts of studies that passed the title screen. Two reviewers independently screened the full text of all included records. Discrepancies were resolved by consensus.

Eligibility Criteria of Systematic Reviews

When available, topically relevant reviews were to be included to answer one or more of the key questions. As per the Cochrane Collaboration definition,[121] a systematic review includes a: specific research question; search strategy (e.g., sources such as electronic databases, period covered by the search); and methods used to assess the risk of bias of studies included in the review. Narrative reviews were excluded. We limited our review to those systematic reviews judged to be of 'Good' quality (see below for how quality of a review was assessed). Reasons for exclusion were noted. We planned to replace de novo evidence synthesis with good quality systematic review evidence only when it was deemed current obviating the need to update.

Eligibility Criteria of Primary Studies

We aimed to include hypothesis-testing as opposed to hypothesis generating studies (case-reports and series). We thus included experimental and observational comparative studies (i.e. those with independent controls) evaluating the benefits or harms of concomitant dietary supplement use in adults taking cardiovascular medications versus no dietary supplement (or other dietary supplement). In a *post hoc* decision we expanded the study design criteria to allow inclusion of single arm controlled before-after pharmacokinetic studies in which post-treatment values were compared with baseline values. This was because we considered such evidence as a reasonable comparison between drug-supplement and drug alone for pharmacokinetic outcomes when an adequate washout period was employed. This review was limited to human studies with specific eligibility criteria presented in Table 4.

Table 4. Study inclusion criteria

Population		
KQs 1–4	Adult participants (the majority of participants ≥16 years of age or with subgroup data presented for adults) taking at least one specific cardiovascular drug or one specific class of cardiovascular drugs such as α-adrenergic antagonists , antiarrhythmic drugs, anticoagulants, antilipemic agents, antiplatelet agents, β-adrenergic antagonists, calcium channel antagonists, diuretics, inotropic agents, renin-angiotensin-aldosterone system antagonists, and other vasodilators (e.g. centrally acting, phosphodiesterase inhibitors, prostaclyclin derivates, endothelin anatagonsts, etc)	The drugs were restricted to those commonly used in U.S. outpatient settings for treatment and prevention of cardiovascular disorders.
Intervention		
KQs 1–4	Coenzyme Q10 *Echinacea* Garlic Ginger *Gingko biloba* Ginseng Hawthorne Magnesium (oral)	Niacin (≤ 250 mg/d) Omega-3 fatty acids/fish oils Red yeast rice extract Resveratrol Vitamin A Vitamin D ± calcium Vitamin E Vitamin K

Comparator		
KQs 1–4	No dietary supplement (placebo, no treatment) or another dietary supplement.	
Outcomes		
KQ 1 Clinical outcomes	Mortality • All-cause mortality • Vascular death • Specific vascular death (e.g., fatal MI, fatal stroke) Ischemic Heart Disease (Coronary Artery Disease) • All myocardial infarction (MI, acute MI) • Nonfatal MI (MI, acute MI) • Unstable angina • Acute coronary syndrome • Coronary artery disease composite outcomes (combination) • Coronary (re)stenosis/graft occlusion/vasospasm (post hoc) Arrhythmias • Sudden death • Ventricular fibrillation • Ventricular tachycardia • Atrial fibrillation • Heart block Other heart disease • Congestive heart failure • Valvular disease Adherence to prescribed cardiovascular drug or regimen Hospitalization	Cerebrovascular disease • All stroke • Hemorrhagic stroke • Thrombotic stroke • Transient ischemia attack (TIA) • Carotid artery disease (not measured by IMT or Doppler) • Other Peripheral arterial disease (PAD) • Limb thrombosis/leg ischemia • Claudication (pain walking) • Mesenteric ischemia • Abdominal aortic aneurysm • Ankle-brachial index • Other reported clinical PAD CVD surgery and procedures • Coronary artery revascularization (coronary artery bypass graft [CABG], percutaneous transluminal coronary angioplasty [PTCA], stent) • Valve replacement • Carotid revascularization (± stent) • Peripheral revascularization (± stent) • Amputation Syncope Quality of life Renal replacement therapy
KQ 2 Intermediate outcomes (limited to established outcomes)	Lipids • Total cholesterol • Low-density lipoprotein cholesterol (LDL-C) • High-density lipoprotein cholesterol (HDL-C) • Triglycerides • Lipoprotein a (LP(a)) • Non–HDL-C Other serum markers • C-reactive protein (CRP) Blood pressure • Systolic (SBP) • Diastolic (DBP) • Hypertension (HTN), new or worsening (e.g., need for change in therapy) • Hypotension	Electrocardiographic (ECG) measurements (≥24 hr, Holter monitor, PR interval) other than established arrhythmias (based on context, this might be evaluated as harms outcome rather than efficacy) Other diagnostic tests • Carotid intima-media thickness (IMT), as measured by Doppler ultrasound • Coronary/cerebral arterial calcification Platelet aggregability Bleeding and coagulation times Ejection fraction Incidence of metabolic syndrome and change in 10-year Framingham risk profile
KQ 3 Harms	Clinical adverse events • Serious adverse events (composite outcome)[c] • Neurologic adverse events (e.g., neuropathy, seizure) • Allergic reactions (e.g., anaphylaxis, skin, transient acute airway disease) • Gastrointestinal adverse events (e.g., diarrhea, constipation, nausea/vomiting) • Clinically significant bleeding (e.g., intracerebral/intraventricular,	Organ toxicity • Liver (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], or hepatitis) • Renal (blood urea nitrogen [BUN], creatinine, glomerular filtration rate [GFR]) • Bone marrow (e.g., leukopenia, anemia, neutropenia, thrombocytopenia) Fasting blood glucose Hemoglobin A_{1c} QT interval

	gastrointestinal, hematuria) • Withdrawal due to adverse events • Other reported important clinical adverse events	Other harms
KQ 4 Pharmacokinetic and pharmacodynamic outcomes	Absorption • Bioavailability (F), maximum drug concentration (Cmax) and time to Cmax (tmax) (latter two were added post hoc) Area under the concentration curve (AUC)	Distribution • Volume of distribution (Vd; e.g., in L/kg) Metabolism/Excretion • Clearance, elimination constant (Kel), half life (t1/2)
Timing		
KQs 1–4	No restrictions have been prespecified based on the timing of an intervention and/or duration of length of followup of the studies.	This will be considered as a dose (or exposure) response modifier in the assessment of heterogeneity and applicability.
Setting		
KQs 1–4	No restrictions have been prespecified based on the setting of the studies.	This will be considered in the assessment of heterogeneity and applicability.
Study Design		
KQs 1–4	Experimental (randomized or nonrandomized controlled trial) and observational (cohort, case-control, cross-sectional) comparative studies with independent (concurrent or historical) control group including at least five participants.	For KQ 4, studies employing participants as their own control were also eligible (*post hoc* decision).
Report Characteristics		
KQs 1–4	No limits on publication year or status Publication language: Systematic reviews: limited to English	Primary studies: limited to the English language or German

Abbreviations: KQ = key question.

Data Extraction and Data Management

Prior to data abstraction, we iteratively developed and pilot tested a standardized data extraction form. One reviewer extracted relevant data from each study and a second reviewer independently verified data from a 10 percent random sample of studies. As we noted some missed harms outcome data extraction across some studies, a second reviewer verified that all reported outcomes data of interest were extracted. Before this harms data verification was carried out, we clarified understanding of the reporting of harms. For example, we decided that when authors reported regular laboratory harms surveillance by testing for liver enzymes, glomerular filtration rate, blood urea nitrogen and serum creatinine, and then disclosed that no adverse events were identified, zero patients with events of raised levels of these enzymes should be extracted. Likewise a statement that no thrombotic event was identified was extracted as zero patients with stroke, angina and myocardial infarction. We could not generate extractable harms data from reports stating for example, “no significant adverse events were observed,” “no adverse effects of clinical importance occurred,” or “all remaining adverse events were mild in severity.” We extracted all harms data, not merely those thought to be drug related. Discrepancies in data extractions were resolved through discussions or with a help of third reviewer. Data extractors were not blinded to study information. If a study was reported in multiple publications, we extracted data from the latest and/or most complete publication and supplemented it with data from companion publications, as appropriate. We sought additional information from authors, when necessary. Data were extracted using DistillerSR.[120] During the

data extraction process, one reviewer with clinical background rated study populations' 10-year CHD risk as per Table 5 below, according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP, ATP III) guidelines.[24]When all participants were healthy non-smokers, study level 10-year CHD risk was categorized as low.

Table 5. Ten-year coronary heart disease risk strata used to categorize study participants

Category		Details
High risk (10-year risk >20%)	A	Participants with established coronary heart disease, i.e., anyone or more of the following: *coronary death, acute coronary syndromes, myocardial infarction, angina, heart failure, and coronary artery procedures (angioplasty or bypass surgery)*
	B	Participants with noncoronary form of atherosclerotic disease, i.e. anyone or more of the following: *peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease (transient ischemic attacks or stroke of carotid origin or > 50% obstruction of a carotid artery)*
	C	Those diagnosed with diabetes or those reported in the paper as high risk according to NCEP ATP III criteria
Moderate to moderately high risk (10-year risk <10% to maximum of 20%)		Two or more of the following risk factors in >80% of participants: *cigarette smoking, hypertension (BP ≥140/90 mmHg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years)*
Low risk (0-1 risk factors)		Zero or just one of the above risk factors
Mixed risk		Participants clearly in more than one of the above categories
Unclear risk		Participants could be in one or a mix of the above categories

Abbreviations: BP = blood pressure; CHD = coronary heart disease; HDL = high density lipoprotein; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

There was some additional attrition after studies were included during screening. Of the included studies, we extracted data when the following additional criteria were met:

- the dietary supplement was added to one or more cardiovascular drug(s) that were all taken by 100 percent or the majority (at least 80 percent) of participants in randomized controlled trials;
- non-randomized controlled trials, or observational studies reported effect estimates reflective of a supplement plus drug(s) versus drug(s) alone comparison (or with another supplement);
- studies reported, or data could be obtained from authors, for at least one relevant outcome;
- studies were of a study design lower in the hierarchy of evidence and did not contribute evidence which was more pragmatic and applicable when higher quality of studies were available;
- studies were on a cardiovascular drug not marketed in the U.S.A.;
- dosing of the dietary supplement was specified.

Remaining studies were transparently eliminated from data synthesis with reasons.

Extracted data elements

The following elements were extracted:

- Study and report characteristics (first author, study design, study setting, duration of followup, year and language of publication, funding source, treatment sequence generation, treatment allocation concealment, use of blinding)
- Population characteristics (inclusion/exclusion criteria, number of enrolled and analyzed participants, age, gender, ethnicity/race, health status, comorbidities, baseline nutrient exposures and/or background diet, methods used to assess baseline nutrient exposures, specific cardiovascular drugs and drug classes, drug doses, dose regimens, duration of treatment, potential confounders such as blood pressure, concomitant medication, smoking, lipid levels, number and reasons for withdrawals or drop-outs)
- Intervention characteristics (name, brand, and country of manufacturer of a dietary supplement or extract, license/registration of the product in the country of manufacture, source from which a dietary supplement or extract was manufactured, method of authentication, dosage regimen and quantitative description, dose form, qualitative testing for authenticity of herbal species, purity assessment for contamination/substitution, standardization, storage conditions and length, methods and instruments for assessing nutrient-intake exposures including validation by using nutrient biomarkers)
- Control (comparator) intervention characteristics:
- Placebo - description/definition in placebo-controlled trials, duration of treatment, similarity of treatments
- Other dietary supplement - same data as above
- Outcomes
- Continuous measures (mean baseline and final values, within-treatment arm mean change, between-treatment arm mean difference, standard deviation, if reported means – the corresponding variance, standard error, 95 percent confidence interval)
- Binary outcomes (number of participants with an event, risk of an event, odds of an event, risk ratio, odds ratio, hazard ratio, variance, standard error, 95 percent confidence interval, crude or adjusted measures of effect)
- Definitions
- Measurement method(s)
- Timing of measurement
- Data analysis details
- Statistical test used
- Regression models (model type, covariates)

For systematic reviews, we planned to extract data on the research question, search strategy, design of individual studies included in a review, risk of bias assessment methods, population characteristics (inclusion and exclusion criteria, type of cardiovascular drug intake), and treatment characteristics (name and type of dietary of supplement).

Assessment of Study Risk of Bias and Quality of Systematic Reviews

Risk of bias of individual studies was assessed according to outcomes. One reviewer assessed risk of bias of all individual primary studies (randomized trials, non-randomized controlled trials, cohort, and case-control studies). The risk of bias for gradable outcomes was verified by two reviewers, while a random ten percent of risk of bias assessment was verified for other outcomes. Disagreements were resolved by discussions with a third team member.

We used generic criteria to assess study risk of bias (Table 6). These criteria estimate risk of bias across five domains (selection bias, performance bias, attrition bias, detection bias, and other bias). The domains were tailored according to study design. For example, specific sub-domains such as randomization sequence generation were assessed only for randomized trials (parallel arm and cross-over). Cross-over randomized trials were assessed with the following additional criteria: appropriateness of cross-over design; washout period (the length of time had to be at least 3 times the half life of drug elimination); and the report of appropriate data analysis (i.e., based on within-subject differences). The sub-domain of blinding (within the Performance Bias domain) of participants, health care providers, and outcome assessors to treatment allocation was assessed only for experimental designs (i.e., randomized and non-randomized trials). We assessed the completeness of outcome data (i.e., attrition bias due to loss to followup or withdrawals) by comparing the number of participants who entered the study with the number of participants reported in outcome table(s). We then assessed whether there was complete followup of all participants, small lost to followup (more than 20 percent) or differential lost to followup.

Other forms of bias assessed included potential financial conflict of interest and selected criteria from the McMaster Quality Assessment Scale of Harms (McHarm).[25] All domains had response options of "Yes," "No," or "Unclear" with allowance for justifications of such judgments. For each gradable outcome in a study we provided an overall risk of bias rating designated as high, or low (Table 7). In order to be classified as high risk of bias, a study must have demonstrated some apparent and major flaw (within that study design category) that would invalidate results.

Table 6. Criteria for risk of bias assessment

Criteria	Experimental controlled trials (RCT and non-RCT)	Observational controlled studies	Uncontrolled experimental studies
Selection Bias			
Appropriateness of participant selection*		X	X
Randomization sequence generation†	X		
Allocation concealment	X		
Control for important baseline/prognostic factors‡: restriction, similarity of groups at baseline, matching, and/or adjustment in the analysis	X	X	
Performance Bias			
Purity/standardization of dietary supplement§	X	X	X
Blinding of subjects and providers to treatment allocation	X		
Attrition Bias			
Completeness of outcome data (attrition and exclusions) with focus on differential loss to followup or overall high loss to followup and potential for associated confounding‡	X	X	X
Detection Bias			
Blinding of outcome assessors to treatment or exposure status in experimental or cohort studies or blinding of exposure assessors to case/control status in case-control studies.	X	X	X
Extent to which valid outcomes were described¶	X	X	X
Other			
Financial conflict of interest	X	X	X
Criteria for assessment of harms (from the McHarm checklist[122]): prespecified and valid	X	X	X

definition of harms, mode of harms collection (e.g., active or passive, standard tool)

Notes: *Appropriateness of participant selection included whether participants from each arm were from the same or different populations, the use of adequate definitions and measurements of exposed/nonexposed or case/control status and demonstration that outcomes were not present at beginning of prospective studies.
†For RCTs only.
‡Important baseline/prognostic factors evaluated: age, gender, race, baseline diet/nutrient exposures for dietary substance of interest, smoking, concomitant medications/supplements, and health status, including comorbidities and LDL-C and blood pressure if these measures were not included as study outcomes.
§Description of the source, methods of extraction, and constituents of the dietary supplement (e.g., quantification or quality assurance/standardization of dose/purity, stability and length of storage).
¶Definition and methods used to assess outcome including timing, and comparability of assessment across study arms.
Abbreviation: RCT = randomized controlled trial.

Table 7. Overall risk of bias ratings

Low risk of bias. These studies have the least bias and results are considered valid. Examples of characteristics of these studies include the following: a formal randomized controlled design; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
Moderate risk of bias. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of low risk of bias because they have some deficiencies, but no flaw is likely to cause major bias. Study deficiency may be missing information, making it difficult to assess limitations and potential problems.
High risk of bias. These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Methodological quality of included systematic reviews was assessed using the AMSTAR tool,[26] which rates each systematic review with a 'Yes,' 'No,' 'Can't answer,' or 'Not applicable' across the 11 domains. The overall assessment of quality for each systematic review was based on a reviewer's overall judgment given their responses to the individual AMSTAR items, and had three overall ratings: 'Good,' 'Fair,' or 'Poor.' In general, 'Good' quality systematic reviews were defined as those having few or no methodological/reporting shortcomings (low risk of bias). 'Fair' quality systematic reviews were defined as those having some methodological flaws although not sufficient to seriously bias or invalidate the review results. 'Poor' quality systematic reviews were defined as those having serious flaws sufficient to seriously bias or invalidate the review results. An independent reviewer helped to resolve any discrepancies regarding the AMSTAR tool assessment between the reviewers. We limited our review to those systematic reviews judged to be of 'Good' quality.

Grading the Strength of the Body of Evidence

The strength of a body of evidence was graded based on the following four domains, per previously published guidance: overall risk of bias by outcome, consistency, directness, and precision.[27] A methodologist and a content expert graded the strength of the body of evidence as "High," "Moderate," "Low," or "Insufficient" (Table 8) A third methodologist with clinical background adjudicated to resolve disagreements. Optional domains such as dose-response association and existence of confounders were not applicable in this comparative effectiveness review. Given the uncertainties involved in interpreting asymmetry tests for publication bias in most reviews, especially in presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.[123,124]

In consultation with the Technical Expert Panel (TEP), the review team chose the following outcomes for grading:
KQ 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
KQ 2: Blood pressure (systolic and diastolic), lipid profile (low density lipoprotein, high density lipoprotein, and non–high density lipoprotein cholesterol; and triglycerides), international normalised ratio for coumarin derivatives, incidence of metabolic syndrome, and change in 10-year Framingham risk profile.
KQ 3: Serious adverse events (composite outcome according to the Food and Drug Administration definition of serious adverse events),[28] 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
KQ 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.
Strength of evidence was rated insufficient when there was no evidence for an outcome, when results were too conflicting between studies without an identifiable cause, or when the confidence interval was wide enough to incorporate clinically meaningful benefit and harm (i.e. type II error).

Table 8. Strength of evidence grade and definition[27]

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

Applicability

We followed previously published guidance, and summarized the population, intervention, comparator, outcome, timing and setting (PICOTS) to assess the applicability of the body of evidence for outcomes or categories of similar outcomes.[29]We considered age, race/ethnicity and gender representation; strictness of exclusion criteria; 10-year CHD risk; study setting; whether or not the cardiovascular drug(s) was administered in therapeutic doses; frequent of monitoring of adherence; surrogacy of outcomes; and short versus long-term treatment duration as important aspects determining applicability. Applicability is reported for all conclusive results. When direction of effect was indeterminate either because of lack of evidence or under powered evidence (with imprecise and nonsignificant data), applicability of evidence was not reported.

Data Synthesis and Analysis

All analyses compared the combination of dietary supplement plus cardiovascular drug with cardiovascular drug alone (or plus placebo or another dietary supplement). The decision to meta-analyze or qualitatively synthesize outcome specific evidence from primary studies depended upon the presence or absence of homogeneity in clinical and methodological characteristics across studies, and the statistical format of outcome reporting. For pharmacokinetic outcomes in Key Question 4, we followed the US FDA guidance for analysis and interpretation of drug interaction studies.[30] Because data are usually skewed, the guidance recommends that the pharmacokinetic outcomes in drug interaction studies be reported, after log transformation, as geometric mean ratios (GMR) with their 90 percent confidence intervals (CI) based on a procedure termed the *two one-sided test procedure*. A conservative margin of bioequivalence for most drug interactions is recommended to be between the lower and upper bound 90 percent GMR CI of 0.8 and 1.25. We refer to this as the zone of clinical nonsignificance.

Meta-analysis was considered, or studies were considered suitable for pooling if they were randomized trials that included similar populations in terms of demographics, morbidity, and intake of cardiovascular drug(s) or classes of drugs (e.g., participants aged 65 years or younger, healthy or with diabetes or history of myocardial infarction, use of warfarin or nitrates), compared the same type of dietary supplement (e.g., niacin, oral magnesium, fish oil) versus comparator treatment (e.g., other dietary supplement, no treatment, placebo), and reported the same outcome measures in the same statistical format (e.g. mean difference or geometric mean ratios (GMR)). Where risk of bias differed across studies, this was explored by sensitivity analyses. We did not plan to meta-analyze observational and experimental studies; however, we pooled parallel with crossover randomized studies.[32] We did not consider pre-crossover data for synthesis except when it was judged that the treatment given to participants in a given cross-over trial was not appropriate for the condition under consideration.[32,125] Similarly, we did not pool cross-over trials that had not employed sufficient washout period between the two treatment periods because of bias arising from carryover treatment effects. We planned not to meta-analyze observational studies because of the differences in adjustment for confoudnders and residual confounding.

We used a DerSimonian and Laird random-effects model to generate pooled estimates of relative risk (RR) if an outcome was measured on a dichotomous scale, and weighted between-group mean difference (for end points and within group changes), if an outcome was measured on a continuous scale.[31] The measure of variability of the pooled estimates was a 95 percent confidence interval. Statistical heterogeneity was assessed using Cochran's Q (α=0.10) and the I^2 statistic. All analyses were performed using *Comprehensive Meta Analysis* version 2.2.057 (New Jersey, USA); StatsDirect Ltd. *StatsDirect* statistical software (http://www.statsdirect.com. England: StatsDirect Ltd. 2008) and *R: A Language and Environment for Statistical Computing*, Foundation for Statistical Computing (http://www.r-project.org) Vienna, Austria (2011).

When studies failed to report summary statistics (e.g., mean score, standard deviation, standard error), we calculated the needed parameters if individual participant data were provided. If a study reported only a standard error of the mean response, we converted it into a standard deviation. Trials were not meta-analyzed if the mean and standard deviation could not be ascertained. Trials with obvious between-group baseline imbalance in a continuous outcome were not pooled unless the mean change from baseline and corresponding standard deviation for the compared study groups were reported.

We used the Peto odds ratio method 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.[33] Studies with zero events in both arms were excluded from meta-analysis.[32]

Heterogeneity exploration was planned to examine clinical and methodological diversity, to answer subquestion (a) of the four Key Questions by carrying out subgroup and sensitivity analyses, and/or meta-regression if there were a sufficient number of studies (four studies for each categorical subgroup variable, and 6 to10 for a continuous subgroup variable).[32] This was not carried out because of a paucity of studies for each outcome.

Prespecified clinical subgroups included: gender (male, female), ethnicity (including Hispanic, Asian, African American, and Native American), age (those aged 65 years and above, and 80 years and above), baseline health status (healthy volunteers, participants according to coronary heart disease risk category, participants at risk for cardiovascular disease, participants with known cardiovascular disease, participants with diabetes, participants with hepatic or renal dysfunction or end-stage renal disease, participants taking a cardiovascular drug for an indication other than cardiovascular disease), and genotypic polymorphisms (e.g., in CYP2D6, 2C9, 2C19).

Sensitivity analyses were to be conducted to explore whether the effect estimates of dietary supplement treatment were influenced by methodological variables such as overall study risk of bias, adequacy of participant selection, important confounding, blinding of outcome assessors, purity/dose/stability of a dietary supplement, or duration of treatment or followup.

Statistical interaction was to be investigated for all four key questions. To determine measureable interactions between CV drugs and dietary supplements, we followed the procedures described below:

- If a study explicitly examined interaction between CV drug and dietary supplement, then we extracted the study's findings along with the method for assessing interaction.
- When studies did not investigate statistical interaction between the DS plus CV drug group and the CV drug group alone, we carried out test for interactions when data for at least four groups were reported. These groups had to be DS plus CV drug group, DS alone group, CV drug alone group, and a common comparator placebo or no treatment group. For studies that presented dichotomous data we calculated the synergy index (S).[34]

$$\text{Synergy Index (S)} = \frac{1 - RR_{11}}{1 - RR_{01}RR_{10}}$$

Where RR_{11} is the relative risk for subjects exposed to CV drug and dietary supplement, and RR_{01} and RR_{10} are the relative risks for subjects exposed to CV drug alone and dietary supplement alone respectively. An S-index greater than 1 describes a positive interaction (synergism) and an S-index less than 1 indicates a negative interaction (antagonism). For continuous outcomes we would need individual patient data to model it in a linear regression with an interaction term.

Definitions

Pharmacokinetic Measurements: Absorption, Distribution, Metabolism, and Excretion. Adapted from Rowland and Tozer 1995[126]

Pharmacokinetics

The study of the mechanisms of absorption, distribution, metabolism and elimination of an administered drug in the living organism

Absorption

Absorption can refer to any route of administration except intravenous administration (i.e., enteral, subcutaneous, transdermal)

a) Fractional bioavailability (F): the fraction of a non-intravenously administered dose of a drug that reaches the systemic circulation (unit: percent)

b) Time to maximum concentration (t_{max}): the time at which the maximum plasma concentration of a drug occurs following administration of an extravascular dose (unit: minute or hour)

c) Maximum concentration (C_{max}): the highest drug concentration in plasma after an extravascular dose (unit: $\mu g\ mL^{-1}$)

d) The area under the plasma drug concentration-time curve ($AUC_{0\text{-}t}$): the measure of an exposure of plasma to a drug over a given time period. It is calculated as the area under the serum concentration-time curve which is based on multiple drug concentration measurements at various time points (unit: $\mu g\ mL^{-1}$ hour)

Distribution

Volume of distribution (Vd) is the apparent volume into which a drug distributes in the body at equilibrium. Alternatively, it is the volume of plasma at the drug concentration required to account for all the drug in the body (unit: L/kg) Volume is not limited to plasma. For example, volume of distribution will exceed plasma volume or total body water volume for highly lipophylic drugs.

Metabolism/Excretion

a) Clearance (CL): the volume of plasma in the vascular compartment cleared of drug per unit time by the processes of metabolism and excretion (unit: mL/hour)

b) The elimination half-life ($t_{1/2}$): the time required to reduce the plasma concentration of a drug or the total amount of drug in the body to one half of its initial value (unit: hour)

Results

Screening and Inclusion of Records

Overall, 32,314 records were identified by searches of databases and 113 from other sources (gray literature; reference list checking). The PRISMA diagram in Figure 2 depicts the flow of retrieved records through the phases of screening and inclusion

A total of 168 English publication studies were included after title/abstract, and full text screening. None of the 68 German publications screened at full text level met the eligibility criteria.

Eighty eight studies were subsequently excluded from the data synthesis for the following reasons:

Proportion of population taking cardiovascular drugs was less than 80 percent, preventing accurate analysis of results related to interaction of supplement and cardiovascular disease (CVD) drug (n=76);

No outcome of interest was reported (n=4)[127-130]

Administered CVD drug were not used in U.S.A. (n=2)[131,132]

Dose of supplement was not reported (n=1)[133]

Included outcome data only for the 1st period cross-over (n=1)[134]

A sequential study was not included in synthesis of evidence because superior study design randomized controlled trial (RCT) evidence was available for the same pharmacokinetic outcome, for the same drug-supplement combination (n=1)[135]

No response was received to a data request made to authors (n=1)[136]

High quality systematic review with limited utility due to being out of date. Inclusion would have necessitated a *de novo* process for the included studies; (n=1)[137]

Observational study reporting outcomes where higher level of evidence was available from RCT for the same outcomes (n=1)[138]

Data from 88 studies that were not eligible for data synthesis was not extracted and quality of experimental or observational studies was not assessed.

As a result, 80 reports were included in the evidence synthesis of this review and therefore entered the quality assessment and data extraction. Of these eight studies were reported in more than one publication, amounting to 19 records. (Table 9) We identified one of these records as the primary report of the study and other(s) as a companion; however, if relevant to this review, data from all reports were used in the evidence syntheses. With this approach, 69 primary studies were included and are referenced accordingly in this review.

One of the included studies was observational,[138] two were controlled clinical trials,[58,59] and the remaining 66 studies were RCTs. Twenty two RCT studies contributed to meta-analyses and the remaining were included in the qualitative syntheses of evidence. [35,36,39-41,44,53,70,71,76,77,79,84-87,91,94-96,139,140] We contacted authors of two records requesting additional data or seeking data clarification.[38,136] One of the authors,[38] responded to our query and provided additional data which was incorporated in the evidence syntheses.

Additional individual study data and quality assessment are presented in Appendix C.

Included studies for each Key Question were:

- KQ1 (n = 22) [35-56]
- KQ1a- subgroups with quantitative data (n = 1)[51]
- KQ1b- interaction (n = 0)

- Studies included for KQ2 (n = 59) [36,37,39-42,44,59-75,79,81,86-88,94,96,139, 46,49-56,58,76-78,80,82-85,90-93,97,98,140-142]
- KQ2a- subgroups with quantitative data (n = 1)[39]
- KQ2b- interaction (n = 2)[44,80]
- Studies included for KQ3 (n =58)[35-42,60-72,74,75,79,87-89,94-96,99, 44,46-49,51-56,58,76-78,80,82-85,90-93,97,98,100]
- KQ3a- subgroups with quantitative data (n = 0)
- KQ3b- interaction (n = 1)[89]
- KQ4 (n = 14)[35,63,65,67,71,73-75,95,96,99]
- KQ4a- subgroups with quantitative data (n = 0)
- KQ4b- interaction (n = 0)

Figure 2. PRISMA flow chart of study identification, screening, eligibility and inclusion

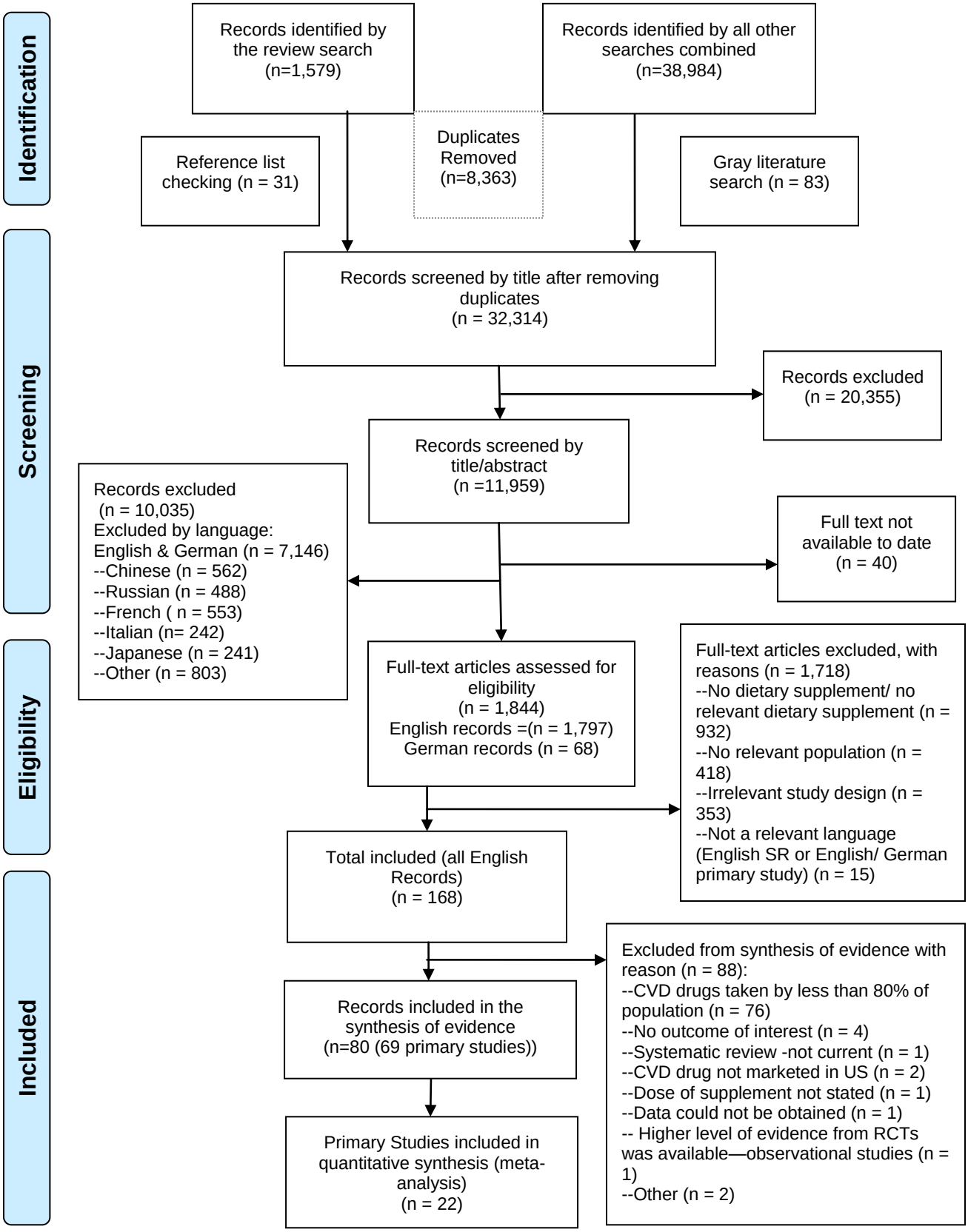


Table 9. Primary and companion records for studies with multiple reports

Primary record	Companion record(s)
Davidson 2007[40]	Maki 2010[143]
Gardner 2007[69]	Chan 2002[144]
Rombouts 2007[39]	Lee 2005[145]
Chan 2002[44]	Chan 2006,Chan 2003,Chan 2002,Chan 2010,Chan 2002,Chan 2002[130,144,146-149]
Nordøy 1998[150]	Nordøy 2000[98]
Nordøy 2003[93]	Nordøy 2001[151]
Roth 2009[56]	Bays 2009[152]
Budoff 2004[66]	Budoff 2006[153]
Davidson 2007[40]	Maki 2010[143]

Key Question 1: In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction [MI] and stroke)?

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

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

Overview

Twenty-two RCTs addressed Key Question 1.[35-56] No relevant data was available from observational studies. No evidence on clinical outcomes was found for Echinacea, garlic, ginger, ginseng, hawthorne, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, and vitamin D with or without calcium supplementation (Table 10). There was insufficient evidence for the gradable outcomes of hospitalization and those related to peripheral arterial disease across all supplement-cardiovascular drug(s) combinations, due to lack of data. A paucity of studies for each supplement-drug combination of interest precluded exploration of heterogeneity in terms of pre-identified subgroups (KQ 1a). No study examined any statistical interaction between supplement and drug on clinical outcomes (KQ1b). Table 11 summarizes characteristics of included studies and Table 12 summarizes their risks of bias. Below we report results separately for each supplement and cardiovascular drug combination, by outcomes for which evidence was available. We then grade the evidence for the prestated gradable outcomes, and summarize the PICOTS determinants of applicability for conclusive results across all outcomes – i.e. when results were not impacted by the possibility of type II error. In all analyses, the intervention was administration of a dietary supplement along with one or more cardiovascular drug or class of drugs, while the comparator was administration of the drug or its class alone. Details of individual study characteristics, risk of bias and outcomes data are reported in Appendix C.

Table 10. Overview of availability of evidence addressing key question 1

Supplement and cardiovascular drug(s)	Outcome	Number of Studies
Coenzyme Q10		
Statins (*Dm)*	Adherence	1
ACE inhibitor with other CV drugs (*Dm)*	Mortality	1*
ACE inhibitor with other CV drugs (*Cs)*	Quality of life	1*
Ginkgo biloba		
Aspirin (*Dm)*	Mortality	1
Aspirin (*Cs)*	Other clinical outcomes	1 (NRS)
Magnesium (oral)		
Beta-blocker (*Dm)*	Myocardial infarction	1*
Omega-3 fatty acids/fish oils		
Statins (*Dm)*	Adherence	3*
	Mortality	1*
	Arrhythmia	1
	Other clinical outcomes	1 (exacerbation of CHF)
Calcium channel antagonist plus aspirin (*Dm)*	Myocardial infarction	1
	Procedures	1 (CABG and PCI)
	Other clinical outcomes	1 (Restenosis)
Aspirin plus dipyridamole plus calcium channel antagonist (*Dm)*	Other clinical outcomes	1 (Restenosis)
Aspirin plus dipyridamole plus calcium channel antagonist (*Cs)*	Other clinical outcomes	1 (Restenosis)
Aspirin (*Dm)*	Other clinical outcomes	1 (Graft occlusion[†])
Warfarin (*Dm)*	Other clinical outcomes	1 (Graft occlusion)
Calcium channel antagonist (*Cs)*	Other clinical outcomes	1 (induced coronary vasospasm)
Fibrates (*Dm)*	Mortality	1
Vitamin E		
Aspirin (*Dm)*	Composite outcome	1
	Stroke	1
	TIA	1
Statin (*Dm)*	Adherence	1
Calcium channel antagonist (*Cs)*	Unstable angina	2
Vitamin K		
Phenprocoumon/warfarin (*Dm)*	Adherence	1
	Mortality	2
	Myocardial infarction	2
	Stroke	2
	Unstable angina	2

Notes: *At least one crossover RCT; [†] omega-3 fatty acids supplement also contained α-tocopherol
Abbreviations: ACE = angiotensin converting enzyme; CABG = coronary artery bypass grafting; Cs = continuous; CHF = congestive heart failure; Cs = outcomes data were continuous Dm = outcomes data were dichotomous; NRS = neurologic recovery score; PCI = percutaneous coronary intervention; QoL = quality of life; RCT = randomized controlled trial; TIA = transient ischemic attack; UA = unstable angina.

Table 11. Summary of study characteristics

Study Characteristic	Distribution
Sample CHD risk	Low 4.5% Moderate to moderately high 4.5% High 41% Mixed 13% Unclear 37%
Geographical region	North America 32% Europe 27% Australia/New Zealand 9% East Asia 14% Rest of Asia 9% NR 9%
Setting	Primary care/community 36% Specialty care 27% NR 37%
Duration	Mean 39 weeks (SD 105), range 2 weeks to 10 years
Total N randomized	Mean 1004 (SD 4230), range 11 to 19934, total across studies = 22095
Age	Mean age 55 years (SD 9)
Gender	Two trials exclusively in males,[44,52] and one in females.[38] Of the mixed gender studies, 55% included females representing less than 40% of study sample.
Race/Ethnicity	Eight studies reported race/ethnicity distribution. Most included a majority of Caucasian participants. One study included all Asians and another majority Hispanics.[50,55]

Abbreviations: CHD = cardiovascular heart disease; SD = standard deviation.

Table 12. Risk of bias and potential for conflict of interest

Items	% Yes	% No	% Unclear
All RCTs (N=22)			
Adequate generation of allocation sequence	41	0	59
Allocation concealment	4.5	0	95.5
Comparability of groups	18	18	64
Purity of supplement	73	18	9
Blinding of allocated intervention	36	5	59
Adequately addressed missing data	55	0	45
Freedom from potential conflict of interest	23	31	46
Crossover RCTs (N=4)			
Suitability of crossover design for the study condition	100	0	0
Freedom from carryover effect	50	25	25
Appropriateness of statistical analysis for crossover design	0	50	50
Comparability of groups between periods 1 and 2	25	0	75
Freedom from bias introduced by dropouts	100	0	0

Abbreviations: CHD = coronary heart disease; RCT = randomized controlled trial.

Coenzyme Q10

Coenzyme Q10 plus ACE inhibitors versu ACE inhibitors alone

All-cause mortality and quality of life. These outcomes were reported in one crossover randomized placebo-controlled trial with a duration of three months, in 30, mostly male patients with left ventricular dysfunction, at a specialty center. Coenzyme Q10 (33 mg three times a day) plus maximally tolerated doses of angiotensin-converting enzyme (ACE) inhibitors was compared with ACE inhibitors alone. The majority of patients (i.e. greater than 80 percent) were also taking digoxin, frusemide, hydralazine and/or nitrates. A single death in the placebo group was noted.[54] No significant differences were noted in quality of life scores using the Minnesota "Living With Heart Failure" questionnaire (mean sum of all scores post-treatment 26.7±17.9 versus 26.5±18.7). It is not clear whether the statistical analysis incorporated within patient differences in order to fully utilize the robustness of this crossover design. The strength of evidence is summarized in Table 13.

Table 13. Strength of evidence for coenzyme Q10 plus ACE inhibitors versus ACE inhibitors alone

Risk of Bias	Consistency	Directness	Precision	Additional Domain(s)	Strength of Evidence	Conclusions
All-cause mortality						
Moderate	NA	Direct	Imprecise		Insufficient	The study was grossly underpowered for this outcome
Quality of life						
Moderate	NA	Direct	Imprecise		Insufficient	No significant differences were noted. Type II error could not be excluded.

Abbreviations: ACE = angiotensin converting enzyme; NA = not applicable.

Coenzyme Q10 plus statins versus statins alone

Adherence. A 12 week pilot study of limited internal validity (unclear adequacy of sequence generation, allocation concealment and blinding) assessed adherence to statins. A select group of patients with moderate to high 10 year CHD risk and self reported statin associated myalgia were included. The trial did not demonstrate any difference in rates of adherence to simvastatin (10 mg/day to 40 mg/day) between add-on coenzyme Q10 (200 mg/day) and statin alone in patients with previous statin related myalgia. Adherence to simvastatin was 98 percent in both groups, but it is not clear how adherence was assessed.[37]

Ginkgo biloba

Ginkgo Biloba plus antiplatelets versus antiplatelets alone

All-cause mortality and neurologic recovery score. These outcomes with *Ginkgo biloba* extract (40 mg every six hours) were investigated over 4 weeks in 62 South Asian patients with previous ischemic stroke, who were on regular aspirin and/or pentoxphilline. [48] Trial limitations included unclear allocation concealment, attrition bias and potential imbalance between groups in terms of the nature of neurologic deficits. The trial was clearly underpowered and of too short duration to detect differences in all-cause mortality and neurologic improvement in the modified Mathew's scale. There were no deaths and no significant differences in neurologic recovery score after one month of treatment. The mean relative change from baseline in linear transformed Mathew's scale averaged approximately 20 in both groups, and showed improvement over time (mean difference 0.81 [95 percent CI, -9.12, 10.74]).[48] Strength of evidence is summarized in Table 14.

Table 14. Strength of evidence for *Ginkgo biloba* plus aspirin and/or pentoxphilline versus aspirin and/or pentoxphilline alone

Outcome	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
All-cause mortality	Moderate	NA	Direct	Imprecise	Insufficient	The study was grossly underpowered for this outcome

Abbreviations: NA = not applicable.

Oral Magnesium

Magnesium plus beta-blockers versus beta-blockers alone

Myocardial infarction. A single event of myocardial infarction was observed in a randomized crossover controlled trial of 365 mg oral magnesium aspartate or placebo administered daily for 8 weeks to a selective group of 40 hypertensive patients with no comorbidities on therapeutic doses of beta-blockers. The trial was underpowered to detect differences in clinical outcomes and lacked a clear description of several risk of bias items.[42] Strength of evidence is summarized in Table 15.

Table 15. Strength of evidence for oral magnesium plus beta-blockers versus beta-blockers alone

Outcome	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
Myocardial Infarction	Moderate	NA	Direct	Imprecise	Insufficient	The study was grossly underpowered for this outcome

Abbreviations: NA = not applicable.

Omega-3 fatty acids/fish oils

Omega-3 fatty acids/fish oils plus statins versus statins alone

Mortality, arrhythmia, and adherence to medication. These outcomes were assessed in 5 trials.

Zero mortality in one randomized crossover pharmacokinetic study of 4 grams of omega-3 fatty acids with 80 mg atorvastatin daily versus 80 mg/day atorvastatin monotherapy, over 14 days in 50 healthy nonsmoking adults provided insufficient evidence.[35]

In another study, a single case of supraventricular tachycardia (in the add-on 4 g/day omega-3 fatty acid group) in an 8-week efficacy trial in 256 highly selected dyslipidemic patients on statin therapy constituted insufficient evidence for the arrhythmia outcome.[40] There was also one case of exacerbation of congestive heart failure in the add-on omega-3 fatty acid group.[40]

Rates of adherence to statin therapy were reported in three efficacy trials of 6-12 weeks duration in highly selected patient populations with dyslipidemia with or without add-on 4-9 g/day of omega-3 fatty acids. All studies had unclear risk of bias for adequacy of sequence generation and allocation concealment. Adherence to statin therapy was judged by pill count. No differences in statin adherence rates were noted between both groups – across all three studies, adherence rates in the two groups were equal to or greater than 95 percent.[36,44,53] Strength of evidence is summarized in Table 16.

Omega-3 fatty acids/fish oils plus cardiovascular Drugs versus cardiovascular drugs alone

Mortality, myocardial infarction, cardiovascular procedures, restenosis, coronary vasospasm and graft occlusion. These outcomes were assessed with various cardiovascular drugs. Insufficient evidence from single efficacy trials with sparse events did not demonstrate a difference in the outcome of all-cause mortality when study cardiovascular drugs were either aspirin (291 high risk patients followed for 1 year, with 9 deaths), warfarin (319 high risk patients followed for 1 year with 5 deaths), or fenofibrate (unclear 10 year CHD risk in 167 participants with hypertriglyceridemia followed for 8 weeks with no deaths) (Table 16).[47,56]

In a 6 month efficacy study in 58 patients who underwent successful coronary angioplasty, with ten capsules of fish oil daily (1.8 g eicosapentaenoic acid plus 1.2 g docosahexaenoic acid) in addition to therapeutic doses of aspirin plus calcium channel antagonist versus the latter two drugs alone, six cases of acute myocardial infarction were identified (RR 1.70 [95 percent CI 0.32, 8.84]) (Table 16).[51] The same study reported non-significant differences in numbers of patients undergoing angioplasty (n=26; RR 1.35 [95 percent CI 0.68, 2.70]) and coronary artery bypass graft (CABG) (n=4; RR 0.84 [95 percent CI 0.12, 5.78]).[51]

Table 16. Strength of evidence for omega-3 fatty acids/fish oils plus cardiovascular drug(s)* versus the cardiovascular drug(s) alone

	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
Statins						
All-cause mortality and arrhythmia	Moderate	NA	Direct	Imprecise	Insufficient	Studies were grossly underpowered for both outcomes
Aspirin, warfarin or fenofibrate						
All-cause mortality	Moderate	NA	Direct	Imprecise	Insufficient	Studies were grossly underpowered. Aspirin+omega-3 fatty acids RR 1.29 (95% CI, 0.35, 4.72) Warfarin+omega-3 fatty acids RR 1.25 (95% CI, 0.21, 7.38) Fenofibrate+omega-3 fatty acids RR was not estimable because of zero deaths
Aspirin and calcium channel antagonist						
Acute myocardial infarction	Moderate	NA	Direct	Imprecise	Insufficient	Single study, underpowered for clinical events

*Cardiovascular drugs were either aspirin, warfarin, or fenofibrate
Abbreviations: CI = confidence interval; NA = not applicable; RR = relative risk;

Coronary artery restenosis. Rates of restenosis were investigated with coronary angiography 3 to 4 months following successful angioplasty, in 82 highly selected male patients. We included this outcome in a post hoc decision given its clinical relevance.[52] Restenosis was defined as 50 percent narrowing of the luminal diameter. Outcome assessors were blinded to treatment allocation. In this randomized trial, patients were treated either with a daily dose of 3.2 grams of eicosapentaenoic acid added to therapeutic doses of the combination of aspirin, dipyridamole, and calcium channel antagonists, or the latter three drugs alone in combination. Significantly lower rates of restenosis were observed in the treatment group (RR 0.40, 95 percent CI, 0.20, 0.82); however, the mean percentage reduction in luminal diameter was not significantly different between the two groups. These results conflict with a similar trial conducted in India in 107 patients, that found no significant difference in rates of early restenosis (RR 1.33, 95% CI, 0.76, 2.30).[51] Restenosis rates were not significantly influenced by gender nor age (p greater than 0.05 for interaction).[51] Possible explanations for these differing trial results, besides differences in patient populations, include that in the Indian trial patients were not treated with dipyridamole, and that followup angiography was only conducted in those with anginal symptoms or a positive exercise test (unlike the previous trial that undertook followup angiography in all patients), thereby potentially biasing the results by excluding healthier individuals.

Coronary vasospasm induced by intracoronary acetylcholine was studied in 22 Japanese patients with variant angina randomized to 4 months treatment with therapeutic doses of diltiazem plus 1.8 g eicosapentaenoic acid, or diltiazem alone. Patients served as their own controls. Acetylcholine induced vasoconstriction, measured as percentage change in post nitrate coronary artery diameter compared to the baseline response, was significantly improved in the omega-3 fatty acids but not the control group.[50] The report was unclear as to how the randomization sequence was generated, allocation was concealed, and outcome assessors were blinded. Based on the reported data, our comparative analysis of post treatment percentage change in coronary artery diameter following intracoronary acetylcholine injection showed nonsignificant differences between supplement plus diltiazem and diltiazem alone groups (percentage mean difference in spastic segment was -1.3 [95 percent CI -10.34, 7.74)] and in nonspastic segments was 0.9 [95 percent CI -4.56, 6.36])

Coronary bypass graft occlusion rates were evaluated after one year, in 610 participants on either aspirin (300 mg/day) or warfarin (target prothrombin International Normalized Ratio [INR] 2.5-4.2), in conjunction with placebo or with 4 g/day of omega-3 fatty acids plus 15 mg/day of α-tocopherol as an anti-oxidant.[47] Graft occlusion was predefined as visualization of the lack of contrast flow on followup angiography. An important limitation of this randomized trial was its lack of clear reporting of adequate allocation concealment. No significant differences in graft occlusion rates were noted, but studies were likely underpowered to detect a difference (Table 17).

Table 17. Graft occlusion rates with omega-3 fatty acids and α-tocopherol

Occlusion subtype	Drugs and supplements	RR (95% CI)
Internal mammary artery graft occlusion		
	Warfarin+ omega-3 fatty acids+ α-tocopherol	1.25 (0.70, 2.23)
	Aspirin+ omega-3 fatty acids+ α-tocopherol	1.03 (0.50, 2.14)
Vein graft occlusion, distal anastomosis		
	Warfarin+ omega-3 fatty acids+ α-tocopherol	0.84 (0.66, 1.07)
	Aspirin+ omega-3 fatty acids+ α-tocopherol	0.83 (0.65, 1.06)
Patients with > 1 occluded vein graft		
	Warfarin+ omega-3 fatty acids+ α-tocopherol	0.79 (0.62, 1.01)
	Aspirin+ omega-3 fatty acids+ α-tocopherol	0.89 (0.69, 1.15)

Abbreviations: CI = confidence interval; RR = relative risk.

Vitamin E (α-Tocopherol)

Vitamin E plus cardiovascular drug versus cardiovascular drug alone

Stroke, transient ischemic attacks, adherence, angina, myocardial infarction, and vascular death. These outcomes were assessed in five trials.

In an efficacy trial, 100 highly selected patients with previous reversible or irreversible ischemic neurologic deficit and good performance status presenting to a university hospital were randomized to vitamin E (0.4 g/day) plus aspirin (325 mg/day) versus aspirin alone for a period of two years. Few patients experienced outcomes of stroke (n=9; ischemic 7, hemorrhagic 2), and recurrent transient ischemic attack (n=3), precluding definitive conclusions (Table 18).[49]

Table 18. Strength of evidence for vitamin E plus aspirin versus aspirin alone

	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
Aspirin						
All stroke, ischemic stroke, hemorrhagic stroke and transient ischemic attacks	Moderate	NA	Direct	Imprecise	Insufficient	Small efficacy trial clearly underpowered for clinical events

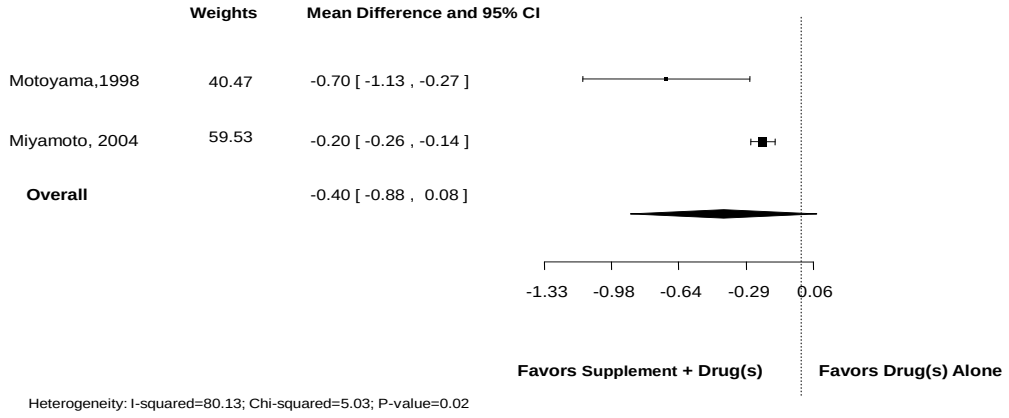
Abbreviation: NA = not applicable

Adherence to a statin was reported as an outcome in one trial that randomized a highly selected group of 220 hypercholestrolemic patients with normal triglycerides on a standardized diet of 100 mg/day of vitamin E plus 20 to 40 mg/day of pravastatin versus pravastatin alone.[46] Ninety eight percent of all patients were compliant with their treatment.

In one pragmatic trial in 19934 women randomized to 600 IU of vitamin E plus 100 mg/day of aspirin versus aspirin alone for 10 years, no significant differences were noted for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95 [95 percent CI 0.79, 1.13]).[38] Data regarding the total number of participants randomized into the two groups were obtained from the authors.

Two trials, each of one month duration, in a total of 60 highly selected Japanese patients with variant angina, were inconclusive for the mean number of angina attacks per patient following addition of vitamin E (400 mg/day) to therapeutic doses of diltiazem (mean difference [MD] -0.40 [95 percent CI -0.88, 0.08]) (Figure 3) .[43,45]

Figure 3. Forest plot of the mean number of angina attacks for participants administered vitamin E plus aspirin versus aspirin alone



Applicability. Cardiovascular drug adherence was investigated in outpatient specialty clinics in Italy over a period of three months, in nondiabetic patients with hypercholesterolemia but normal triglycerides, in good general health, and without recent CVD.[46] The composite cardiovascular outcome was investigated in a pragmatic trial in women, over a period of 10 years.[38]

Vitamin K

Vitamin K plus coumarin derivative versus coumarin derivative alone

Mortality, stroke and myocardial infarction. These outcomes were investigated in two 6 month efficacy trials in selected groups of patients anticoagulated for a period of 9 months to a year, with or without add-on daily vitamin K ranging from 100 μg/day to 150 μg/day. No thrombotic event of unstable angina, myocardial infarction or stroke was reported.[39,41] Sparse data on mortality precluded meaningful synthesis; a total of 3 deaths in 270 patients were observed across the two trials.[39,41] Over 90 percent of patients for whom adherence data were available (i.e. 80 percent of 200) in both groups were considered adherent because they had used over 90 percent of their study medication.[39] Strength of evidence is summarized in Table 19.

Table 19. Strength of evidence for vitamin K plus coumarin derivative versus coumarin alone

Cardiovascular drug / Outcome	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
Coumarin derivative						
All-cause mortality, stroke, and myocardial infarction	Moderate	NA	Direct	Imprecise	Insufficient	Two small trials clearly underpowered for clinical events

Abbreviations: NA = not applicable

Applicability. The trial reporting data on adherence included specialty clinic patients with an expected survival greater than 6 months who were previously known to be compliant with study medication.[39] Another trial included patients with atrial fibrillation anticoagulated with warfarin, and having unstable INR.

Summary of Results for KQ1

- For Key Question 1, we compared dietary supplement(s) coadministered with cardiovascular drug(s), with the cardiovascular drug(s) alone to investigate comparative clinical efficacy/effectiveness, subgroup effect and statistical interactions.
- Twenty-two randomized controlled trials contributed evidence.
- No data was available from observational studies.
- With no data, there was insufficient evidence for the outcomes of hospitalization and those related to peripheral arterial disease across all supplement-cardiovascular drug(s) combinations.
- No evidence on clinical outcomes was found for Echinacea, garlic, ginger, ginseng, hawthorne, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, and vitamin D (with or without calcium supplementation) coadministered with a cardiovascular drug(s)
- A paucity of studies of supplement-drug combinations for which data was available precluded exploration of heterogeneity in terms of pre-identified subgroups.
- No study analyzed statistical interaction between a supplement and a cardiovascular drug on clinical outcomes.
- For all predetermined gradable clinical outcomes for which evidence was found, the strength of evidence of comparative efficacy or effectiveness was graded insufficient because type II error could not be excluded due to the low power of studies. When compared with the specific cardiovascular drug alone, insufficient evidence was found for an effect of coenzyme Q10 coadministered with ACE inhibitors on all-cause mortality and quality of life; Ginkgo biloba plus aspirin and/or pentoxyphilline on all-cause mortality; oral magnesium and β-blockers on myocardial infarction; omega-3 fatty acids/fish oils plus statins on all-cause mortality and arrhythmia; omega-3 fatty acids/fish oils plus aspirin, warfarin or fenofibrate on all-cause mortality; omega-3 fatty acids/fish oils plus aspirin and calcium channel antagonist on acute myocardial infarction; vitamin E plus aspirin on stroke and transient ischemic attacks; and vitamin K plus coumarin derivative on all-cause mortality, stroke and myocardial infarction.
- No differences in adherence to statins were noted with coadministration of coenzyme Q10, omega-3 fatty acids, and vitamin E, with adherence rates greater than 90 percent in both drug plus supplement and drug alone groups. Evidence supporting benefit of omega-3 fatty acids added to conventional antiplatelet therapy and calcium channel antagonists on rates of restenosis following successful coronary angioplasty is conflicting. Underpowered studies addressed all other outcomes such as exacerbation of congestive heart failure, number of patients undergoing cardiac procedures, graft occlusion, neurologic recovery score, coronary vasospasm, and number of angina attacks in patients with variant angina for various dietary supplement and cardiovascular drug combinations
- Most studies were short-term efficacy trials, except one pragmatic trial on 19934 women randomized to 600 IU of vitamin E plus 100 mg/day of aspirin versus aspirin alone for 10 years. In this trial, no significant differences were noted for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95, 95 percent CI, 0.79, 1.13).

Key Question 2

In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on intermediate cardiovascular efficacy outcomes (e.g., lipids, blood pressure, electrocardiographic measurements, serum markers, bleeding, and coagulation times)?

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

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

Overview of included studies

Fifty-eight RCTs and one CCT addressed Key Question 2. The dietary supplements used in the studies were the following: co-enzyme Q10 (5 studies),[37,54,60-62] echinacea (1 study),[63] garlic (4 studies),[58,64-66] ginger (1 study),[67] ginkgo biloba (5 studies),[67-71] ginseng (3 studies),[72-74] hawthorne (1 study),[75], magnesium (3 studies),[42,76,77] niacin (1 study),[78] omega-3/fish oil (23 studies),[36,40,44,50-53,55,56,79,80,90-94,96-98,139-142] vitamin E (11 studies),[46,49,59,81-88] and vitamin K (2 studies)[39,41].

The trials were conducted in North America (15.3 percent), Australia/New Zealand (10.2 percent) , Europe (17 percent), and Asia (10.2 percent) (Table 20). The geographic region was unclear in about 36 percent of studies.

The participants across studies received the following cardiovascular drugs: statins, calcium channel blockers, niacin (above 250 mg), angiotensin-converting enzyme inhibitors (ACEI), aspirin, thienopyridine antiplatelets, beta-blockers, anticoagulants, fenofibrates, cilostazol, diuretics, or nitrates. Most participants had either mixed (low and/or moderate) or unclear CHD risk (27.1 percent and 37.3 percent respectively). The studies were conducted in specialty care (23.7 percent) or primary care/community (32.2 percent) settings (Table 20). Study setting was unclear for 44 percent of the studies. Ten trials included only male participants.[44,52,63,65,67,68,70,71,74,97] Of the 18 studies that reported race or ethnicity, the majority of participants were Caucasian in 5 studies, Asian in 3 studies, and Hispanic in 2 studies. Sparse data addressed subgroups, such as males/females, ethnic groups, and the elderly. Few studies for each supplement-drug combination of interest precluded exploration of heterogeneity in terms of pre-identified subgroups.

All evidence was based on data from RCTs of which 20 percent reported adequate generation of allocation sequence and only 7 percent reported adequate allocation concealment (Table 21). In about 20 percent of studies, participants, healthcare providers, or outcome assessors were blinded to treatment allocation. In all crossover trials the study design was deemed to be suitable for the studied condition. Most of these trials were judged to be free of carryover effect (63 percent). In about half of the trials (46 percent), groups were judged to be not comparable in one or more baseline characteristics. For a little over a half of the studies (56 percent), blinding of participants, healthcare providers, or outcome assessors was unclear.

No study addressed the following outcomes: incidence of metabolic syndrome, incidence of hypotension, carotid-intima media thickness, and change in 10-year Framingham risk profile. Only two studies examined statistical interaction.[44,80] One study used general linear modeling to assess interaction between fish/marine oils and atorvastatin on lipid parameters.[44] The other study used ANOVA to assess interaction between omega-3 fatty acids and niacin/aspirin on triglycerides.[80]

No relevant data were available from observational studies. There was one systematic review which reported the effectiveness of concomitant administration of omega-3 fish oil plus statins compared to statins alone on lipid profiles in participants requiring lipid lowering therapy.[137] Details of individual study characteristics, risk of bias and outcomes data are reported in Appendix C.

Table 20. Characteristics of studies addressing key question 2

Characteristic	Distribution
Sample CHD risk	• Low 8.0% • Moderate to moderately high 1.7% • High 20.3% • Mixed 27.1% • Unclear 37.3%
Geographical region	• North America 15.3% • Europe 17.0% • Australia/New Zealand 10.2% • East Asia 6.8% • Rest of Asia 3.4% • NR 35.7%
Setting	• Primary care/community 32.2% • Specialty care 23.7% • NR 44.1%
Duration	Mean 10 weeks (SD 14.7) Range 1 week to 2 years
Total N randomized	Mean 50.6(SD 51.7), range 10 to 256, total across studies = 2,987
Age	Mean age 49.8 years (SD 14.4)
Gender	Ten Trials exclusively in males.[44,52,63,65,67,68,70,71,74,97] Of the mixed gender studies, 32.6% included females representing less than 40% of study sample
Race/Ethnicity	Eighteen (30.5%) studies reported race/ethnicity distribution. Five studies included a majority of Caucasian participants. Three studies included all Asians,[50,61,71] Two studies included majority of Hispanics.[55,96]

Abbreviations: CHD = coronary heart disease; N = total number in trial; NR = not reported; SD = standard deviation.

Table 21. Risk of bias and potential for conflict of interest in included studies.

Items	Yes	No	Unclear
All RCTs	**% of total studies (N=59)**		
Adequate generation of allocation sequence	20.3	1.7	78.0
Allocation concealment	6.8	0.0	93.2
Comparability of groups	8.5	45.8	45.8
Purity of supplement	81.4	11.9	6.8
Blinding of allocated	20.3	23.7	55.9

intervention			
Adequately addressed missing data	62.7	3.4	33.9
Freedom from potential for conflict of interest	22.0	30.5	47.5
Crossover RCTs	**% of total crossover studies (N=19)**		
Suitability of crossover design for the study condition	100	0	0
Free of carryover effect	26.3	63.2	10.5
Appropriateness of statistical analysis for crossover design	21.1	21.1	57.9
Comparability of groups between periods 1 and 2	10.5	0.0	89.5
Freedom from bias introduced by dropouts	5.3	78.9	15.8

The availability of evidence is summarized in Table 22. Across studies, participants received the following cardiovascular drugs: statins; calcium channel blockers; niacin; angiotensin-converting enzyme inhibitors (ACE-I); aspirin; thienopyridine antiplatelets; beta-blockers; anticoagulants; fenofibrates; cilostazol; diuretics; and nitrates. No study addressed the following outcomes: incidence of metabolic syndrome; incidence of hypotension; carotid-intima media thickness; or change in 10-year Framingham risk profile. Only two studies examined statistical interaction.[44,80] One study used general linear modeling to assess interaction between fish/marine oils and atorvastatin on lipid parameters.[44] The other study used ANOVA to assess interaction between omega-3 fatty acids and niacin plus aspirin on triglyceride levels.[80]

Table 22. Overview of availability of evidence.

Supplement and cardiovascular drug(s)	Outcome	Number of Studies
Coenzyme Q10		
ACE inhibitors*	Ejection Fraction	1
Fenofibrate	Lipid Profile Blood Pressure – Systolic	1
Statins	Lipid Profile	3
Echinacea		
Warfarin	INR Platelet Aggregation	1
Garlic		
Nitrates	Lipid Profile	1
Statins + Aspirin	Lipid Profile CRP Platelet Count Coronary Artery Calcification	1
Warfarin	Lipid Profile Blood Pressure – Systolic and Diastolic Platelet Count Platelet Aggregation	1
	INR	2
Ginger		
Warfarin	INR Platelet Aggregation	1
Ginkgo biloba		
Aspirin	Lipid Profile Blood Pressure – Systolic and Diastolic Clotting Time Bleeding Time Platelet Count Partial Thromboplastin Time	1
	Platelet Aggregation	2
Antiplatelet drugs – thienopyridines	Blood Pressure – Systolic Clotting Time Platelet Count	1
	Platelet Aggregation Bleeding Time	2
Cilostazol	Blood Pressure – Systolic Platelet Aggregation Bleeding Time Clotting Time Platelet Count	1
Warfarin	INR Platelet Aggregation	1
Ginseng		
Warfarin	INR	3
	Prothrombin Time Platelet Count Platelet Aggregation	1
Hawthorne		
Digoxin	PR Interval	1
Magnesium		
Beta-Adrenergic Antagonists	Blood Pressure – Systolic and Diastolic	1
Hydrochlorothiazide	Lipid Profile	1
	Blood Pressure – Systolic and Diastolic	2
Niacin ≤ 250 mg		
Propranolol	Lipid Profile	1
Omega-3 Fatty Acids /		

Supplement and cardiovascular drug(s)	Outcome	Number of Studies
Fish Oil		
ACE inhibitors	Lipid Profile Blood Pressure – Systolic and Diastolic	2
	Urinary Protein Excretion Reduction in Proteinuria	1
Aspirin	Lipid Profile Platelet Count Bleeding Time	2
	Blood Pressure – Systolic and Diastolic	1
Beta-Adrenergic Antagonists	Blood Pressure – Systolic and Diastolic	1
Calcium Channel Blockers	Lipid Profile	1
Calcium Channel Blockers with + Aspirin (with or without dipyridamole)	Lipid Profile	2
	Platelet Count	1
Fenofibrate	Lipid Profile Incidence of Hypertension	1
Niacin + Aspirin	Lipid Profile	1
Statins	Lipid Profile	11
	Blood Pressure – Systolic and Diastolic Platelet Count	3
	CRP Blood Coagulation Bleeding Time	1
Warfarin	INR	1
Vitamin E		
Antiplatelets	Lipid Profile Platelet Aggregation	1
Furosemide	Blood Pressure – Systolic and Diastolic	1
Gemfibrozil	Lipid Profile Blood Pressure – Systolic and Diastolic	1
Nifedipine	Lipid Profile Blood Pressure – Systolic and Diastolic	1
Statins	Lipid Profile	6
	CRP Prothrombin Time Platelet Count	1
Vitamin K		
Anticoagulants	INR	2

Note: * Subjects were also taking digoxin, furosemide, hydralazine, or nitrates.
ACE = angiotensin converting enzyme; CRP = C-reactive protein; INR = international normalized ratio

Coenzyme Q10

Five RCTs, including four parallel-arm trials,[37,60-62] and one crossover trial[54] examined cardiovascular drugs with and without coenzyme Q10. The trials were conducted in Australia,[37,54,60] North America,[62] and East Asia.[61] The number of included participants across these trials ranged from 30[54] to 49,[61] and they received statins (atorvastatin, simvastatin),[37,61,62] fenofibrate[60] or Angiotensin-Converting Enzyme inhibitors (ACE-I) (specific agents not specified) in addition to other cardiovascular drugs (digoxin, furosemide, hydralazine, and nitrates).[54] According to the National Cholesterol Education Program, Adult Treatment Panel III,[154] the study participants were categorized as having a high,[54,60] unclear,[61,62] or mixed (moderate and high)[37] risk for coronary heart disease (CHD). The duration of treatment across

the studies ranged from 4[62] to 12 weeks.[37,54,60,61] Further details on study, participant, and treatment characteristics are presented in Appendix C .

Summary of findings, strength of evidence, and applicability data are presented in Table 23. No meta-analysis was possible for coenzyme Q10 studies because when more than one study reported a particular outcome,[37,61,62] the treatment effect was either not reported,[62] or it was reported as a median (interquartile range) change[37] thereby rendering the study results unsuitable for statistical pooling.

Coenzyme Q10 plus statins versus statins alone

C-reactive protein (CRP). One placebo-controlled parallel-arm randomized trial in participants with unclear CHD risk reported this outcome.[61] The 12-week mean CRP levels were not different between groups with add-on dietary supplement treatment (100 mg/d) versus the statin-only (10 mg/d) group (MD 0.02 mg/L [95 percent CI -0.64, 0.68]).

High density lipoprotein-cholesterol (HDL-C). This outcome was reported in two placebo-controlled parallel-arm randomized trials in participants with unclear or mixed CHD risk.[37,61] In one trial, mean HDL-C levels after 12 weeks of treatment were not significantly different for those receiving coenzyme Q10 (100 mg/d) plus statins (10 mg/d) versus those receiving only statins (5.02 mg/dL [95 percent CI -3.73, 13.77]).[61] Similarly, in the second trial (200 mg/d coenzyme Q10, 10-40 mg/d statins), there was no significant between-group difference for the median change in HDL-C (0.39 mg/dL versus -0.77 mg/dL, p=0.65).[37]

Low density lipoprotein-cholesterol (LDL-C), total cholesterol and triglycerides. These outcomes were reported in three trials of participants with mixed[37] or unclear CHD risk.[61,62] Levels were not significantly different following treatment with coenzyme Q10 plus statins compared with statins alone for 4 [62] or 12 weeks.[37,61] In one trial,[61] the mean differences were not significant for LDL-C (MD 8.12 mg/dL [95 percent CI -3.79, 20.03]); total cholesterol (MD 11.9 mg/dL [95 percent CI -3.55, 27.53]); and triglycerides (MD -21.26 mg/dL [95 percent CI -48.88, 6.36]). Similarly, in another trial, there was no significant between-group difference for the median change in LDL-C (-65.73 mg/dL versus -50.27 mg/dL, p=0.53); total cholesterol (-58.00 mg/dL versus -61.87 mg/dL, p=0.57); or triglycerides (-35.43 mg/dL versus -26.57 mg/dL, p=0.90).[37] No numerical data were reported for one trial.[62]

Coenzyme Q10 plus ACE inhibitors versus ACE inhibitors alone

Participants were also taking digoxin, furosemide, hydralazine, or nitrates.

Ejection fraction. One randomized crossover trial in participants with heart failure (HF) at high CHD risk reported this outcome.[54] The 12 week post-treatment ejection fraction in the treatment (100 mg daily coenzyme Q10 plus unknown dose of ACE inhibitors) and control (ACE inhibitors alone) groups did not differ (MD 0 percent [95 percent CI -4.75, 4.75]).

Coenzyme Q10 plus fenofibrate versus fenofibrate alone

Lipid profiles and systolic blood pressure. These outcomes were reported in one parallel arm randomized trial in participants with type II diabetes and high CHD risk.[60] The 12 week post-treatment mean levels in the treatment (200 mg/d coenzyme Q10 plus 200 mg/d fenofibrate) and control (fenofibrate alone) groups did not significantly differ for any of the outcomes assessed. Results were as follows: HDL-C (MD -1.55 mg/dL [95 percent CI -6.78, 3.68]), LDL-C (MD 3.87 mg/dL [95 percent CI -19.30, 27.04]), total cholesterol (MD 0 mg/dL [95 percent CI -23.17,

23.17]), triglycerides (MD 8.85 mg/dL [95 percent CI -52.49, 70.19]), non-HDL-C (mean difference: 0.87 mg/dL [95 percent CI -22.30, 24.04]), and systolic blood pressure (MD -3.40 mm Hg [95 percent CI -15.56, 8.76]).

Risk of bias. Generally, these studies were reported to be double-blind and had moderate risk of bias across the outcomes of interest. The wash-out period in the one cross-over trial was adequate to minimize or avoid a carryover treatment effect.[54]

Applicability. Low grade evidence of no effect on HDL-C was found in a primarily (70 percent) male population, of mean age 53 years, with high risk for cardiovascular disease. Treatment was over 12 weeks, with fenofibrate and with or without coenzyme Q10.

Table 23. Summary of findings and strength of evidence for cardiovascular drugs with and without coenzyme Q10.

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Treatment effect and conclusion* MD (95% CI)
Statins						
CRP[61]	-	-	-	-	-	No difference 0.02 mg/L (-0.64, 0.68)
HDL-C[37,61]	Moderate	Consistent	Indirect	Imprecise	Insufficient	Inconclusive 5.02 mg/dL (-3.73, 13.77)[61] Arm-specific median change [37] †
LDL-C[37,61,62]	Moderate	Consistent	Indirect	Imprecise	Insufficient	Inconclusive 8.12 mg/dL (-3.79, 20.03))[61] Arm-specific median change [37] NR[62]
TC (mg/dL) [37,61,62]	Moderate	Consistent	Indirect	Imprecise	Insufficient	Inconclusive 11.9 (-3.55, 27.53)[61] Arm-specific median change [37] NR[62]
TG (mg/dL)[37,61,62]	Moderate	Consistent	Indirect	Imprecise	Insufficient	Inconclusive -21.26 (-48.88, 6.36) [61] Arm-specific median change[37] NR[62]
ACE inhibitors						
Ejection fraction (%)	-	-	-	-	-	No difference 0 (-4.75, 4.75)
Fenofibrate						
HDL-C (mg/dL) [60]	Moderate	NA	Indirect	Precise	Low	No difference -1.55 (-6.78, 3.68)
LDL-C (mg/dL) [60]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive 3.87 (-19.30, 27.04)
TC (mg/dL) [60]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive 0 (-23.17, 23.17)
TG (mg/dL) [60]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive 8.85 (-52.49, 70.19)
Non-HDL-C (mg/dL) [60]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive 0.87 (-22.30, 24.04)
SBP (mmHg) [60]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive -3.40 (-15.56, 8.76)

Notes: * Mean difference and 95 percent confidence interval; range for mean difference given only when evidence consists of multiple studies that were not pooled
† Arm-specific median change (from baseline) was not used to assess the domain of precision
Abbreviations: ACE = angiotensin-converting enzyme; CHD = coronary heart disease; CRP = C-reactive protein; HDL-C = high density lipoprotein; LDL-C = low density lipoprotein; NA = not applicable; NR = not reported; TC = total cholesterol; TG = triglycerides pressure; RCT = randomized controlled trial; SBP = systolic blood pressure; wk(s) = week(s); yr(s) = year(s).

Echinacea

Echinacea plus warfarin versus warfarin alone

One crossover RCT in 12 healthy male volunteers examined the effect of 2 weeks pre-treatment with *Echinacea* (600 mg of *E. angustifolia* root plus 675 mg of *E. purpurea* root daily) and a single dose of warfarin (25 mg) versus warfarin alone.[63]

There was no effect on INR_{max} (mean difference [MD] 0.10 [95 percent CI -0.20, 0.40] and geometric mean ratio [GMR] 1.04 [90 percent CI 0.95, 1.13]), AUC of INR (MD 2.50 [95 percent CI -17.72, 22.72] and GMR 1.09 [95 percent CI 0.91, 1.31]), or measures of platelet aggregation (using three different platelet agonists: adenosine diphosphate, arachidonic acid and collagen; data not shown). Further details on study, participant, and treatment characteristics are presented in Appendix C. Strength of evidence is summarized in Table 24.

Table 24. Strength of evidence for warfarin with and without *Echinacea.*

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Treatment effect and conclusion MD (95% CI)
Warfarin						
Blood pressure	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** Systolic blood pressure: 2.20 mm Hg (-8.98, 13.38) Diastolic blood pressure: -0.80 mm Hg (-8.21, 6.61)

Abbreviations: CI = confidence interval; MD = mean difference; mm Hg = millimeters of mercury.

Garlic

Garlic plus warfarin versus warfarin alone

Two small RCTs, one parallel-group[64] and one crossover[65] trial, examined the effect of treating patients on warfarin with garlic extracts. Both studies concluded that supplementation with garlic in patients taking warfarin does not further affect INR, based on various measures including INR (MD -0.20 [95 percent CI -0.83, 0.43]),[64] INRmax (MD - 0.10 [95 percent CI -0.63, 0.43]),[65] AUC of INR (MD 4.30 [95 percent CI -35.90, 44.50]) [65] and the number of participants with an INR greater than 4 (no events in either arm).[65]

One study[64] in 48 participants with prosthetic heart valves, or diagnosed with deep vein thrombosis, valvular heart disease, or atrial fibrillation assessed the effect of aged garlic extract (AGE) (10 mL/d) plus warfarin (dose not reported) on lipid levels. No significant effects were seen for total cholesterol (MD 12.50 mg/dL [95 percent CI -3.74, 28.74]), LDL-C (MD 4.20 mg/dL [95 percent CI -12.01, 20.41]) or triglycerides (MD 31.90 mg/dL [95 percent CI -23.66, 87.46]). However, there was a statistically significant increase in HDL-C in the combination group (MD 4.50 mg/dL [95 percent CI 0.19, 8.81]). Blood pressure was not significantly affected (systolic MD 2.20 mmHg [95 percent CI -8.98, 13.38] and diastolic MD -0.80 mmHg [95 percent CI -8.21, 6.61]), nor platelet count (data not shown).

The crossover study[65] found no significant effect of pretreatment with garlic (4 g/d) plus a single dose of warfarin (25 mg) on platelet aggregation (using four different agents: adenoside diphosphate, arachidonic acid, collagen and ristocetin; data not presented). Participants in this trial were 23 healthy male adults of known CYP2C9 and VKORC1 genotype.

All results for major review outcomes, aside from HDL-C, were considered to have insufficient strength of evidence (Table 25). The strength of evidence for HDL-C was initially rated as insufficient by one reviewer because the lower bound confidence interval of 0.19 mg/dL is not clinically meaningful. A second reviewer provided a rating of low because the estimate is statistically significant. Adjudication by a third reviewer led to a final rating of low.

Garlic plus nitrates versus nitrates alone

One CCT[58] recruited 60 participants with coronary artery disease to receive either garlic oil (4 g/day) or placebo in addition to their prescribed nitrates (specific drugs and doses were not reported). Compared to placebo, administration of garlic was found to significantly decrease total serum cholesterol (MD -28.20 mg/dL [95 percent CI -48.30, -8.10]) and increase serum HDL-C (MD 8.40 mg/dL [1.91, 14.89]).[58] Serum triglycerides were also reduced but the comparison was not statistically significant. These results were considered to provide insufficient strength of evidence for triglycerides and low strength of evidence for HDL-C in favor of combination treatment (Table 25).

Garlic plus statins and aspirin versus statins and aspirin alone

One small parallel group trial[66] randomly allocated 23 participants with, or at high risk for, coronary artery disease to receive AGE (4 mL/d) or placebo in addition to their prescribed statins (10-40 mg/d) and aspirin (dose not specified). Compared with placebo, administration of AGE was not found to have a significant effect on lipid parameters (total cholesterol, TC/HDL, HDL-c, LDL-c, triglycerides), CRP, or platelet count.

This study also examined two measures of coronary artery calcification: volume calcium score (using isotropic interpolation method) and Agatston calcium score (multiplying the lesion area by a coefficient based on the peak density within plague). The first measure was found to be significantly lowered by supplementation with garlic compared with placebo (volume calcium score: -83.80 mm^3 [95 percent CI -164.22, -3.38]; percent change in volume calcium score per year: -14.7 mm^3 [95 percent CI -28.93, -0.47]). No differences were found in the second measure.

Strength of evidence was insufficient for LDL-C, HDL-C, and triglycerides (Table25).

Table 25. Summary of findings, and strength of evidence for cardiovascular drugs with and without garlic.

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect MD (95% CI)
Warfarin						
Blood pressure	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** Systolic: 2.20 (-8.98, 13.38) Diastolic (mmHg): -0.80 mmHg (-8.21, 6.61)

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect MD (95% CI)
LDL-C	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** 4.20 mg/dL (-12.01, 20.41)
HLD-C	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** 4.50 mg/dL (0.19, 8.81)
Triglycerides	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** 31.90 mg/dL (-23.66, 87.46)
	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** INR: -0.20 (-0.83, 0.43) INR_{max} : -0.10 (95% CI -0.63, 0.43) AUC of INR : 4.30 (-35.90, 44.50) INR > 4 No events in either arm
Nitrates						
HDL-C	High	N/A	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** 8.40 mg/dL (1.91, 14.89)
Triglycerides	High	N/A	Indirect (surrogate)	Imprecise	Insufficient	**No difference** -10.30 mg/dL (-27.60, 7.00)
Aspirin						
LDL-C	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** -25.10 mg/dL (-54.69, 4.49)
HLD-C	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** 4.30 mg/dL (-7.55, 16.15)
Triglycerides	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** -21.20 mg/dL (-93.42, 51.02)
Statins + Aspirin						
LDL-C	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** -25.10 mg/dL (-54.69, 4.49)
HLD-C	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** 4.30 mg/dL (-7.55, 16.15)
Triglycerides	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** (mg/dL) -21.20 mg/dL (-93.42, 51.02)

Abbreviations: AUC = area under the curve; CI = confidence interval; HDL-C = high density lipoprotein cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; NA = not applicable

Applicability. Combination treatment with garlic and nitrates for 3 months was found to significantly improve total cholesterol and HDL-C compared with nitrates alone, in subjects with healed myocardial infarction with or without angina. [58] Combination treatment with garlic and statins plus aspirin for 12 months significantly lowered a measure of coronary artery calcification in subjects withknown coronary artery disease. [66]

Ginger

One crossover RCT compared a single dose of warfarin following pre-treatment with ginger with warfarin alone in 12 healthy male subjects (Table 26).[67] The study also included a warfarin plus *Ginkgo biloba* group (data for the comparison between warfarin plus ginger and warfarin plus *Ginkgo* is in the *G. biloba* section).

One study reported AUC of INR for combination of ginger plus warfarin versus warfarin alone.[67] One of the two analyses of the data suggest a possible effect of unknown clinical significance. The mean difference in platelet aggregation was not statistically significant (MD 0.6 [95 percent CI -0.42, 1.62]) but the geometric mean ratio was statistically significant (GMR 1.11 [90 percent CI 1.04, 1.16]). Given the inconsistency in findings, strength of evidence was graded as insufficient for INR (Table 26).

Table 26. Strength of evidence for ginger plus warfarin versus warfarin alone.

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
AUC of INR[67]	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD 1.00 (95% CI -43.68, 45.68) GMR 1.01 (90% CI 0.93, 1.15)

Abbreviations : AUC of INR = area under the curve of the international normalized ratio ; CI = confidence interval; GMR = geometric mean ratio; MD = mean difference.

Applicability. This is a single dose study in young, healthy, Caucasian and Asian males.

Ginkgo biloba

Five RCTs investigated *Gingko biloba* with CV drugs (Table 27).[67-71] Four studies included subjects taking antiplatelet agents (aspirin,[68,69] clopidogrel,[70] or ticlopidine[71]). One study included subjects taking an anticoagulant (warfarin[67]) and one study included subjects taking a vasodilator (cilostazol[70]).

Ginkgo biloba plus antiplatelet agents versus antiplatelet agents alone

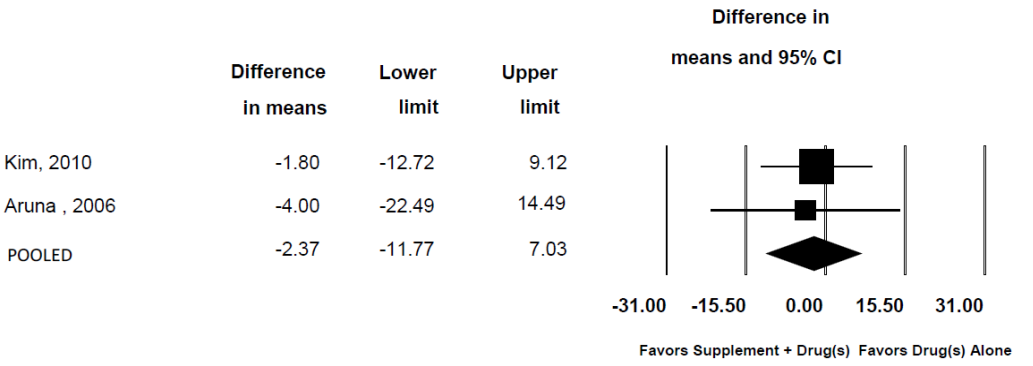
Aspirin was administered with *Ginkgo biloba* in two studies of young healthy males[68] or elderly subjects with peripheral arterial disease or risk factors for cardiovascular disease.[69] Although platelet aggregation was reported in both studies, meta-analysis could not be performed because different post-treatment effect estimates were reported (mean[68] and mean change from baseline[69]). Both studies reported nonsignificant differences in platelet aggregation. Nonsignificant differences were also reported in clotting time,[69] bleeding time,[68] partial

thromboplastin time,[68] and platelet count.[68] No changes were found in lipid parameters and blood pressure (reported qualitatively only).[68]

In two studies, single doses of a thienopyridine antiplatelet drug (clopidogrel[70] or ticlopidine[71]) were administered with or without single doses of *G. biloba* . The pooled estimates for platelet aggregation were statistically nonsignificant (Figures 4 and 5), as was the pooled estimate for bleeding time (Figure 6). There were no significant changes in clotting time, systolic blood pressure, or platelet count (reported qualitatively only).[70]

Strength of evidence was insufficient for blood pressure and lipid profile (Table 27).

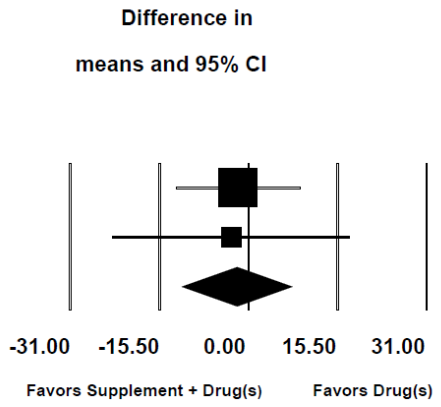
Figure 4. Forest plot of platelet aggregation (percent) for clopidogrel/ticlopidine with or without *G. biloba* (induced by 5 µL of 10 µM ADP or 2.5 µL of 10 µM ADP)



I^2 = 0.0%, p-value = 0.84, chi-square = 0.04

Figure 5. Forest plot of platelet aggregation (percent) for clopidogrel/ticlopidine with or without *G. biloba* (induced by 5 µL of 10 µM ADP or 2.5 µL of 5 µM ADP)

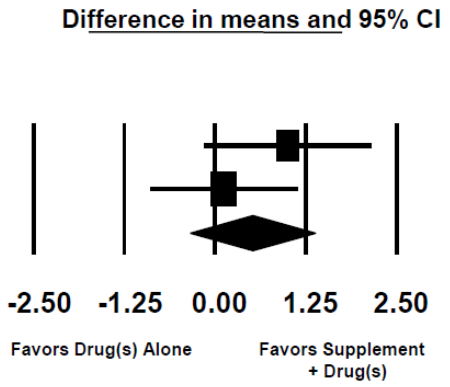
	Difference in means	Lower limit	Upper limit
Kim, 2010	-1.80	-12.72	9.12
Aruna, 2006	-3.00	-23.71	17.71
	-2.06	-11.72	7.60



I^2 = 0.0%, p-value = 0.92, chi-square = 0.01

Figure 6. Forest plot of bleeding time (minutes), for clopidogrel/ticlopidine with or without *G. biloba*

	Difference in means	Lower limit	Upper limit
Kim, 2010	1.00	-0.14	2.14
Aruna, 2006	0.12	-0.89	1.13
POOLED	0.52	-0.34	1.38



I^2 = 21.8%, p-value = 0.26, chi-square = 1.28

G. biloba Plus Warfarin Versus Warfarin Alone

One crossover RCT examined single dose warfarin (25 mg/day) following either no pretreatment or pretreatment with 12 g/day *G. biloba* or 3.6 g/day ginger in healthy subjects.[67] Compared with warfarin alone, there was a statistically significant increase in platelet aggregation (GMR 1.14 [90 percent CI 1.08, 1.20]). However, the difference in AUC of INR was not statistically significant. Compared with warfarin plus ginger, there were no statistically significant differences in platelet aggregation or AUC of INR.

Strength of evidence comparing *G. biloba* plus warfarin with warfarin alone or warfarin plus ginger is insufficient for INR (Table 27).

G. biloba Plus Colostazol Versus Cilostazol Alone

One crossover RCT examined single dose cilostazol (100 mg/day) with or without single dose *G. biloba* (120 mg/day) in healthy South Asian males.[70] Bleeding time was slightly prolonged in the *G. biloba* plus cilostazol group (MD 1.02 min [95 percent CI 0.10, 1.94]). One measure of platelet aggregation was statistically significant (MD 18.00 percent [95 percent CI 1.92, 34.08]). There were no significant changes in clotting time, systolic blood pressure, or platelet count (reported qualitatively only).

Strength of evidence for systolic blood pressure was insufficient (Table 27).

Table 27. Strength of evidence for G. biloba plus a cardiovascular drug versus the cardiovascular drug alone

Cardiovascular drug/ Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Antiplatelet drugs						
Blood Pressure – Systolic and Diastolic	Moderate	NA	Indirect (surrogate)	NA	Insufficient	**Inconclusive**
Lipid Profile (LDL-C, HDL-C, TG)[68]	Moderate	NA	Indirect (surrogate)	NA	Insufficient	**Inconclusive**
Warfarin						
AUC of INR (versus warfarin alone)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD -3.00 (95% CI -62.00, 56.00) GMR 0.93 (90% CI 0.81, 1.05)
AUC of INR (versus warfarin plus ginger)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD -4.00 (95% CI -62.84, 54.84)
Cilostazol						
Blood pressure - Systolic	Moderate	NA	Indirect (surrogate)	NA	Insufficient	**Inconclusive**

Abbreviations: AUC of INR = area under the curve of the International Normalized Ratio; CI = confidence interval; GMR = geometric mean ratio; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; NA = not applicable; TG = triglycerides.

Ginseng

Ginseng plus warfarin versus warfarin alone

Three RCTs compared ginseng plus warfarin with warfarin alone (Table 28).[72-74] Reported outcomes included INR [72-74], prothrombin time [72], platelet aggregation[74] and platelet count.[72]

Meta-analyses were not possible because of differences in patient populations (e.g. healthy versus ischemic stroke) and incompatible effect estimates (e.g. differences in means and differences in medians). One small study in subjects with ischemic stroke reported no statistically significant differences in peak and AUC of INR, peak and AUC of prothrombin time, and platelet count.[72] A study in young, healthy subjects, however, reported significantly lower peak INR and AUC of INR in the ginseng plus warfarin group (difference in medians -0.19 (95 percent CI -0.36, -0.07] and -0.43 (95 percent CI -1.00, -0.09] for peak and AUC of INR respectively).[73] Another small study in healthy males found no differences in AUC of INR and platelet aggregation.[74]

Strength of evidence was graded as insufficient for peak INR and AUC of INR (Table 28).

Table 28. Strength of evidence for ginseng plus warfarin versus warfarin alone

Cardiovascular drugs(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect*
Warfarin						
INR_{peak}	Moderate	Inconsistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD range 0.01-0.11 (95% CI -0.20 to -0.06, 0.08 to 0.42] $M_{ed}D$ -0.19 (95% CI -0.36, -0.07]
AUC of INR MD	Moderate	Inconsistent	Indirect (surrogate)	Imprecise	Insufficient	Inconclusive MD range 0.03-0.49 (95% CI -39.10 to -0.28, 0.34 to 39.30] $M_{ed}D$ -0.43 (95% CI -1.00, -0.09]

Note: * Range is provided when more than one study is being summarized.
Abbreviations: AUC of INR = area under the curve of the International Normalized Ratio; CI = confidence interval; GMR = geometric mean ratio; MD = mean difference; $M_{ed}D$ = difference of the medians; NA = not applicable; TG = triglycerides.

Hawthorne

In a randomized crossover trial, subjects were administered digoxin 0.25 mg/day for 10 days or digoxin 0.25 mg/day plus hawthorne 450 mg twice daily for 3 weeks.[75] Subjects were tested with a standard 12-lead electrocardiogram for PR interval measurements. The difference between groups was statistically nonsignificant.

Magnesium

Three RCTs investigated the use of oral magnesium with CV drugs: magnesium plus hydroclorothiazide [76,77] and magnesium plus beta-adrenergic antagonists[42]. Reported outcomes included total cholesterol, triglycerides, and systolic and diastolic blood pressure.

Magnesium plus hydrochlorothiazide versus hydrochlorothiazide alone

In a trial of 18 elderly subjects with benign essential hypertension, nonsignificant differences were found in total cholesterol, triglycerides, and supine systolic and diastolic blood pressure.[76] Nonsignificant differences for systolic and diastolic blood pressure (supine and standing) were also reported in a trial of subjects with mild to severe uncomplicated essential hypertension.[77] These two studies were meta-analyzed for supine systolic and diastolic blood pressure and the pooled estimates were statistically nonsignificant (Figures 7 and 8).[76,77]

Strength of evidence was graded as insufficient for systolic and diastolic blood pressure and triglyceride level (Table 29).

Figure 7. Forest plot of supine systolic blood pressure (mmHg) for hydrochlorothiazide with or without magnesium

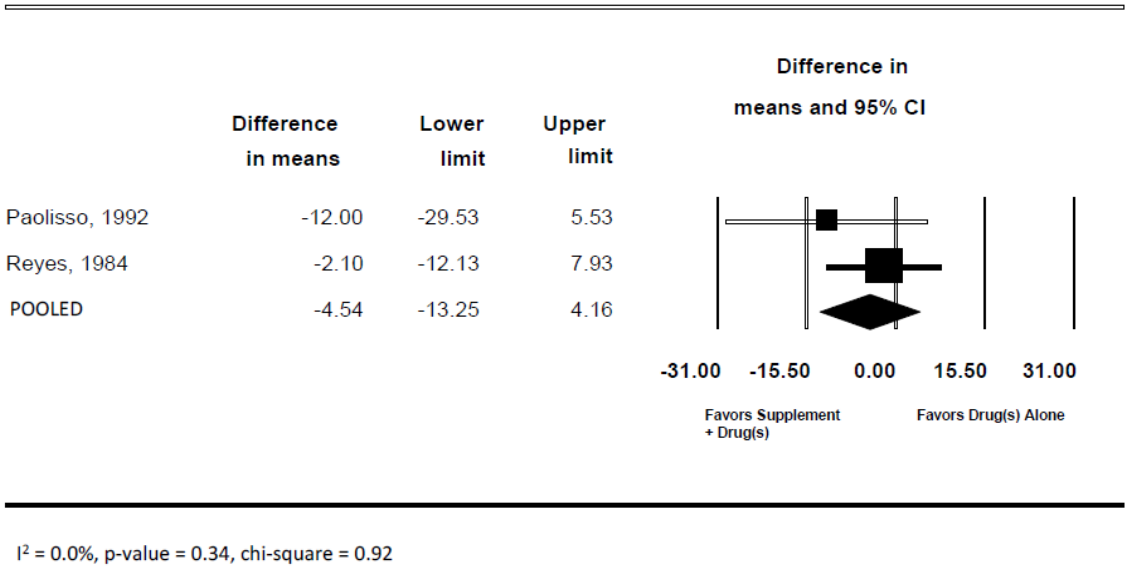
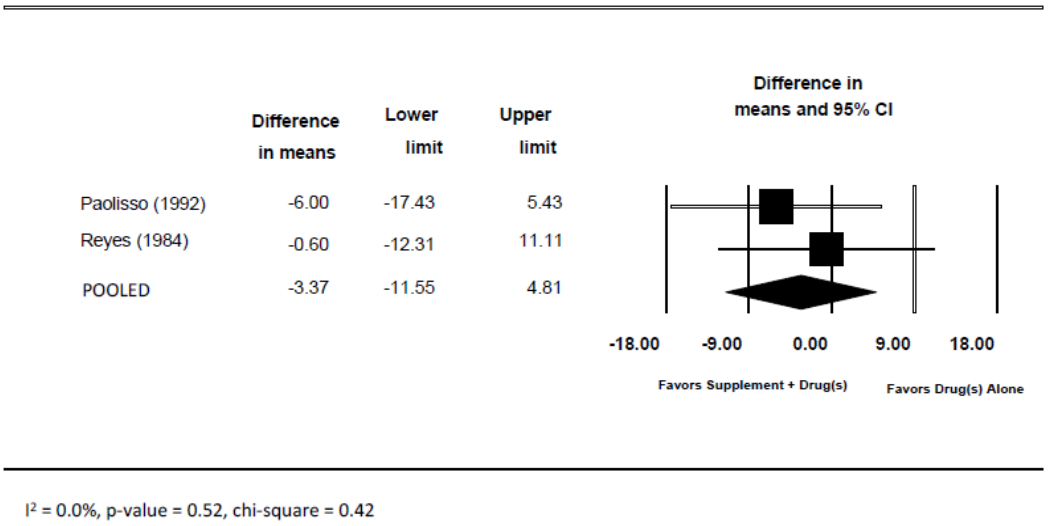


Figure 8. Forest plot of supine diastolic blood pressure (mmHg) for hydrochlorothiazide with or without magnesium



Magnesium plus beta-adrenergic antagonists versus beta-adrenergic antagonists alone

In a crossover RCT, 39 subjects with essential hypertension on atenolol, metoprolol, pindolol, or propranolol were randomized to receive magnesium 15 mmol/day or placebo for 8 weeks. Effect estimates for supine and standing systolic and diastolic blood pressures were statistically nonsignificant.[42]

Strength of evidence was graded as insufficient for systolic and diastolic blood pressure (Table 29).

Table 29. Strength of evidence for magnesium plus cardiovascular drug(s) versus cardiovascular drug(s) alone

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect* MD (95% CI)
Hydrochloro-thiazide						
Blood Pressure	Moderate	Consistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** *Systolic* Supine: Pooled -4.54 mm Hg (-13.25, 4.16) Standing: 0 mm Hg (-5.94, 5.94) *Diastolic* Supine: Pooled -3.37 mm Hg (-11.55, 4.81) Standing: 1.00 mm Hg (-8.84, 10.84)
Triglycerides	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** 1.77 mg/dL (-103.19, 106.73)
Beta-adrenergic antagonists						
Blood Pressure	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** *Systolic* Supine: -4.26 mm Hg (-12.56, 4.04) Standing: -4.34 mm Hg (-13.90, 5.22) *Diastolic* Supine: -2.65 mm Hg (-6.85, 1.55) Standing: -1.65 mm Hg (-6.18, 2.88)

Note: * Range is provided when more than one study is being summarized; pooled data is from meta-analysis of more than one study.
Abbreviations: CI = confidence interval; MD = mean difference; mm Hg = millimeters of mercury; NA = not applicable.

Niacin (≤ 250 mg)

One parallel-arm RCT described the use of niacin with propranolol in 16 subjects with Type II or Type IV hyperlipoproteinemia (Table 30).[78] This study was rated as high risk of bias because groups were administered different dosages of propranolol (20 mg and 60 mg). Effect estimates for total cholesterol and triglycerides were statistically nonsignificant.

Strength of evidence was insufficient for triglycerides (Table 30).

Table 30. Strength of evidence propranolol with or without niacin

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect MD (95% CI)
Triglycerides	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** In Type II hyperlipoproteinemia: 8.40 mg/dL (-114.22, 97.42) In Type IV hyperlipoproteinemia: -49.83 mg/dL (-523.94, 424.28)

Abbreviations: CI = confidence interval; MD: mean difference; NA: not applicable

Omega-3 Fatty Acids/Fish Oil

Twenty-three RCTs, including 17 parallel-arm trials[40,44,50-53,55,56,79,80,93,94,97,98,139-141] and six crossover trials[36,90-92,96,142] contributed evidence. The trials were conducted in North America,[36,40,52,55,56,80,90,94,96,141] Australia,[44,139,140,142] Europe,[53,79,91-93,97,98] and Asia.[50,51] The number of included participants in these trials ranged from 11[55] to 254.[40] The participants across studies received the following cardiovascular drugs: statins (atorvastatin, simvastatin, lovastatin),[36,40,44,53,91-94,96,98,139,141] calcium channel blockers,[50-52] niacin plus aspirin,[80] Angiotensin-Converting Enzyme (ACE) inhibitors,[79,140] aspirin,[90,97] beta-blockers,[142] anticoagulation agents,[55]and fenofibrates.[56] In two trials, calcium channel blockers were used concomitantly with either aspirin[51] or aspirin plus dipyridamole.[52] In most of the trials, participants were categorized as having unclear or mixed (different combinations of low, moderate/moderately high, and high) risk of coronary heart disease according to the National Cholesterol Education Program, Adult Treatment Panel III.[154] The duration of treatment ranged from 2 weeks[96,97] to 25 weeks.[139,140] Further details on study, participant, and treatment characteristics are presented in Appendix C.

Risk of Bias

Generally, most of these studies were reported to be double blind and had a moderate risk of bias across the outcomes of interest. In cross-over trials, the adequacy of wash-out period was not clear for one trial, [36] there was a potential of carryover in one trial (i.e., the treatment effect depended on the order of drug randomization),[90] and no wash-out period was employed for another trial.[142] The wash-out period length reported for three other trials was deemed to be adequate.[91,92,96]

Summary of Findings, Strength of Evidence, and Applicability

Summary of findings, and strength of evidence are presented in Table 30. Meta-analyses were performed for the following outcome measures: HDL-C, LDL-C, total cholesterol, and triglycerides (Figures 9 to 14).

Omega-3 fatty acids/fish oil statins versus statins alone

C-Reactive protein (CRP). This outcome was assessed in one placebo-controlled parallel arm randomized trial in participants at mixed CHD risk.[44,149] The 6 week post-treatment geometric

mean CRP levels were not different between the dietary supplement (fish oil plus atorvastatin) and control (atorvastatin alone) groups (geometric means 1.14 mg/L (95 percent CI 0.6, 2.4] versus 1.80 mg/L (95 percent CI 1.3, 3.2]).

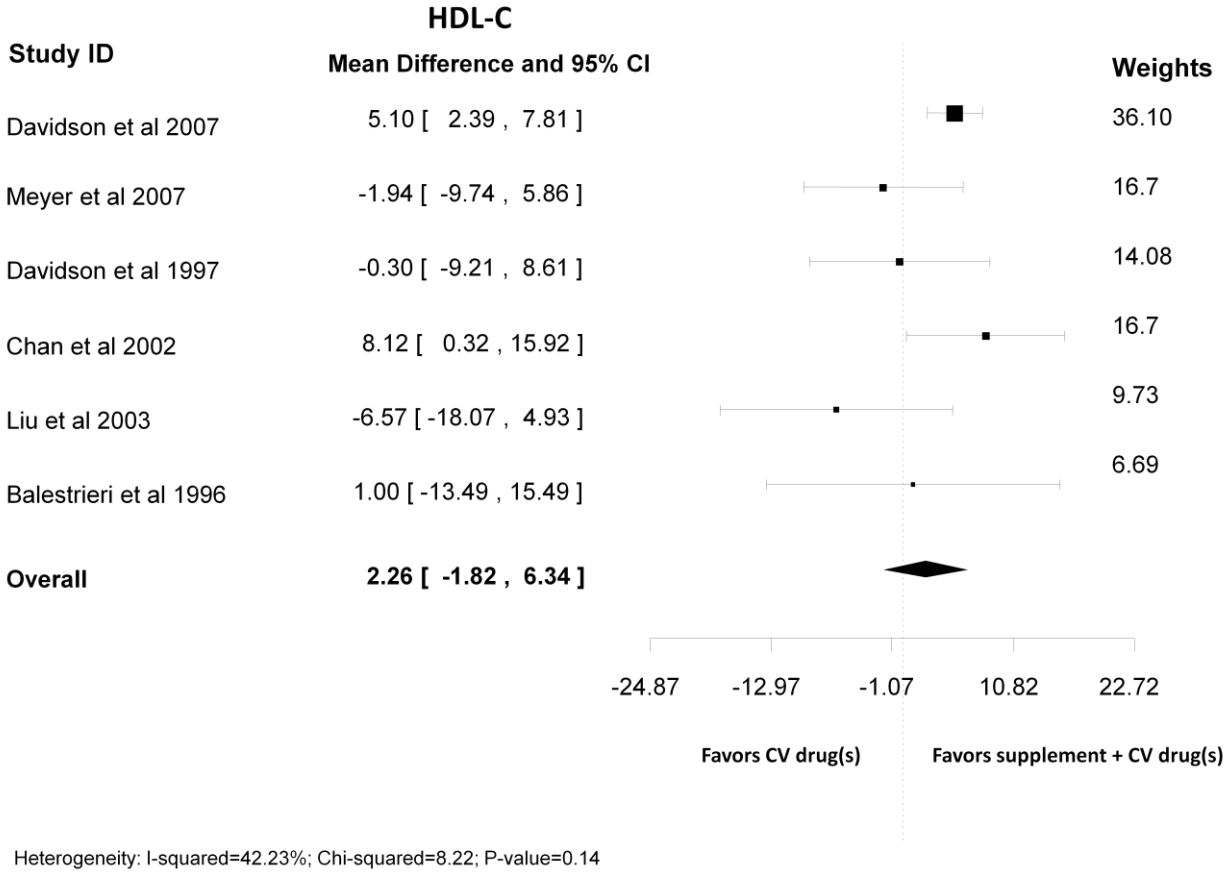
HDL-C. Post-treatment levels of HDL-C were reported in 10 randomized trials.[36,40,44,53,91-94,139,141] In five studies,[44,53,91,139,141] the mean endpoint differences in HDL-C levels for participants with unclear or mixed CHD risk were not significantly different between the omega-3/fish oil combination and statins alone group. In one trial of participants at moderate CHD risk,[40] the 8 week post-treatment mean HDL-C level was significantly greater in the dietary supplement versus control group (mean difference 5.10 (95 percent CI 2.36, 7.83]). A meta-analysis based on the results from six studies (participants with unclear or mixed CHD risk),[40,44,53,91,139,141] indicated that the mean HDL-C levels did not differ between the omega-3/fish oil combination and statins alone group (Figure 9; pooled MD 2.26 mg/dL (95 percent CI -1.82, 6.34]).

Results from the remaining 4 trials reporting mean change,[93] percent change,[92] or percent median change[36,94] were not consistent. Specifically, one trial of participants with mixed CHD risk reported 5 week post-treatment mean change for the omega-3/fish oil combination and statins alone group and found significant difference in favour of the omega-3/fish oil combination group (difference in mean change: 2.32 (95 percent CI 0.18, 4.45]).[93] Similarly, two other trials of participants with unclear[94] and mixed[36] CHD risk reported significantly greater (i.e., improved) post-treatment percent increase in median HDL-C levels at 6 weeks (difference of 7.2 percent, $p=0.001$),[36] at 8 weeks (difference of 2.4 percent, $p<0.001$)[94] or at 16 weeks (difference of 6.3 percent, $p<0.001$)[94] in favor of the dietary supplement intervention. In contrast, the percent change in HDL-C (from baseline) in one cross-over trial of participants with mixed CHD risk was not significantly different between the dietary supplement and control group at 6 weeks after the baseline (6.0 percent versus 14.0 percent).[92]

Authors of one trial[44] conducted a formal assessment of statistical interaction (general linear modeling) in obese men and found no significant interaction between the effects of omega-3 fatty acids/fish oil and cardiovascular drug (atorvastatin) on the levels of HDL-C.

Overall, results indicated no difference in post-treatment HDL-C levels between the dietary supplement and control interventions.

Figure 9. Post-treatment HDL-C levels in subjects taking statins with or without omega-3 fatty acids/fish oils



LDL-C. Post-treatment levels of LDL-C were reported in 9 randomized trials.[36,40,44,53,91-94,139] In 5 trials,[40,44,53,91,139] the mean endpoint differences in LDL-C levels for participants with unclear or mixed CHD risk were not significantly different between the dietary supplement and the control groups. Likewise, one trial that reported mean change for the dietary and control groups, found no significant difference between the two groups (difference in mean change: -5.84 mg/dL (95 percent CI -16.88, 5.20]).[93]

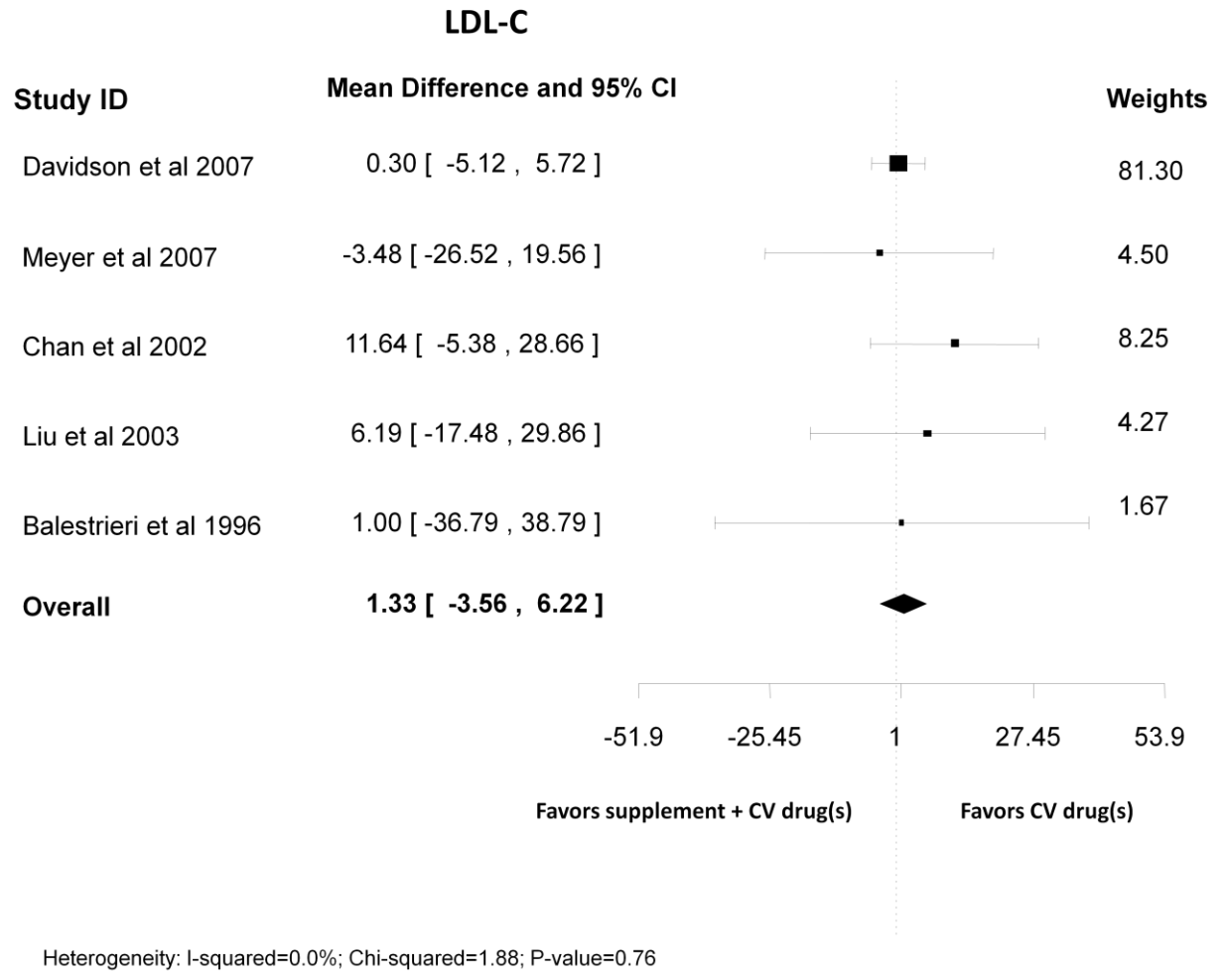
Our meta-analysis based on the results from 5 studies (participants with unclear or mixed CHD risk),[40,44,53,91,139] indicates that the mean LDL-C levels did not differ between the intervention and control groups (Figure 10; pooled MD 1.33 mg/dL (95 percent CI -3.56, 6.22]).

Two other trials of participants with unclear[94] and mixed[36] CHD risk reported that there was no significant difference in either post-treatment percent change in least squares mean (difference of 1.30 percent, p=0.43)[36] or percent change in median (difference at 8 weeks 2.2 percent, p= 0.24; at 16 weeks 0.3 percent, p= 0.64)[94] in LDL-C levels for the dietary supplement versus control groups. The percent change in LDL-C (from baseline) in one cross-over trial of participants at low CHD risk was not significantly different between the dietary supplement and control group at 6 weeks (-39.0 percent versus -37.0 percent, p>0.05).[92]

One trial[44] conducted a formal assessment of statistical interaction (general linear modeling) in obese men and found no significant interaction between the effects of omega-3 fatty acids/fish oil and cardiovascular drug (atorvastatin) on the levels of LDL-C.

Overall, results indicated no difference in post-treatment LDL-C levels between the dietary supplement and control interventions.

Figure 10. Post-treatment LDL-C levels in subjects taking statins with or without omega-3 fatty acids/fish oils



Total cholesterol (TC). Post-treatment levels of total cholesterol were reported for 10 trials.[36,40,44,53,91-94,98,139] In 6 trials,[44,53,91,93,98,139] the mean endpoint/mean change differences in TC levels for participants with unclear or mixed CHD risk were not significantly different between the dietary supplement and the control groups. The pooled results based on our meta-analysis of five trials in participants with unclear or mixed CHD risk [40,44,53,91,139] showed that the mean TC levels did not significantly differ between the intervention and control groups (Figure 11; pooled mean difference: -7.06 (95 percent CI -14.50, 0.37]).

Similarly, one cross-over trial[92] did not find a significant difference for mixed CHD risk participants in the post-treatment TC percent change from baseline between the two treatment groups (-31.0 versus -27.0, $p>0.05$).

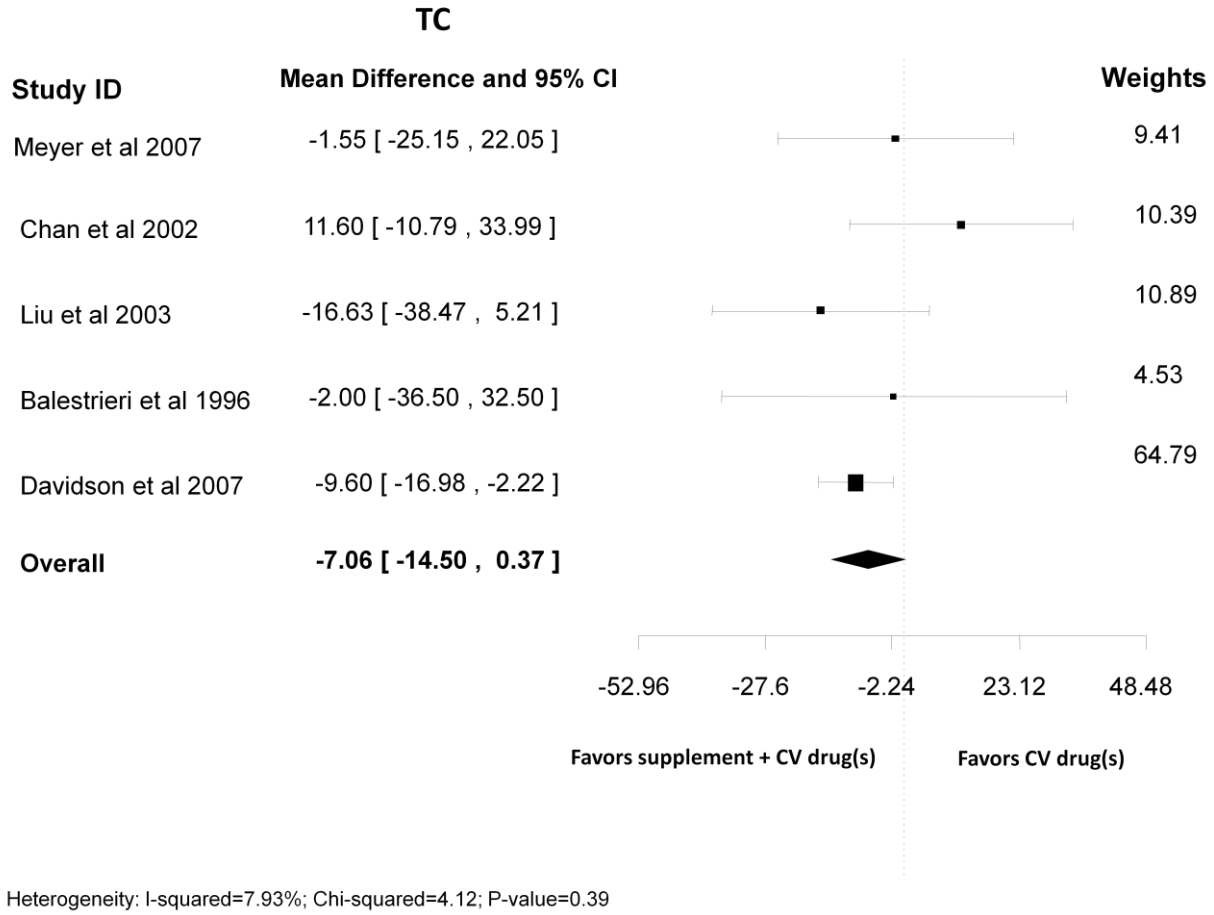
In one trial of participants unclear CHD risk,[40] the 8 week post-treatment mean TC level was significantly improved in the dietary supplement versus control group (mean difference: -9.60 (95 percent CI -17.05, -2.14]). Two other trials reported significantly greater reduction in median total cholesterol percent change from baseline in the dietary supplement versus control groups for participants with mixed and unclear CHD risk (median percent change -2.7, $p= 0.006$[36] and -5.8, $p<0.001$[94]).

One trial in participants with mixed CHD risk did not report numerical data.[98]

The wide confidence intervals around the pooled estimate rendered the results in regards to post-treatment total cholesterol levels between the dietary supplement and control interventions as inconclusive.

Authors of one trial[44] conducted a formal assessment of statistical interaction (general linear modeling) in obese men (mixed CHD risk) and found no significant interaction between the effects of dietary supplement (omega-3 fatty acids/fish oil) and cardiovascular drug (atorvastatin) on the levels of total cholesterol.

Figure 11. Post-treatment total cholesterol levels in subjects taking statins with or without omega-3 fatty acids/fish oils



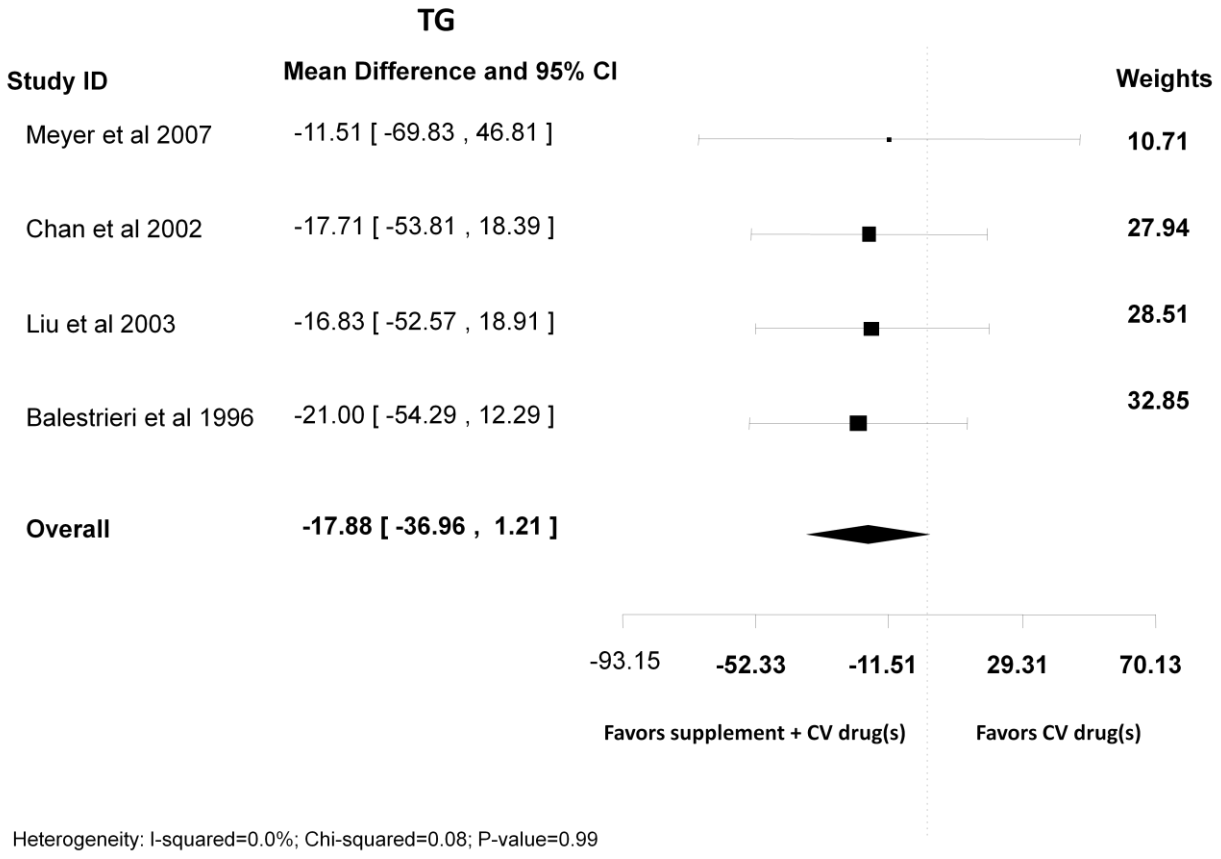
Triglycerides (TG). Post-treatment levels of triglycerides were reported for 11 trials which included participants with unclear or mixed CHD risk. [36,40,44,53,91-94,98,139,141] Initial pooling of six trials reporting post-treatment mean TG levels revealed some degree of statistical heterogeneity (I^2=63.53 percent, Chi-squared statistic=15.95, p=0.01). [40,44,53,91,98,139] After careful examination of the study factors that could potentially explain this discrepancy, we found that in two studies[40,98] which were conducted in specialty clinics, the baseline TG levels of participants were on average higher compared with those in other studies, thereby resulting in greater magnitude of the observed mean differences in favour of the dietary supplement intervention (-73.50[40] and -91.23[98]). The removal of these two studies from the meta-analysis resulted in a non-significant pooled mean difference (Figure 12; -17.88, 95 percent CI -36.96, 1.21) with no significant heterogeneity (I^2=0 percent, Chi-squared statistic=0.08, p=0.99).[44,53,91,139] participants in the pooled trials were mixed or unclear CHD risk. Information on clinical settings for these studies was not reported.

In contrast, trials reporting median[36,94] or mean[92] percent change from baseline in TG levels showed significantly reduced (i.e., improved) TG levels for the dietary supplement versus control groups of participants with mixed[36,92] or unclear CHD risk.[94]

Authors of one trial[44] conducted a formal assessment of statistical interaction (general linear modeling) in obese men (mixed CHD risk) and found no significant interaction between the effects of dietary supplement (i.e., omega-3 fatty acids/fish oil) and cardiovascular drug (i.e., atorvastatin) on the levels of triglycerides.

The wide confidence intervals around the pooled estimate rendered the results in regards to post-treatment TG levels between the dietary supplement and control interventions as inconclusive.

Figure 12. Post-treatment triglyceride levels in subjects taking statins with or without omega-3 fatty acids/fish oils



Non-HDL-C. Post-treatment levels of non-HDL-C were reported for five trials, in which participants had mixed or unclear CHD risk. [36,40,44,94,141] Of three trials reporting mean non-HDL-C levels,[40,44,141] one trial (unclear CHD risk)[40] indicated significantly lower (i.e., improved) post-treatment mean non-HDL in the dietary supplement group compared with the control group (mean difference: -14.70 (95 percent CI -21.77, -7.62]), whereas the remaining two trials showed no significant between-group mean difference: 5.42 (mixed CHD risk; 95 percent CI -15.75, 26.59)[44] and 5.60 (unclear ChD risk; 95 percent CI -34.06, 45.26).[141] The pooling of results from the 3 trials[40,44,141] revealed some degree of statistical heterogeneity across the effect estimates (I^2=58.86 percent, Chi-squared statistic=4.96, p=0.08). There was no readily explainable reason/cause for this discrepancy; the participants across these trials were of either unclear or mixed CHD risk. We did not pool these studies.

Trials reporting median percent change from baseline in non-HDL levels showed significantly greater (i.e., improved) reduction in non-HDL-C for favouring the dietary supplement groups over the control groups in participants (unclear CHD risk: -40.2 percent versus -33.7 percent, p<0.001[94] and mixed CHD risk: -40.0 percent versus -34.3 percent, p<0.001[36]).

Authors of one trial (mixed CHD risk)[44] conducted a formal assessment of statistical interaction (general linear modeling) in obese men and found no significant interaction between the effects of dietary supplement (i.e., omega-3 fatty acids/fish oil) and cardiovascular drug (i.e., atorvastatin) on the levels of non-HDL-C.

The overall results regarding post-treatment non-HDL-C levels between the treatment groups were determined to be inconclusive.

TC/HDL-C ratio. Post-treatment levels of the TC/HDL-C ratio were reported for four trials.[36,40,94,141] Two trials of participants with unclear CHD risk [40,141] reporting post-treatment mean TC/HDL ratio levels yielded discrepant results, one in favor of the dietary supplement group (mean difference -0.60 (95 percent CI -0.83, -0.36]),[40] and the other in favor of neither group (mean difference: 0.29 (95 percent CI -0.90, 1.48]).[141] This discrepancy in the results for TC/HDL-C ratio may have been due to differences between participants' CHD risk across the studies. Based on the differences in CHD risk and the opposite direction of the effect estimates, it was decided not to pool these studies.

Two other trials in participants with mixed[36] or unclear[94]CHD risk reported significant difference in post-treatment percent change in least squares mean (difference of -6.5 percent, p<0.001)[36] or percent change in median (difference at 8 weeks:-38.3 percent versus -34.5 percent, p<0.001)[94] in TC/HDL-C ratio levels favoring the dietary supplement intervention over control intervention.

The overall results regarding post-treatment TC/HDL-C ratio levels between the treatment groups were inconclusive.

Pre-defined thresholds of LDL-C and non-HDL-C. The proportion of participants reaching these thresholds was reported for one 16 week, parallel arm trial in participants with unclear CHD risk.[94] At the end of the treatment, there was no difference in the proportion of participants reaching pre-defined targets of either LDL-C (below 160 mg/dL, 130 mg/dL, or 100 mg/dL; risk ratio: 0.93 (95 percent CI 0.84, 1.03]) or HDL-C (below 190, 160, or 130 mg/dL; risk ratio: 1.00 (95 percent CI 0.91, 1.11]) between the dietary supplement intervention and control groups.

Lipoprotein A. Post-treatment levels of lipoprotein A were reported for one trial.[91] In this cross-over randomized trial, participants with familial hypercholesterolemia (mixed CHD risk) were treated during 4 weeks for each treatment period. The difference in the 4-week post-treatment mean lipoprotein A levels between the dietary supplement and control groups was not significant (mean difference 2.00 (95 percent CI -34.40, 38.40]).

Blood pressure. Systolic and diastolic blood pressure levels post-treatment were reported for three trials; two parallel arm[93,139] and one cross-over.[36] In the first parallel arm trial[93] participants with mixed CHD risk receiving the omega-fish oil (2 gram daily) combined with statins (10 mg daily) for 5 weeks experienced significantly greater reductions in mean SBP (-8.50 (95 percent CI -16.33, -0.66]) but not in DBP (0.20 (95 percent CI -4.76, 5.16]) compared with participants receiving statins alone. In the second parallel arm trial of participants with unclear CHD risk,[139], there was no significant difference after 25 weeks of treatment in the blood pressure between the omega-3/fish oil (4 or 8 grams daily) in combination with statins (unknown dose) versus statins alone. Data for the comparison was not provided.

In one cross-over trial,[36] participants with mixed CHD risk receiving omega-3/fish oil (4 gram daily) and statins (20 mg daily) experienced significantly greater median reductions from baseline in SBP (-5.00 versus 0.30, p=0.008) and DBP (-3.30 versus -1.80, p=0.045) compared with those receiving the control intervention.

We were unable to perform a meta-analysis given the lack of data[139] and the differences in effect measures, reported as reductions in median[36] and mean levels.[93]

The overall results showed decreased post treatment SBP levels for the combination of omega-3 fatty acids/fish oil and statins versus statins alone group.

Blood coagulation. Results of blood coagulation were reported for one trial.[96] This was a cross-over randomized trial in healthy participants. After 2 weeks of treatment, there was no difference between the groups of omega-3/fish oil (4 grams daily) in combination with statins (80 mg daily) versus statins alone in the following blood coagulation parameters: prothrombin time (-0.10 seconds (s] (95 percent CI -0.28, 0.08]), activated partial thromboplastin time (0.10 s, 95 percent CI -0.62, 0.82), platelet aggregation/adenosine diphosphate (1.10 percent (95 percent CI -5.05, 7.25]), or platelet aggregation/collagen (0.90 percent (95 percent CI -5.70, 7.50]).

Platelet count. Post-treatment platelet count ($10^3/\mu L$) were reported for 3 trials, one parallel arm[98] and 2 cross-over trials.[92,96] Study participants in these trials had mixed CHD risk (healthy volunteers, participants with combined or familial hyperlipidemia). The difference between post-treatment mean change (-9.82 $10^3/\mu L$[96] and 6.00 $10^3/\mu L$[98]) or percent change (17.0 versus 20.0 percent, p>0.05)[92] in platelet counts between baseline and 2 to 6 weeks between the dietary supplement and control groups was not significant. We could not pool two trials[96,98] reporting post-treatment mean change in platelet count due to the lack of accurate standard deviations reported for one study.[96]

Bleeding time. Post-treatment of bleeding time was reported for one study.[92] This was a cross-over randomized trial that included participants with mixed CHD risk (familial hyperlipidemia) who were treated for 6 weeks. There was no difference in percent change for bleeding time between the dietary supplement group and control group (mean difference 1.0 percent change, 95 percent CI -0.59, 2.59).

Omega-3 fatty acids/fish oil plus ACE inhibitors versus ACE inhibitors alone

Triglycerides (TG). Post-treatment levels of triglycerides were reported for 2 trials (parallel arm design).[79,140] Both trials included participants with unclear CHD risk. In one trial [79] the difference in end point mean TG levels after 25 weeks of treatment between the dietary supplement and control groups was not significant (mean difference -38.6 mg/dL (95 percent CI -160.62, 83.42]). In contrast in the other trial,[140] the mean TG reduction from baseline to 6 week follow-up significantly favored the supplement over the control group (mean difference -24.35 mg/dL (95 percent CI -45.31, -3.38]). These trials were not pooled due to differences in the reported effect measures (end point mean[79] and mean change from baseline[140]).

The overall results regarding post-treatment TG levels between the treatment groups were inconclusive.

Blood Pressure. Systolic and diastolic blood pressure levels post-treatment were reported for two trials (parallel arm design).[79,140] Both trials included participants with unclear CHD risk. There was no significant between-group difference in either systolic blood pressure (mean difference 0 mm Hg[79] and -1.00 mm Hg[140]) or diastolic blood pressure (-1.40 mm Hg [79] and -2.00 mm Hg[140]).

The pooled analysis of these trials[79,140] indicated that there was no difference in either SBP (Figure 13, pooled mean difference: -0.51, 95 percent CI -10.59, 9.57) or DBP (Figure 14, pooled mean difference: -1.75 (95 percent CI -5.98, 2.48]) between the intervention and control groups.

Figure 13.Post-treatment systolic blood pressure (SBP) in subjects taking ACE inhibitors with or without omega-3 fatty acids/fish oils

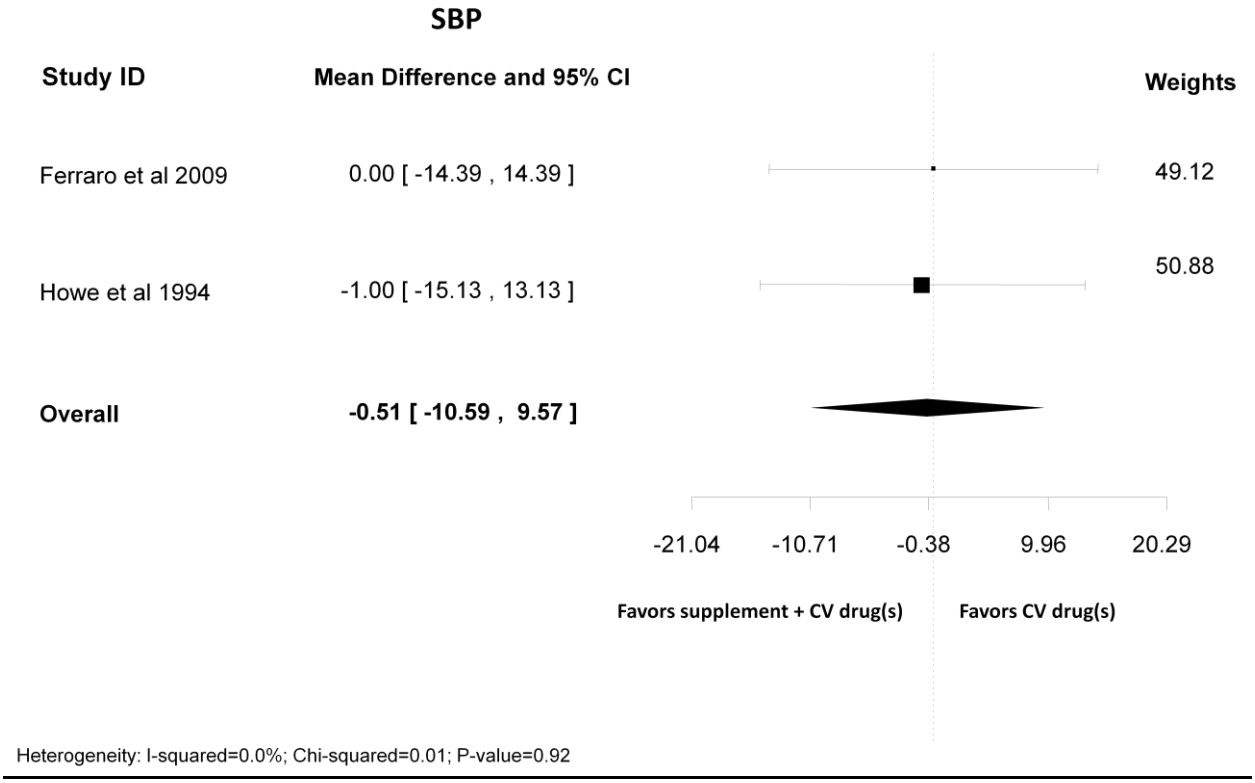
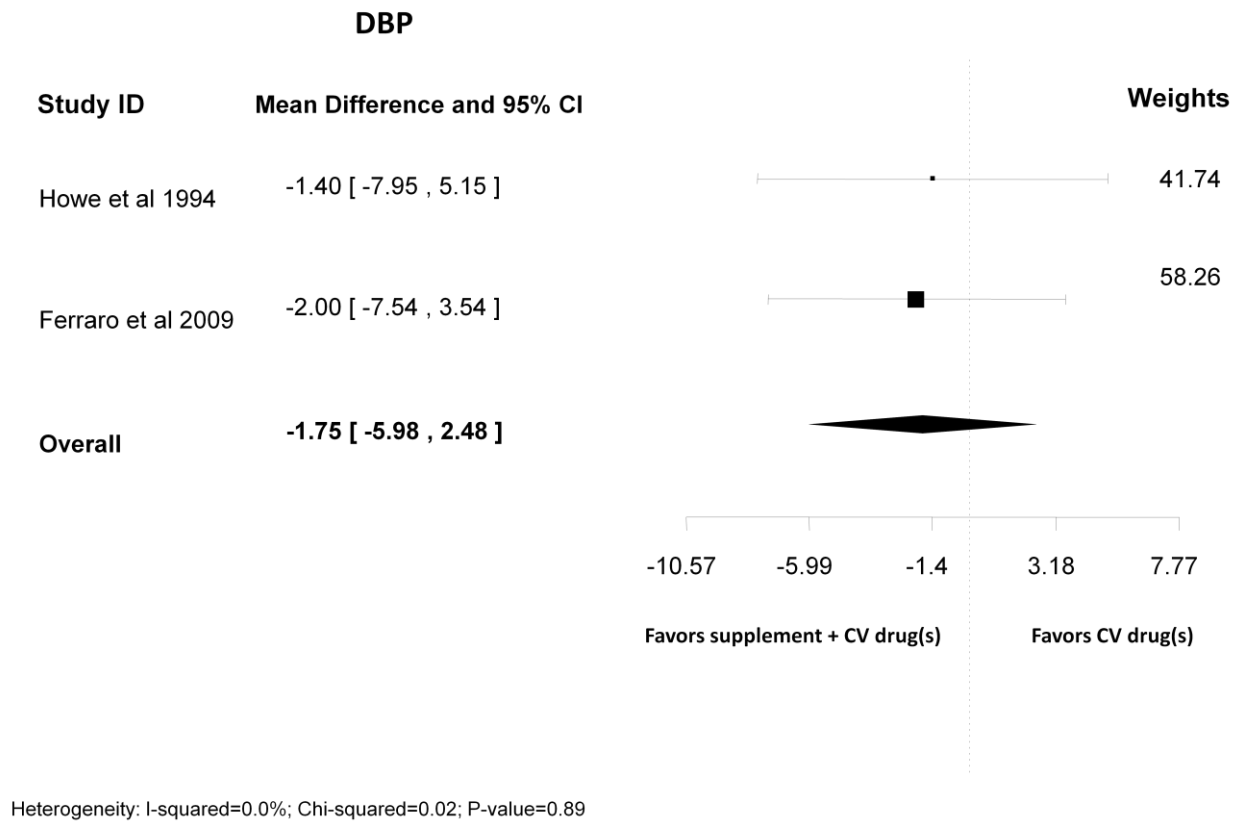


Figure 14. Post-treatment diastolic blood pressure in subjects taking ACE inhibitors with or without omega-3 fatty acids/fish oils



Urinary Protein. Levels of urinary protein post-treatment data (protein excretion, and at least 50 percent reduction in proteinuria) was reported for one parallel arm trial in participants with unclear CHD risk treated for 25 weeks.[79] The participants in the omega-3/fish oil (3 grams daily) plus ACE inhibitors (10 mg daily ramipril + 300 mg daily irbersartan) combination group had significantly reduced (i.e., improved) mean urinary protein excretion compared with participants in the ACE inhibitor alone (367.00 mg/day versus 1353.00 mg/day; mean difference -986.00 mg/day (95 percent CI -1763.43, -208.56]). Similarly, the proportion of participants who achieved at least 50 percent reduction in proteinuria was significantly greater (i.e., improved) in the supplement versus control group (80.00 percent versus 20.00 percent; relative risk 4.00 (95 percent CI 1.40, 11.30]).

Omega-3 fatty acids/fish oil plus fenofibrate versus fenofibrate alone

One study[56]contributed to the evidence relevant to this section. This was a parallel arm double blind placebo-controlled trial in 167 participants in whom the treatment allocation concealment was unclear (moderate risk of bias). Participants had unclear CHD risk and received treatment for 8 weeks (4 g/day omega-3 plus 130 mg/day fenofibrate versus 4 g/day placebo plus 130 mg/day fenofibrate). The trial reported the following post-treatment outcome measures: HDL-C, TC/HDL ratio, LDL-C, TC, TG, non-HDL, and incidence of hypertension/worsening of hypertension. The percent change from baseline to week 8 in HDL-C (-1.90 percent versus 1.30 percent, p>0.05), TC/HDL-C ratio (-4.80 percent versus -8.30 percent, p>0.05), TC (-8.00 percent versus -5.10 percent, p>0.05), non-HDL-C (-8.20 percent versus -7.10 percent, p>0.05),

or TG (-60.80 percent versus -53.80 percent, p=0.059) was not significantly different between participants in the dietary supplement and control groups. In contrast, the percent change (i.e., reduction) from baseline in LDL-C levels was significantly greater in the dietary supplement versus control group (48.20 percent versus 39.00 percent, p=0.03).

The incidence of hypertension was not significantly different between the two groups (2/84 versus 2/83, risk ratio: 0.98 (95 percent CI 0.14, 6.85]).

Given that the outcomes were measured as median percent change, the overall results of this study on levels of HDL-C, TC/HDL-C ratio, TC, and non-HDL-C were inconclusive.

Omega-3 fatty acids/fish oil plus calcium channel blockers versus calcium channel blockers alone

One study[50] contributed evidence relevant for this section. This parallel arm open label active treatment (calcium channel blocker - diltiazem) controlled trial was in 22 participants for whom the treatment allocation concealment was unclear (moderate risk of bias). Participants in this trial were at high CHD risk (variant angina) and received their treatment for 16 weeks (1.8 g/day omega-3 plus 90 to 120 mg/day diltiazem versus 90 to 120 mg/day diltiazem). The post-treatment mean difference in TC (5.00 mg/dL (95 percent CI -91.30, 101.30]), LDL-C (0 mg/dL (95 percent CI -94.30, 94.30]), HDL-C (-2.00 mg/dL (95 percent CI -32.7, 28.70]), and TG (-32.00 mg/dL (95 percent CI -112.60, 176.60]) levels were not significantly different between participants in the dietary supplement and control groups. Due to wide confidence intervals these results were inconclusive.

Omega-3 fatty acids/fish oil plus aspirin and calcium channel blockers versus aspirin and calcium channel blockers alone

One study[51] contributed evidence relevant for this section. This parallel arm single-blind (only assessors blinded) active treatment (calcium channel blockers plus aspirin) controlled trial was in 107 participants for whom the randomization sequence was computer-generated and treatment allocation concealment was unclear (moderate risk of bias). Participants in this trial were at high CHD risk (pre-coronary angioplasty) and received their treatment for 6 weeks (3 g/day omega-3 plus calcium channel blockers plus 150 mg/day aspirin versus calcium channel blockers plus 150 mg/day aspirin). The post-treatment mean TG was significantly lower (i.e., improved) in the participants receiving the dietary supplement versus controls (-54.00 mg/dL (95 percent CI -94.1, -13.90]). The mean differences in TC (9.00 mg/dL (95 percent CI -6.40, 24.40]), HDL-C (0 mg/dL (95 percent CI -4.00, 4.00]), and LDL-C (1.00 mg/dL (95 percent CI -10.90, 12.90]) were not significantly different between the dietary supplement and control groups.

Omega-3 fatty acids/fish oil plus calcium channel blockers, aspirin, and dipyridamole versus calcium channel blockers, aspirin, and dipyridamole

One study[52]contributed evidence relevant for this section. This parallel arm single-blind active treatment (calcium channel blockers plus aspirin plus dipyridamole) controlled trial was in 82 male participants for whom the randomization sequence was computer-generated and treatment allocation concealment was unclear (moderate risk of bias). All men in this trial were at high CHD risk (post-coronary angioplasty) and received their treatment for 12 weeks (3.2 g/day omega-3 plus calcium channel blockers plus 325 mg/d aspirin plus 225 mg/d dipyridamole

versus calcium channel blockers plus 325 mg/day aspirin plus 225 mg/day dipyridamole). Although the post-treatment mean LDL-C was significantly greater (i.e., worsened) in the participants receiving the dietary supplement versus controls (21.00 mg/dL (95 percent CI 3.30, 38.70]), the mean TG levels were significantly lower (i.e., improved) in the dietary supplement versus the control group (-81.0 mg/dL (95 percent CI -125.30, -36.70]). The between group mean differences for HDL-C (0 mg/dL (95 percent CI -4.00, 4.00]), total cholesterol (19.00 mg/dL (95 percent CI -1.70, 39.70]), and platelet count (-2.80 per 10^3/µL (95 percent CI -56.20, 0.20]) were not significantly different.

Omega-3 fatty acids/fish oil plus niacin (≤ 250 mg), and aspirin versus niacin (≤ 250 mg), and aspirin

One study[80]contributed evidence relevant for this section. This parallel arm placebo controlled active treatment (niacin plus aspirin) trial was in 14 participants for whom the randomization sequence and treatment allocation concealment were unclear (moderate risk of bias). The participants in this trial had unclear CHD risk (atherogenic dyslipidemia) and received their treatment for 12 weeks (4 g/day omega-3 plus 500 to 3000 mg/day niacin plus 325 mg/day aspirin versus 500 to 3000 mg/day niacin plus 325 mg/day aspirin).

The post-treatment mean differences in total cholesterol (9.00 mg/dL (95 percent CI -19.10, 37.10]), HDL-C (1.00 mg/dL (95 percent CI -13.20, 15.20]), LDL-C (17.00 mg/dL (95 percent CI -6.60, 40.60]) and triglycerides (-94.00 mg/dL (95 percent CI -196.80, 8.80]) were not significantly different between the dietary supplement and control groups.

Authors of the same trial[80] conducted a formal assessment of statistical interaction using ANOVA and found that the decrease in triglycerides resulting from the combination of omega-3 fatty acids and niacin was more than twice the additive effect of the therapies alone.

Omega-3 fatty acids/fish oil plus aspirin versus aspirin alone

In two trials in healthy participants with low or mixed CHD risk, a single dose of aspirin (325 mg[90] or 100 mg[97]) was administered following 2 to 3 weeks of omega-3 fatty acids/fish oil or placebo pre-treatment. Relevant outcome measures were presented, but use of only a single dose of aspirin precluded drawing meaningful conclusions relevant to this review, so results for this study are not presented.

Omega-3 fatty acids/fish oil plus beta-adrenergic antagonists versus beta-adrenergic antagonists

Blood Pressure. Systolic and diastolic blood pressure (SBP/DBP) response post-treatment was reported for one trial.[142] This double-blind cross-over trial was in 25 participants with unclear CHD risk, on beta-blocker monotherapy (dose not reported) who were randomized to receive omega-3 fatty acids (4 g/day) or placebo for 6 weeks. No wash-out period was reported for this trial. The data for this study were not reported clearly, which precluded meaningful synthesis of the evidence.

Omega-3 fatty acids/fish oil plus warfarin versus warfarin alone

One study[55] contributed evidence relevant for this section. This was a parallel double blind (blinding status of participants, care providers, or study assessors was unclear), placebo-controlled trial in 11 participants for whom the randomization sequence and treatment allocation

concealment were unclear (high risk of bias – there was a baseline between-group imbalance in gender and age). The participants whose CHD risk was unclear received their treatment for 4 weeks (3 g/day or 6 g/day omega-3 plus warfarin versus placebo plus warfarin). This trial reported post-treatment International Normalized Ratio (INR). There was no significant difference in post-treatment INR values between the dietary supplement and control groups (p=0.41; no additional numerical data was provided).

Table 31. Summary and strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids/fish oil

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect*
Statins						
CRP[44,149]	-	-	-	-	-	**No difference** Geometric mean difference: 1.14 mg/L (95% CI 0.6, 2.4) vs. 1.80 mg/L (95% CI 1.3, 3.2)
HDL-C[36,40,44,53,91-94,139,141]	Moderate	Inconsistent	Indirect	Precise	Low	**No difference** Pooled mean difference: 2.26 mg/dL (95% CI -1.82, 6.34) [40,44,53,91,139,141]
LDL-C[36,40,44,53,91-94,139]	Moderate	Inconsistent	Indirect	Precise	Low	**No difference** Pooled mean difference: 1.33 mg/dL (95% CI -3.56, 6.22) [40,44,53,91,139]
TC[36,40,44,53,91-94,98,139]	Moderate	Inconsistent	Indirect	Imprecise	Insufficient	**Inconclusive** Pooled mean difference: -7.06 mg/dL (95% CI -14.50, 0.37) [40,44,53,91,139]
TG[36,40,44,53,91-94,98,139,141]	Moderate	Consistent	Indirect	Imprecise	Insufficient	**Inconclusive** Pooled mean difference: -17.88 mg/dL (95% CI -36.96, 1.21) [44,53,91,139]
Non-HDL-C [36,40,44,94,141]	Moderate	Inconsistent	Indirect	Imprecise	Insufficient	**Inconclusive** -14.70 mg/dL (95% CI -21.77, -7.62) [40] 5.42 mg/dL (95% CI -15.75, 26.59) [44] 5.60 mg/dL (95% CI -34.06, 45.26) [141] Reported medians [36,94]
TC/HDL-C ratio[36,40,94,141]	-	-	-	-	-	**Inconclusive** -0.60 (95% CI -0.83, -0.36) [40] 0.29 (95% CI -0.90, 1.48) [141] Reported medians [36,94]
LDL-C (<160/130/ 100 mg/dL) [94]	Moderate	NA	Indirect	Precise	Low	**No difference** RR 0.93 (95% CI 0.84, 1.03)

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect*
HDL-C (<190/160/ 130 mg/dL) [94]	Moderate	NA	Indirect	Precise	Low	**No difference** RR 1.00 (95% CI 0.91, 1.11)
Lipoprotein A [91]	-	-	-	-	-	**Inconclusive** 2.00 mg/dL (95% CI -34.40, 38.40)
Systolic Blood Pressure[36,93,139]	Moderate	Inconsistent	Indirect	Precise	Low	**In favor of supplement-CV drug combination** -8.50 mm Hg (95% CI -16.33, -0.66) [93] No difference (data not given) [139] Reported medians [36]
Diastolic Blood Pressure[36,93,139]	Moderate	Inconsistent	Indirect	Precise	Low	**No difference** 0.20 mm Hg (95% CI -4.76, 5.16) [93] No difference (data not given) [139] Reported medians [36]
Blood Coagulation PT aPTT[96]	-	-	-	-	-	**No difference** -0.10 sec (95% CI -0.28, 0.08) 0.10 sec (95% CI -0.62, 0.82)
Blood Coagulation PA/AD PA/Collagen[96]	-	-	-	-	-	**No difference** 1.10 % (95% CI -5.05, 7.25) 0.90 % (95% CI -5.70, 7.50)
Platelet Count[92,96,98]	-	-	-	-	-	**Inconclusive** -9.82 10^3/µL (95% CI -42.79, 23.15) [96] 6.00 10^3/µL (95% CI 1.74, 10.25) [98] Reported percent change [92]
Bleeding Time[92]	-	-	-	-	-	**No difference** 1.0 percent (95% CI -0.59, 2.59)
ACE inhibitors						
TG[79,140]	Moderate	Inconsistent	Indirect	Imprecise	Insufficient	**Inconclusive** -38.6 mg/dL (95% CI -160.62, 83.42) [79] -24.35 mg/dL (95% CI -45.31, -3.38) [140]
Systolic Blood Pressure[79,140]	Moderate	Consistent	Indirect	Precise	Low	**No difference** Pooled mean difference: -0.51 mm Hg (95% CI -10.59, 9.57)
Diastolic Blood Pressure[79,140]	Moderate	Consistent	Indirect	Precise	Low	**No difference** Pooled mean difference: -1.75 mm Hg (95% CI -5.98, 2.48)
Urinary Protein excretion[79]	-	-	-	-	-	**In favor of supplement-CV drug combination** -986.00 mg/d (95% CI -1763.43, -208.56)
≥50% reduction in proteinuria[79]	-	-	-	-	-	**In favor of supplement-CV drug combination** RR 4.00 % of participants (95% CI 1.40, 11.30)
Fenofibrate						

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect*
LDL-C, HDL-C, TC, TC/HDL ratio, TG, non-HDL-C[56]	Moderate	NA	Indirect	Unclear	Insufficient	**Inconclusive** Reported percent change
Incidence of hypertension (% of participants)	-	-	-	-	-	**Inconclusive** RR 0.98 (95% CI 0.14, 6.85)
Calcium Channel Blockers						
LDL-C[50]	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 0 mg/dL (95% CI -94.30, 94.30)
HDL-C[50]	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** -2.00 mg/dL (95% CI -32.7, 28.70)
TC[50]	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 5.00 mg/dL (95% CI -91.30, 101.30)
TG[50]	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** -32.00 mg/dL (95% CI -112.60, 176.60)
Calcium Channel Blockers + Aspirin						
LDL-C[51]	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 1.00 mg/dL (95% CI -10.90, 12.90)
HDL-C[51]	Moderate	NA	Indirect	Precise	Low	**No difference** 0 mg/dL (95% CI -4.00, 4.00)
TC[51]	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 9.00 mg/dL (95% CI -6.40, 24.40)
TG[51]	Moderate	NA	Indirect	Precise	Low	**In favor of supplement-CV drug combination** -54.00 mg/dL (95% CI -94.1, -13.90)
Calcium Channel Blockers + Aspirin + Dipyridamole						
LDL-C[52]	Moderate	NA	Indirect	Precise	Low	**In favor of supplement-CV drug combination** 21.00 mg/dL (95% CI 3.30, 38.70)
HDL-C[52]	Moderate	NA	Indirect	Precise	Low	**No difference** 0 mg/dL (95% CI -4.00, 4.00)
TC[52]	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 19.00 mg/dL (95% CI -1.70, 39.70)
TG[52]	Moderate	NA	Indirect	Precise	Low	**In favor of supplement-CV drug combination** -81.0 mg/dL (95% CI -125.30, -36.70)

Cardiovascular drug(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect*
Platelet count[52]	-	-	-	-	-	**Inconclusive** -2.80 mg/dL 10^3/µL (95% CI -56.20, 0.20)
Niacin + Aspirin						
LDL-C (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 17.00 (95% CI -6.60, 40.60)
HDL-C (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 1.00 (95% CI -13.20, 15.20)
TC (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 9.00 (95% CI -19.10, 37.10)
TG (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** -94.00 (95% CI -196.80, 8.80)

Note: * Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.
Abbreviations: ACE = angiotensin-converting enzyme; CHD = coronary heart disease; CRP = C-reactive protein; HDL-C = high density lipoprotein; LDL-C = low density lipoprotein; NA = not applicable; NR = not reported; PA/AD = platelet aggregation/adenosine diphosphate PT = prothrombine time; aPTT = activated partial thromboplastin time; RCT = randomized controlled trial; RR=relative risk; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; wk(s) = week(s); yr(s) = year(s).

Applicability. Statin combinations were examined in populations with 22 to 100 percent males, with unclear to mixed coronary heart disease risk, and mean age ranging from 30 years to 63 years. ACE inhibitors were examined in populations with 40 to 85 percent males, with unclear or high coronary heart disease risk, and mean age 40 years to 60 years. Calcium channel blockers plus aspirin plus dipyridamole were examined in a male population, with high coronary heart disease risk, and mean age 56 years. Trial duration ranged from 4 to 25 weeks.

Vitamin E

Ten RCTs and one CCT examined the use of Vitamin E with cardiovascular drugs [46,49,59,81-88] Subjects were concomitantly taking antiplatelet agents (aspirin or ticlopidine)[49,81], furosemide [82], gemfibrozil[59], nifedipine[83], or statins.[46,84-88]

Vitamin E plus antiplatelet agents verus antiplatelet agents alone

Two parallel-arm RCTs examined the effect of concomitant use of vitamin E and antiplatelet agents.[49,81] In comparison to no treatment, 6 weeks of treatment with vitamin E was not found to effect total cholesterol in atherosclerotic plaque in participants taking aspirin or ticlopidine[81]. No changes in serum total cholesterol and triglyceride levels at follow-up were noted (reported qualitatively only). These results were likely impacted by Type II error due to small sample size (N=16).

Platelet aggregation was assessed in a trial comparing vitamin E plus aspirin to aspirin in elderly, primarily white, subjects with transient ischemic attack, minor stroke, or residual neurologic deficits.[49] Treatment was administered for two years. Platelet adhesion was significantly decreased by vitamin E supplementation (MD -1.70 platelets adherent/cm^2 x 10^5 (95 percent CI -2.06, -1.34]).

Strength of evidence was insufficient for triglycerides (Table 32).

Vitamin E plus furosemide versus furosemide alone

One small parallel-arm RCT of 24 participants examined the concomitant use of Vitamin E and furosemide.[82] Participants were randomized to receive either Vitamin E (600 mg/day) and furosemide (25 mg/day) or furosemide (25 mg/day) with placebo for 4 weeks. No significant differences were found in systolic and diastolic blood pressure. Strength of evidence for blood pressure was insufficient (Table 32).

Vitamin E plus nifedipine versus nifedipine alone

One small crossover RCT (N=30) examined vitamin E plus nifedipine versus placebo with nifedipine.[83] Nifedipine was administered as a long-acting formulation at an average dose of 88 ± 11 mg/day and Vitamin E at a dose of 900 mg/day for 4 months.

Supplementation with Vitamin E was found to significantly lower total serum cholesterol (MD -35.96 mg/dL (95 percent CI -46.96, -24.96], LDL-C (MD -39.83 mg/dL (95 percent CI -71.29, -8.37]), and triglycerides (MD -23.91 mg/dL [95 percent CI -35.89, -11.93]). HDL-C was slightly raised by administration of vitamin E, but the estimate was not statistically significant (MD 4.26 mg/dL [95 percent CI -2.02, 10.54]). There were no statistically significant differences in systolic and diastolic blood pressure.

The strength of evidence was insufficient for systolic and diastolic blood pressure, and HDL-C. Strength of evidence for improvement in LDL-C and triglyceride levels with combination treatment was low (Table 32).

Applicability. This study recruited elderly (mean age 73.8 ± 2.1 yrs), moderately obese subjects with stable effort angina and high CHD risk.

Vitamin E plus gemfibrozil versus gemfibrozil alone

The combination of vitamin E and gemfibrozil was assessed in one CCT of 67 participants.[59] Subjects were hyperlipidemic and were divided into young (mean age 29.5 ± 4.9 yrs) and elderly (mean age 71.5 ± 3.6 yrs) groups. No statistically significant effects were observed in lipid parameters or blood pressure. Effect estimates had very wide 95 percent confidence intervals, so this study was likely underpowered to detect statistically significant results. Strength of evidence for blood pressure and lipid parameters was insufficient (Table 32).

Vitamin E plus statins versus statins alone

Six RCTs addressed combined use of vitamin E and statins, including atorvastatin[88], simvastatin[84-87], and pravastatin[46]. All studies included subjects with hypercholesterolemia. In some studies, subjects also had additional conditions, such as diabetes[88] and vascular disease[87].

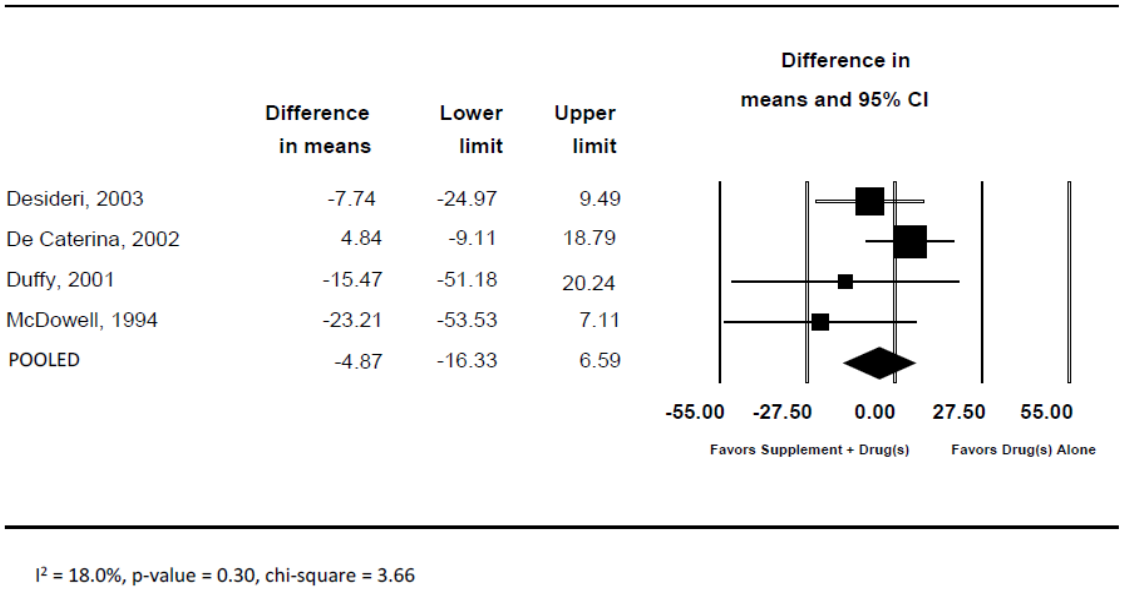
Lipid parameters were reported in all studies. Meta-analyses of total cholesterol, LDL-C, HDL-C, and triglycerides were undertaken for four trials.[84-87] Two trials could not be meta-analyzed because different effect estimates were reported (i.e. one trial reported serum lipid parameters in a qualitative manner only[88] and one trial reported lipid parameters as percent change from baseline[46]).

One study reported nonsignificant differences in cholesterol and triglyceride levels in non-HDL subfraction for combination vitamin E plus atorvastatin.[88] Another study reported nonsignificant differences for percent change in baseline for total cholesterol, LDL-C, HDL-C, and triglycerides for combination vitamin E plus pravastatin.[46]

The four trials that were pooled included administration of vitamin E with simvastatin (total sample size 106).[84-87] Dosages of vitamin E and simvastatin ranged from 400 to 1000 U/day and 10 to 40 mg/day respectively. The pooled effect estimates for total cholesterol, LDL-C, HDL-C, and triglycerides were all statistically nonsignificant (Figures 15-18). Heterogeneity was minimal for all pooled estimates aside from LDL-C (I^2 = 64.6 percent, p-value = 0.04). The most pronounced effect of statins is on lowering LDL-C. The observed heterogeneity, therefore, may reflect variations in LDL-C response to the different simvastatin dosages used in the trials. Based on these pooled estimates, strength of evidence was insufficient for LDL-C, HDL-C, and triglycerides (Table 32).

Other reported outcomes included C-reactive protein, prothrombin time, and platelet count. In a study of middle aged hypercholesterolemic subjects at low CHD risk, a statistically significant difference for C-reactive protein in favor of Vitamin E plus simvastatin was found (MD -0.40 mg/L (95 percent CI -0.66, -0.14]).[86] In another study of hypercholesterolemic subjects, no differences were found in prothrombin time and platelet count between Vitamin E plus pravastatin and pravastatin alone (reported qualitatively only).

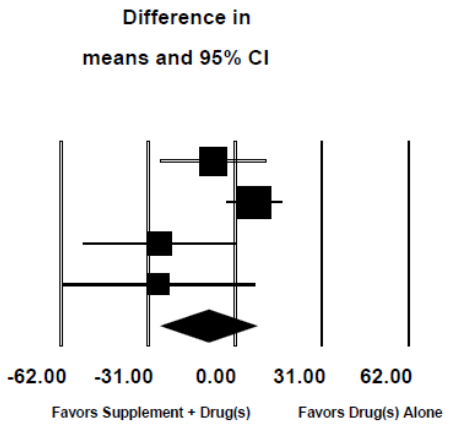
Figure 15. Forest plot of total cholesterol (mg/dL) for statins with or without vitamin E



I^2 = 18.0%, p-value = 0.30, chi-square = 3.66

Figure 16. Forest plot of LDL-C (mg/dL) for statins with or without vitamin E

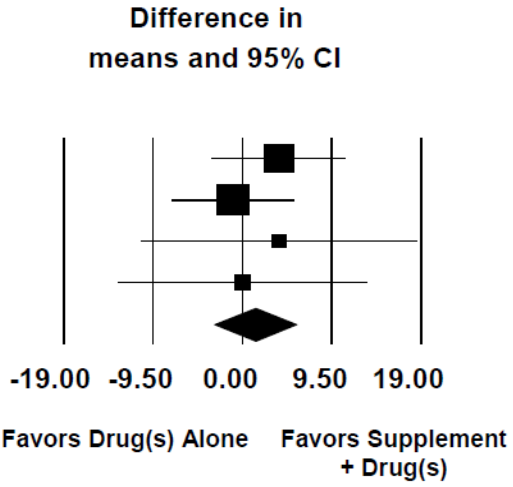
	Difference in means	Lower limit	Upper limit
Desideri, 2003	-7.74	-26.72	11.24
De Caterina, 2002	6.88	-3.34	17.10
Duffy, 2001	-27.07	-54.37	0.23
McDowell, 1994	-27.07	-61.39	7.25
POOLED	-9.46	-26.81	7.89



I^2 = 64.6%, p-value = 0.04, chi-square = 8.49

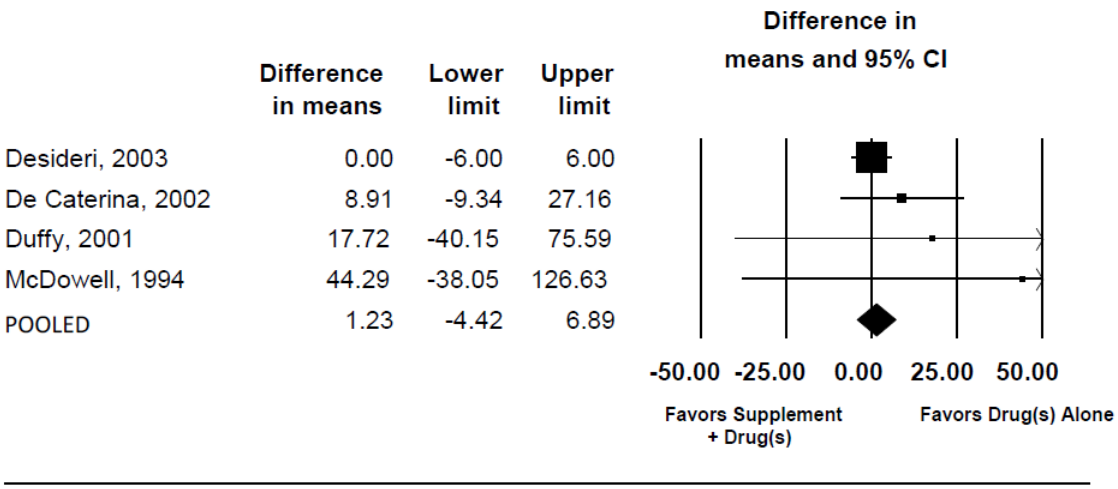
Figure 17. Forest plot of HDL-C (mg/dL) for statins with or without vitamin E

	Difference in means	Lower limit	Upper limit
Desideri , 2003	3.86	-3.34	11.06
De Caterina, 2002	-1.00	-7.57	5.57
Duffy, 2001	3.87	-10.85	18.59
McDowell,1994	0.00	-13.40	13.40
POOLED	1.31	-3.04	5.67



I^2 = 0.0%, p-value = 0.78, chi-square = 1.11

Figure 18. Forest plot of triglyceride levels (mg/dL) for statins with or without vitamin E



I^2 = 0.0%, p-value = 0.53, chi-square = 2.20

Table 32. Summary and strength of evidence for cardiovascular drug(s) with and without vitamin E

Cardiovascular drugs(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect* MD (95% CI)
Antiplatelet Agents						
Triglycerides	Moderate	NA	Indirect (surrogate)	NA	Insufficient	**Inconclusive** No changes observed at end of follow-up (reported qualitatively only)
Furosemide						
Blood pressure	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Systolic -3.00 mmHg (-7.69, 1.69) Diastolic -2.00 mmHg (-6.36, 2.36)
Nifedipine						
Blood pressure	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Systolic -2.00 mmHg (-19.55, 15.55) Diastolic -1.00 mmHg (-3.79, 1.79)
LDL-C	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** -39.83 mg/dL (-71.29, -8.37)

Cardiovascular drugs(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect* MD (95% CI)
HDL-C	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** 4.26 mg/dL (-2.02, 10.54)
Triglycerides	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** -23.91 mg/dL (-35.89, -11.93)
Gemfibrozil						
Blood Pressure	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Systolic 7.00 mmHg (-14.07, 28.07) (elderly) -3.00 mmHg (-22.46, 16.46) (young) Diastolic 4.00 mmHg (-11.29, 19.29) (elderly) -1.00 mmHg (-13.00, 11.00) (young)
LDL-C	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** 6.96 (-132.08, 146.00) (elderly) -4.25 (-16.85, 8.35) (young)
HDL-C	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** 0 (-4.42, 4.42) (elderly) 6.19 (-1.28, 13.66) (young)
Triglycerides	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** -23.91 (-336.44, 288.62) (elderly) -7.97 (-45.23, 29.29) (young)
Statins						
HDL-C	Moderate	Inconsistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Pooled MD 1.31 mg/dL (-3.04, 5.67)
LDL-C	Moderate	Consistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Pooled MD -9.46 mg/dL (-26.81, 7.89)
Triglycerides	Moderate	Consistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Pooled MD 1.23 mg/dL (-4.42, 6.89)

Note: * Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.
Abbreviations: CI = confidence interval; HDL-C = high density lipoprotein; LDL-C = low density lipoprotein; MD = mean difference; NA = not applicable.

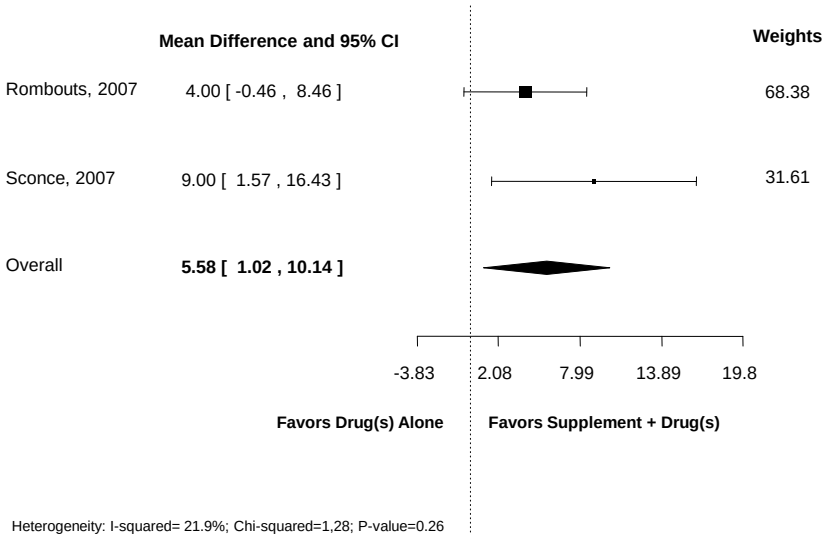
Vitamin K

Vitamin K plus coumarin derivatives versus coumarin derivatives alone

Two parallel-group RCTs examined the effect of concomitant use of Vitamin K and coumarin derivatives in subjects with high and unknown CHD risk. One parallel-group RCT examined the effect of concomitant use of Vitamin K with phenprocoumon (40 mg/day)[39] and the other with warfarin (varied doses).[41] One case-control study was also identified that assessed whether vitamin K intake in subjects taking anticoagulants is associated with subtherapeutic INR.[138] The results of this study have not been included in the evidence synthesis as it added no further insights to the existing randomized trials.

Both trials reported the percentage of time that INR remained in the therapeutic range (defined as INR within 0.5 of 2.0 to 3.0,[41] or as 2.0 to 3.5 for low-intensity treatment and 2.5 to 4.0 for high intensity treatment[39]). A meta-analysis of this outcome for two studies, randomizing 270 participants with data for 257, found that Vitamin K increases the percentage of time in the INR therapeutic range (MD 5.58 (95 percent CI 1.02, 10.14], I^2 = 21.9 percent) (Figure 19).

Figure 19. Forest plot of time in INR therapeutic range (percent), for coumarin derivatives with or without vitamin K



INR control was also examined in terms of percent of time spent outside target INR range (stratified into above or below),[39] the standard deviation of the INR,[41] number of participants in therapeutic range 100 percent of the time,[39] and number of participants achieving improved INR control compared with 6 months prior to study.[41] In all cases except percent of time above or percent of time below INR target range, for which no significant difference was found between the treatment groups, Vitamin K was found to increase stability of anticoagulation treatment

(Table 32). Furthermore, the number of participants achieving stable INR was higher in combination with warfarin (RR 2.56 [95 percent CI 1.24, 5.28]).[41]

Strength of evidence for the statistically significant INR measures was low (Table 33).

Subgroups of interest. One of the two studies[39] examined the effect of Vitamin K on percentage of time within target INR range in the following pre-specified subgroups of interest: male/female, age (≥65 years - in this case ≥ 70 years). No significant differences were found by gender (calculated mean difference in males = 5 percent (-0.7, 10.7]; females = 3 percent (-6.8, 12.8]) or age (≥65 yrs = 5.0 percent (-3.0, 13.0]) compared to those for all groups combined.

Applicability. Participants in both studies were at unclear CHD risk. Participants in one trial,[39]had an indication for long-term treatment with oral anticoagulants while participants in the other had atrial fibrillation anticoagulated with warfarin for thromboembolic prophylaxis but with unstable INR control.[41] Both groups consisted of participants between the ages of 58 and 86 years. The race of subjects was not reported in one study[41] while 100 percent of subjects were white in the other.[39] Both trials were of six months duration.

Table 33. Summary and strength of evidence for coumarin derivatives with and without vitamin K

Cardiovascular drugs(s) / Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect* (95% CI)
% time in INR therapeutic range	Moderate	Consistent	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** Pooled MD 5.58% (1.02 , 10.14)
% time below INR therapeutic range	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD -1.00 (-2.87, 0.87)
% time above INR therapeutic range	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD -2.90 (-6.89 1.09)
SD of INR	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** MD -0.12 (-0.20, -0.04)
N in therapeutic range 100% of time	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** N in therapeutic range 100% of time RR 1.80 (1.10, 2.70)
N achieving INR control	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** N achieving INR control RR 1.30 (1.04, 1.62)
N achieving stable INR	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** N achieving stable INR RR 2.56 (1.24, 5.28)

Note: * Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.

Abbreviations: CI = confidence interval; INR = International Normalized Ratio; MD = mean difference; N = number; NA = not applicable; SD = standard deviation.

Summary of results for Key Question 2

For key Question 2, we compared a dietary supplement coadministered with a cardiovascular drug(s) with the cardiovascular drug(s) alone (or in conjunction with another supplement) to investigate comparative clinical efficacy/effectiveness, subgroup effect and statistical interactions.

- Fifty-seven RCTs and two CCTs addressed this key question. Most evidence was from small, underpowered RCTs that provided inconclusive results. The strength of evidence (SOE) for gradable outcomes was generally insufficient. Further details are presented below, by supplement-CV drug combination.
- No study addressed the following outcomes: incidence of metabolic syndrome, incidence of hypotension, carotid-intima media thickness, and change in 10-year Framingham risk profile.

Coenzyme Q10: This supplement was coadministered with statins, ACE inhibitors, and fibrates in five trials. Underpowered studies found no differences in CRP, HDL-C, non-HDL-C, LDL-C, TC, TG, ejection fraction, and systolic blood pressure.

Echinacea-warfarin: A single small study found nonsignificant differences in INR and platelet aggregation.

Garlic-warfarin: Nonsignificant differences were found in LDL-C, triglycerides, blood pressure, INR, platelet aggregation, and platelet count from few small, underpowered studies. HDL-C significantly improved in the combination group (MD 4.50 mg/dL (95 percent CI 0.19, 8.81]). The strength of evidence favoring combination treatment for HDL-C was low.

Garlic-nitrates: When in combination, garlic nitrates improve total cholesterol (mean difference (MD] -28.20 mg/dL (95 percent CI -48.30, -8.10]) and HDL-C (MD 8.50 mg/dL (95 percent CI 1.91, 14.89]). The SOE for improvement in HDL-C was low.

Garlic-statins and aspirin: Nonsignificant differences were found for lipid parameters, c-reactive protein, platelet count, and Agatston calcium score. One measure of coronary artery calcification (volume calcium score) was statistically significant in favor of combination treatment (MD -83.80 mm^3 (95 percent CI -164.22, -3.38]).

Ginger-warfarin: Nonsignificant differences were observed in mean differences for INR and platelet aggregation from one underpowered trial.

Ginkgo-antiplatelets: Nonsignificant differences were found in clotting time, partial thromboplastin time, platelet count, lipid parameters, and blood pressure. Pooled estimates for platelet aggregation and bleeding time were nonsignificant. Data came from small trials that were likely underpowered.

Ginkgo-warfarin: Compared to warfarin alone or warfarin with ginger, there were no significant differences in platelet aggregation or INR. This evidence came from only one underpowered trial.

Ginkgo-cilostazol: Platelet aggregation and bleeding time were significantly different in a single dose study of healthy South Asian males (MD 18.00 percent (95 percent CI 1.92, 34.08] and 1.02 min (95 percent CI 0.10, 1.94] respectively).

Ginseng-warfarin: Inconsistent results were reported for INR. One study found a significant difference in healthy subjects (MD -0.19 (95 percent CI -0.36, -0.07]) and two studies found no differences. Platelet count and prothrombin time were not significant.

Hawthorne-digoxin: A single, underpowered trial found no significant difference in PR interval.

Magnesium-hydrochlorothiazide: Nonsignificant differences were found in total cholesterol and triglycerides. Pooled estimates for systolic and diastolic blood pressure were nonsignificant. Data came from small, underpowered trials.

Niacin-propranolol: Effect estimates for total cholesterol and triglycerides were statistically nonsignificant in one small trial at high risk of bias.

Omega-3 – statins: In 12 RCTs, no differences were found for c-reactive protein, HDL-C, LDL-C, diastolic blood pressure, blood coagulation parameters (PT, aPTT, platelet aggregation), and bleeding time. The mean systolic blood pressure was significantly lower in the supplement combination versus statins alone group. The results for non-HDL-C, TC/HDL-C ratio, and platelet count were either non-significant with wide confidence intervals or conflicting, thus inconclusive.

Omega-3 – ACE inhibitors: No differences were found for blood pressure in two small trials. However, significantly more participants achieved ≥ 50 percent reduction in proteinuria with combination treatment in one trial (relative risk (RR] 4.00 (95 percent CI 1.40, 11.30]). Results for triglycerides were conflicting and inconclusive.

Omega-3-fenofibrate: Results for lipid profile reported in one trial were not interpretable due to reported percent changes. The incidence of hypertension did not significantly differ between the combination and control groups.

Omega-3-calcium channel blockers: One underpowered trial found no differences in total cholesterol, LDL-C, HDL-C, and triglycerides. Two trials using aspirin in addition to calcium channel blockers found significant difference in triglycerides in favor of combination treatment (MD -81.00 mg/dL (95 percent CI -125.30, -36.70][52] and -54.00 mg/dL (95 percent CI: -94.10, -13.90][51]). The SOE for triglycerides was low.

Omega-3-niacin+aspirin: In one small trial, no significant differences were found for total cholesterol, LDL-C, HDL-C, and triglycerides.

Omega-3- aspirin: In two trials, single aspirin dose was given, which precluded meaningful interpretation of results.

Vitamin E-antiplatelets: No differences were found in total cholesterol or triglycerides in one small underpowered trial. Platelet aggregation was significantly decreased with vitamin E supplementation compared with aspirin alone (MD -1.70 platelets adherent/cm^3 (95 percent CI -2.06, -1.34]).

Vitamin E-furosemide: No significant differences were found in systolic and diastolic blood pressure in one small study.

Vitamin E-nifedipine: Supplementation with Vitamin E significantly lowered total cholesterol (MD -35.96 mg/dL (95 percent CI -46.96, -24.96]), LDL-C (MD -39.83 mg/dL (95 percent CI -71.29, -8.37]), and triglycerides (MD -23.91 mg/dL (95 percent CI -35.89, -11.93]) in elderly subjects at high CHD. Strength of evidence favoring combination treatment was low for LDL-C and triglycerides. No differences were found in HDL-C and blood pressure.

Vitamin E-gemfibrozil: No differences were found for lipid parameters and blood pressure in one trial that was likely underpowered.

Vitamin E-statins: Most trials had small sample sizes (largest one recruited 108 subjects). Pooled effect estimates for total cholesterol, LDL-C, HDL-C, and triglycerides were statistically nonsignificant. Single trials reported nonsignificant differences for c-reactive protein, prothrombin time, and platelet count.

Vitamin K-warfarin: Percentage of time that INR was in the therapeutic range was significantly higher in the combination group based on meta-analysis of two trials (pooled MD 5.58 (95

percent CI 1.02, 10.14]). Significantly more subjects were in the INR range 100 percent of time (pooled RR = 1.80 (95 percent CI 1.10, 2.70]), achieved INR control (pooled RR 1.30 (95 percent CI 1.04, 1.62]), and achieved stable INR (pooled RR 2.56 (95 percent CI 1.24, 5.28]). Strength of evidence for INR was low.

Key Question 3

In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement(s]) on clinical or intermediate harms outcomes (e.g., organ toxicity, serious adverse events, withdrawal due to adverse events)

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

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

Overview

A total of 58 unique studies were included for Key Question 3 (Table 34).[38,44,46,47,49,51-53,55,56,80,82-85,87-93, 35-37,39-42,48,54,58,60-72,74-79,94-100]

One of the included studies was a retrospective cohort study,[100] while the rest were RCTs. The retrospective cohort study [100] examined the effects of omega-3 fatty acids plus aspirin and clopidogrel versus aspirin and clopidogrel alone among patients at high CHD risk. For this study, most of the risk of bias components were scored as unclear (e.g., appropriateness of participant selection, freedom from confounding, similarity of provider care between study arms, freedom from financial conflict of interest).[100]

One study examined the statistical interaction between vitamin E and aspirin [89] on harms. The characteristics of included studies are summarized in Table 34. Overall, the studies were generally of moderate risk of bias across all gradable harms, and the risk of bias is summarized in Table 35. The harms outcomes examined across the included studies ranged from minor (e.g., flatulence) to serious (e.g. major bleeding). Although a higher proportion of the harms outcomes were reported as continuous data versus dichotomous data, the dichotomous outcomes were the focus of the present work, as these are the most suitable type of data for examining harms. A carryover effect was not a major concern in the crossover trials because most of the studies incorporated adequate washout periods in their design – well over five times the half-life of the drug/supplement under investigation. However, a carryover effect may have influenced the results of 5 of the included crossover studies because it was not clearly reported [36], the washout period was only 1 week [90] or there was not a washout period.[42,78,87] Detailed study characteristics and data from each of the included studies are available in Appendix C. For each supplement examined, we compared the different cardiovascular drug and supplement combination(s) versus the cardiovascular drug alone. For most supplement-cardiovascular drug related harms outcomes, data were either absent or too sparse with occasional events, precluding meaningful synthesis (Appendix C). Where subgroup analysis could be carried out, we report subgroup results as an additional consideration under the corresponding supplement.

Table 34 Overview of included studies for Key Question 3

Dietary supplement	N of studies included for KQ3	Cardiovascular drug(s)	Study design(s)	Participants	Study region	Race/Ethnicity	Overall risk of bias for gradable harms outcomes	Industry funding or potential for conflict of interest
Coenzyme Q10	5[37,54,60-62]	Atorvastatin, simvastatin, fenofibrate, ACE-Inhibitors	4 Parallel RCT, 1 crossover RCT	Low CHD risk [37], moderate to moderately high CHD risk [61,62], high CHD risk [54,60]	North America, East Asia, Australia/NZ	Caucasians and Asians	Moderate	Yes [61] Unclear [37,54] No [60,62]
Echinacea	1[63]	Warfarin	Crossover RCT	Low CHD risk	Australia/New Zealand	Mixed – Caucasians and Asians/South Asians	Moderate	Yes
Garlic	4[58,64-66]	Warfarin, nitrates, statin + aspirin	3 Parallel RCT, 1 crossover RCT	Low CHD risk [65], high CHD risk [58,64,66]	Europe, Australia/NZ, NR	Caucasians	Moderate	Unclear [65,66] No [58,64]
Ginger	1[67]	Warfarin (single dose)	1 Crossover RCT	Low CHD risk	Australia/New Zealand	Asians, Caucasians	Moderate	No
Ginkgo biloba	7[48,67-71,99]	Warfarin, aspirin, aspirin and/or pentoxiphylline, digoxin, nitrates, statin + aspirin, ticlopidine	Parallel RCT (2), crossover RCT (5)	Low CHD risk [67,68,70,71,99], Moderate to moderately high CHD risk [48,69]	East Asia, North America, Europe, rest of Asia, Australia/New Zealand	Asians, Caucasians	Moderate	Yes [71] Unclear [99] No [67]
Ginseng	3[72-74]	Warfarin	1 crossover, and 2 parallel RCTs	Low CHD risk [74], mixed low/moderate to moderately high [73], high CHD risk [72]	East Asia, NR	Mixed – Caucasians Asians and Hispanics	Moderate	Yes [73] No [72,74]
Hawthorne	1[75]	Digoxin	Crossover RCT	Low CHD risk	North America	Caucasians	Moderate	Unclear
Magnesium (oral)	3[42,76,77]	Hydrochlorthiazide, metoprolol, atenolol, pindolol, propanolol	2 Parallel RCTs and 1 crossover RCT	Low CHD risk	NR	Africans?, NR	Moderate	Unclear
Niacin (≤ 250 mg/d)	1[78]	Propanolol	Crossover RCT	Low CHD risk	Europe	Caucasians	High	Unclear

Dietary supplement	N of studies included for KQ3	Cardiovascular drug(s)	Study design(s)	Participants	Study region	Race/Ethnicity	Overall risk of bias for gradable harms outcomes	Industry funding or potential for conflict of interest
Omega- 3 fatty acids (or fish oils)	22[35,36,40,44,47,51-53,55,56,79,80,90-98,100]	Statins; Aspirin; Aspirin + Clopidogrel; Aspirin + Dipyridamole + Ca Channel Blockers; Warfarin; Ramipril and/or irbesartan; Fenofibrate	13 Parallel RCT, 8 crossover RCT, 1 retrospective cohort	Low CHD risk [35,56,79,90,92,93,95-97], moderate to moderately high CHD risk [36,40,44,51,52,80,91,94], high CHD risk [47], mixed CHD risk [53], unclear CHD risk [55]	North America, Australia/NZ, Europe,	Mostly Caucasian	Moderate	Yes [35,36,40,47,56,94-96] Unclear [51-53,55,79,90-93,97,98,100] No [44,80]
Red yeast rice extract	0	-	-	-	-	-	-	-
Resveratrol	0	-	-	-	-	-	-	-
Vitamin A	0	-	-	-	-	-	-	-
Vitamin D with Calcium	0	-	-	-	-	-	-	-
Vitamin D without Calcium	0	-	-	-	-	-	-	-
Vitamin E	10[38,46,49,82-85,87-89]	Aspirin, simvastatin, atorvastatin, pravastatin, furosemide	8 Parallel RCT and 2 crossover RCT	Low CHD risk [38,46,82,84,89], high CHD risk [49,83,85,87,88]	East Asia, Central & South America; Europe, unclear, Australia?, NR	Caucasians, Asians, South Americans	Moderate	Yes [87] Unclear [46,49,82-84,88,89] No [38,85]
Vitamin K	2[39,41]	Warfarin, phenprocoumon	Parallel RCT	High CHD risk	Europe	Caucasians	Moderate	Unclear

Abbreviations: ACE-I = Angiotensin-converting enzyme inhibitors; Ca = calcium; CHD = coronary heart disease; KQ3 = key question 3; N = total number; NR = not reported.

Table 35. Risk of bias and potential for conflict of interest

All RCTs	*% of total studies (N=57)*		
Items	Yes	No	Unclear
Adequate generation of allocation sequence	22.8	0.0	77.2
Allocation concealment	7.0	0.0	93.0
Comparability of groups	49.1	17.5	33.3
Purity of supplement	82.5	14.0	3.5
Blinding of allocated intervention	24.6	24.6	50.9
Adequately addressed missing data	59.6	3.5	36.8
Freedom from potential for conflict of interest	21.1	33.3	45.6
Crossover RCTs	% of total crossover studies (N=21)		
Suitability of crossover design for the study condition	100		
Freedom from carryover effect	19.0	71.4	9.5
Appropriateness of statistical analysis for crossover design	23.8	14.3	61.9
Comparability of groups between periods 1 and 2	9.5	0.0	90.5
Freedom from bias introduced by dropouts	76.2	9.5	14.3

Abbreviations: N = total number; RCTs = randomized controlled trials.

Coenzyme Q10

Five RCTs examined coenzyme Q10 plus statins, fenofibrate or angiotensin-converting enzyme (ACE) inhibitors versus statins, fenofibrate or ACE inhibitors alone. [37,54,60-62] The included patients ranged from those with ischemic or idiopathic dilated cardiomyopathy, [54] or diabetes, [60] to individuals with myalgia,[37] or myopathic pain.[62] The majority of studies were parallel RCTs (one crossover RCT [54]) with moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Coenzyme Q10 plus statins versu statins alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 plus statins versus statins alone, including serious adverse events,[61] withdrawal due to adverse events,[37,61] hepatoxicity (elevated alanine transaminase,[37] elevated aspartate aminotransferase[37]), and renal dysfunction (abnormal glomerular filtration rate[37]) (Table 36). None of the included studies examined the gradable outcome bleeding. One RCT examined adverse events in general and zero events were observed.[61] One RCT found a higher frequency of decreased myopathic pain in the coenzyme Q10 plus statin group (16/18) versus the statin alone group (3/14), and the relative risk (RR) was 4.18 (95 percent confidence interval (CI] 1.50, 11.46).[62] Similarly, significantly lower pain severity scores on the 4 pain intensity items of the Brief Pain Inventory (BPI) Questionnaire (mean difference (MD] -1.76 (95 percent confidence interval (CI) -2.93, -0.58]) and lower average pain interference scores on the 7 items of the BPI Questionnaire (MD -1.43 (95 percent CI -2.76, -0.10]) were observed in the coenzyme Q10 plus statins versus the statins alone group.[62] However, another RCT examining myalgia using the Visual Analogue Scale did not find a statistically significant difference between coenzyme Q10 plus statins versus statins alone.[37] Two RCTs examined fasting blood glucose as a continuous outcome; no differences were observed for atorvastatin.[61] Other

continuous outcomes reported for the statins included myoglobin,[61] creatine kinase (CK), or creatine phosphokinase (CPK);[61,62] no statistically significant differences were observed.

Coenzyme Q10 plus fenofibrate versus fenofibrate alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 plus fenofibrate versus fenofibrate alone, including withdrawal due to adverse events,[60] elevated alanine transaminase,[60] and elevated creatinine[60] (Table 36). None of the included studies examined the gradable outcomes serious adverse events or bleeding. RCTs also reported abnormal electrocardiogram (ECG) [60] and abnormal CK/CPK;[60] zero events were observed. In another RCT, frequency of retinopathy was the same with coenzyme Q10 plus fenofibrates (5/20) versus fenofibrate alone (6/20).[60] One RCT examined fasting blood glucose as a continuous outcome; no differences were observed.[60]

Coenzyme Q10 plus ACE Inhibitors versus ACE Inhibitors alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 plus ACE inhibitors versus ACE inhibitors alone, including hepatoxocity (elevated alanine transaminase,[54] aspartate aminotransferase[54]) and renal dysfunction (creatinine,[54] blood urea nitrogen [54]) (Table 36). None of the included studies examined the gradable outcomes serious adverse events, withdrawal due to adverse events or bleeding. One RCT also reported adverse events in general;[54] zero events were observed.

Table 36. Strength of evidence for coenzyme Q10 with or without cardiovascular drugs

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Coenzyme Q10						
Serious adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Withdrawal due to adverse events [2 studies]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** Study 1: 0 events Study 2: no significant differences; 6/22 events in intervention group vs. 4/22 events in placebo group
Renal dysfunction (glomerular filtration rate [1 study])	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Hepatotoxicity hepatoxicity (alanine transaminase, aspartate aminotransferase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Fenofibrate						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 2 events total (not reported by group)
Renal	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive**

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
dysfunction (creatinine [1 study])			surrogate			No significant differences between groups, number of events not reported
Hepatotoxicity (alanine transaminase [study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
ACE inhibitors						
Renal dysfunction (creatinine, blood urea nitrogen [n=1 study])						0 events observed in 1 study
Hepatotoxicity (alanine transmainase, aspartate aminotransferase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	0 events observed in 1 study

Abbreviations: ACE = angiotensin-converting enzyme; NA = not applicable.

Echinacea

Using a randomized open-label crossover trial, total adverse events and withdrawals due to adverse events were investigated for a mixture of 600 mg of *Echinacea angustifolia* roots plus 675 mg of *E. purpurea* root given four times a day for over two weeks with a single dose of 25 mg warfarin versus warfarin alone.[63] Insufficient evidence was noted for the gradable outcome withdrawal due to adverse events (Table 37). Furthermore, this study did not report data on the gradable outcomes serious adverse events, bleeding, renal dysfunction or hepatotoxicity.[63] Zero adverse events were observed in the 12 healthy non-smoking males in the *Echinacea* plus warfarin group and the 12 healthy non-smoking males in the warfarin alone group.

Table 37. Strength of evidence for warfarin with or without *Echinacea*

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed

Abbreviation: NA = not available.

Garlic

Four RCTs examined garlic (4g/day to 10g/day) plus warfarin, nitrates, or statins/aspirin versus warfarin, nitrates, or statins/aspirin alone.[58,64-66] The included patients ranged from healthy non-smoking males [65] to individuals with cardiac conditions, [58,64,66] and the majority of studies were parallel RCTs (one crossover RCT [65]) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Garlic plus warfarin versus warfarin alone

Insufficient evidence was available for the gradable harm bleeding for garlic plus warfarin versus warfarin alone (Table 38).[64,65] In one study, bleeding was defined as hemorrhage, epistaxis, hemoptysis, hematuria, bloody stools, hemorrhage into organs, hemarthrosis, hematomas, or bruising.[64] The other study simply indicated major bleeding episodes.[65] None of the included RCTs examined the gradable outcomes serious adverse events, withdrawal due to adverse events, renal dysfunction or hepatotoxicity. One RCT examined fasting blood glucose [64] and anemia;[64] no statistically significant effects were observed.

Garlic plus nitrates versus nitrates alone

One RCT examined garlic plus nitrates versus nitrates alone and did not report the results for any of the gradable harms.[58] This RCT reported only one harm (fasting blood glucose as a continuous outcome) and found no statistically significant effects.[58]

Garlic plus statins/aspirin versus statins/aspirin alone

Insufficient evidence was noted for the gradable outcomes renal dysfunction[66] and hepatoxocity[66] for garlic plus statins/aspirin versus statins/aspirin alone (Table 38). The RCT also reported harms data related to leukopenia[66] and fasting blood glucose;[66] no statistically significant effects were observed.

Table 38. Strength of evidence for warfarin with or without garlic.

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Warfarin						
Bleeding [2 studies]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Aspirin						
Renal dysfunction* (creatinine, serum potassium [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed
Hepatotoxicity* (aspartate aminotransferase, alanine transaminase, alkaline phosphatase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Ginger

No evidence of gradable outcomes were found for this supplement. Mild diarrhea in 1/12 subjects was found in one RCT after 2 days of supplementation with ginger plus a single dose of warfarin.[67]

Ginkgo biloba

Seven RCTs examined Ginkgo biloba plus warfarin, aspirin, aspirin and/or pentoxiphylline, digoxin, statin/aspirin, cilostazol/clopidogrel or ticlopidine versus these cardiovascular medications alone.[48,67-71,99] Two of these studies included a single dose of a cardiovascular medication so their results should be interpreted with caution.[70,71] The included patients ranged from those at risk for peripheral artery disease[69] or stroke,[48] to healthy adults[68,99] or males.[67,70,71] The majority of studies were crossover RCTs (two parallel RCTs [48,69]) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Ginkgo biloba plus aspirin versus apirin alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for *G. biloba* plus aspirin versus aspirin alone, including withdrawal due to adverse events,[69] bleeding (nosebleeds and/or unusual bleeding),[69] renal dysfunction,[68] and hepatotoxicity[68] (Table 39). None of the included studies examined the gradable outcome serious adverse events. No statistically significant differences were observed across the total adverse events (11/34 *G. biloba* plus aspirin group versus 15/33 aspirin alone group) and upset stomach (6/34 *G.biloba* plus aspirin group versus 5/33 aspirin alone group) harms.[69] One RCT reported anemia and white blood cell count using continuous data but found no significant differences between the groups taking *G. biloba* plus aspirin group and aspirin alone.[68]

Ginkgo biloba plus aspirin and/or pentoxiphylline versus aspirin and/or pentoxiphylline alone

Insufficient evidence was noted for the gradable harm withdrawal due to adverse events for *G. biloba* plus aspirin and/or pentoxiphylline versus aspirin and/or pentoxiphylline alone[48] (Table 39). None of the included studies reported the gradable outcomes serious adverse events, bleeding, renal dysfunction or hepatotoxicity. One RCT reported 4/33 gastrointestinal events in the *G. biloba* plus aspirin and/or pentoxiphylline group compared with 3/29 events in the control group,[48] which was not statistically significant.

Ginkgo biloba plus ticlopidine versus ticlopidine alone

Insufficient evidence was noted for the gradable harms renal dysfunction (raised creatinine,[71] abnormal blood urea nitrogen[71]) and hepatotoxicity (elevated aspartate aminotransaminase,[71] or elevated alkaline phosphatase [71]) for *G. biloba* plus ticlopidine versus ticlopidine alone (Table 39). None of the included RCTs examined the gradable outcomes serious adverse events, withdrawal due to adverse events or bleeding. One RCT examined the effects of *G. biloba* plus ticlopidin versus ticlopidin alone on hypoglycemia, hyperglycemia, leukopenia, thrombocytopenia, anemia, and abnormal ECG; 0 events were observed.[71]

Ginkgo biloba plus warfarin versus warfarin alone

Insufficient evidence was noted for the gradable harms serious adverse events and withdrawal due to adverse events for *G. biloba* plus warfarin versus warfarin alone (Table 39).[67] None of the RCTs examined the other gradable harms, including bleeding, renal dysfunction, and hepatotoxicity. Furthermore, zero events were observed for constipation and no statistically significant differences were reported for diarrhea (0/12 intervention group vs. 1/12 control group).[67]

Ginkgo biloba plus digoxin versus digoxin alone

Insufficient evidence was noted for G. biloba plus digoxin versus digoxin alone related to withdrawal due to adverse events (Table 39).[99] However, no data was available on the other gradable harms, including serious adverse events, bleeding, renal dysfunction, and hepatotoxicity. Furthermore, zero events were reported for adverse events and no statistically significant differences were noted for gastrointestinal adverse events (1/8 intervention group vs. 0/8 control group).[99]

Ginkgo biloba plus cilostazol/clopidogrel versus cilostazol/clopidogrel alone

Insufficient evidence was noted for *Ginkgo biloba* plus cilostazol/clopidogrel versus cilostazol/clopidogrel alone across all gradable outcomes, as none of these were reported.[70] One RCT examined total adverse events; 0 events were reported.[70]

Table 39. Strength of evidence for *G. biloba* plus cardiovascular drugs versus cardiovascular drugs alone.

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Aspirin						
Withdrawal due to adverse events [1 study]	Low	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences, 3/34 intervention group vs. 2/33 control group
Bleeding [1 study]	Low	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant difference; 5/34 events intervention group vs. 4/33 events control group
Renal dysfunction* (creatinine, blood urea nitrogen [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed
Hepatotoxicity* (aspartate aminotransaminase, alanine transaminase, [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed
Aspirin and/or pentoxiphylline						
Withdrawal due to adverse events [n=1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Ticlopidine						
Renal dysfunction (creatinine, blood urea nitrogen [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Hepatotoxicity (aspartate aminotransaminase, alkaline phosphatase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Warfarin						
Serious adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Digoxin						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Ginseng

One parallel RCT examined the effects of 1.5g/day ginseng plus warfarin versus warfarin alone among patients who had experienced a stroke.[72] Another parallel RCT examined the same comparison but with 2 g/day ginseng among healthy patients,[73] while a crossover RCT examined the same comparison but with 3 g/day ginseng among healthy non-smoking males.[74] All three RCTs were of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes. Insufficient evidence was noted across the gradable clinical adverse events, including withdrawal due to adverse events[74] and bleeding (no description provided)[72] (Table 40). None of the included RCTs examined the gradable outcome serious adverse events. Furthermore, insufficient evidence was noted for the organ toxicity outcomes (elevated creatinine,[72] abnormal blood urea nitrogen,[72] elevated aspartate aminotransaminase,[72] and elevated alanine transaminase [72]), yet these were based on continuous data only (dichotomous data was not available). One RCT also examined prothrombin time, total adverse events, headache, dizziness, indigestion, international normalized ratio (INR) above 3.5, diarrhea, and constipation;[72] zero events were observed across all of these outcomes. Another RCT reported zero adverse events of clinical importance.[73] One RCT examined the outcomes hematocrit and anemia using continuous data;[72] no statistically significant differences were observed between intervention and control groups.

Table 40. Strength of evidence for warfarin with or without ginseng.

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Renal dysfunction* (creatinine, blood urea nitrogen [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed
Hepatotoxicity* (aspartate aminotransaminase, alanine transaminase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Hawthorne

Tankanow and colleagues investigated the occurrence of harms with hawthorne and digoxin in 8 healthy male volunteers in an open-label, randomized crossover trial of digoxin 0.25 mg/day for a 10-day period plus 900 mg/day of extract of hawthorne leaves with flowers standardized to 84.3 mg of oligomeric procyanidines for a 21 day period, versus digoxin alone for 10 days.[75] This RCT did not report results for any of the gradable harms, including serious adverse events, withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity. Furthermore,

no statistically significant differences were observed between groups in incidence of flatulence (intervention: 1/11 versus control: 0/11), nausea (intervention: 2/11 versus control: 0/11), insomnia (intervention: 1/11 versus control: 1/11), headache (intervention: 1/11 versus control: 0/11), and dizziness (intervention: 1/11 versus control: 0/11).

Magnesium (oral)

One parallel RCT examined the effects of 4.5g/day oral magnesium plus hydrochlorthiazide versus hydrochlorthiazide alone,[76] while another examined the same comparison but with 15.78 mmol twice daily among hypertensive patients.[77] In addition, one crossover RCT examined the effects of 365mg/day oral magnesium plus various beta adrenergic antagonists versus beta adrenergic antagonists alone among hypertensive patients.[42] All three RCTs had moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Magnesium plus hydrochlorthiazide versus hydrochlorthiazide alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for magnesium plus hydrochlorthiazide versus hydrochlorthiazide alone, including withdrawal due to adverse events[76] and renal dysfunction (elevated creatinine [77]) (Table 41). None of the included RCTs examined the gradable outcomes serious adverse events, bleeding or hepatotoxicity. One RCT examining hydrochlorthiazide observed 0 events across diarrhea, vomiting, nausea, adverse events, hyperkalcemia, and fasting blood glucose harms.[76] Furthermore, no statistically significant differences were observed for abnormal ECG (number of events not reported).[76]

Magnesium plus beta adrenergic antagonists versus beta adrenergic antagonists alone

Insufficient evidence was noted for magnesium plus beta adrenergic antagonists versus beta adrenergic antagonists alone for the gradable harms serious adverse events,[42] withdrawal due to adverse events,[42] and renal dysfunction (abnormal serum potassium[42]) (Table 41). None of the studies reported the gradable outcomes bleeding or hepatotoxicity.

Table 41. Strength of evidence for magnesium plus CVD drugs versus CVD drugs alone

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Hydrochlor-thiazide						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Renal dysfunction (creatinine [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Beta-adrenergic antagonists						
Serious adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Renal dysfunction* (serum potassium [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Niacin (≤ 250 mg)

Harms were investigated among 20 patients with hyperlipoproteinemia in an open-label, randomized crossover trial of niacin 250 mg/day plus propranolol 20 mg/day versus propranolol alone for 1 month.[78] There was insufficient evidence for the gradable outcome withdrawals due to adverse events (0/10 intervention group versus 1/10 control group) (Table 42).[78] This study did not report gradable harms, such as serious adverse events, bleeding, renal dysfunction or hepatotoxicity. Furthermore, there were no statistically significant differences in nausea plus flushing (0/10 intervention group versus 0/10 control group) or hypotension plus asthenia (0/10 intervention group versus 1/10 control group).

Table 42. Strength of evidence for niacin plus propranolol versus propranolol alone

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Withdrawal due to adverse events [n=1 study]	High	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; 0/10 intervention group vs. 1/10 control group

Abbreviation: NA = not applicable.

Omega-3 Fatty Acids/Fish Oils

Twenty-two studies (21 RCTs, and one retrospective cohort study) examined ω-3 fatty acids (or fish oils) plus statins,[35,36,40,53,91-96] aspirin,[47,52,80,90,90,97] aspirin and clopidogrel,[100] aspirin in

combination with dipyridamole and calcium channel blockers ,[52] warfarin,[47,55] rampril,[79] or fenofibrate,[56]. The included participants ranged from elderly patients with CHD,[83] to adults with diabetes [88] or stroke,[49] to healthy males [38] or adults.[35,90,95,96] The majority of studies were parallel RCTs, yet there were 7 crossover RCTs,[35,36,90-92,95,96] and one retrospective cohort study.[100] The majority were deemed as having moderate risk of bias, although two had low risk of bias [51,93] and one had high risk of bias.[55] Meta-analysis was only possible for the statins; for all other cardiovascular medications, low event rates across all of the harms outcomes precluded pooling.

Omega-3 fatty acids/fish oils plus statins versus statins alone

Ten RCTs examined omega-3 fatty acids (or fish oils) plus statins versus statins alone.[35,36,40,53,91-96] One RCT had low risk of bias,[93] while the rest were of moderate risk of bias, including the 7 RCTs included in the meta-analyses.[35,36,40,91,94-96] Insufficient evidence was noted across all gradable outcomes, including serious adverse events meta-analysis (Figure 20), withdrawal due to adverse events meta-analysis (Figure 21), aminotransaminase meta-analysis (Figure 22), and alanine transaminase meta-analysis (Figure 23, Table 43). None of the included RCTs examined the gradable outcome bleeding.

Meta-analysis was also possible for total adverse events (n=5 studies; RR 0.94 [95 percent CI 0.78, 1.12] Figure 24), dyspepsia (n=2 studies, odds ratio [OR] 1.61 [95 percent CI 0.46, 5.55] Figure 25), headache (n=2; OR 0.76 [95 percent CI 0.25, 2.30] Figure 26), constipation (n=2; RR 0.94 [95 percent CI 0.63, 1.39] Figure 27), upper respiratory infection (n=2; RR 1.33 [95 percent CI 0.34, 5.21] Figure 28), and CK/CPK (n=3; RR 1.50 [95 percent CI 0.43, 5.25] Figure 29); no statistically significant effects were observed. Results were consistently not statistically significant despite differences in low [35,95,96] versus moderate [36,40,91,94] CHD risk, and healthy patients [35,95,96] versus those with hyperlipidemia or dyslipidemia [36,40,91,94]. We were unable to discern any effects of sex, ethnicity or age on the results, as these were not examined in the RCTs for which meta-analysis was deemed appropriate.

RCTs also reported many other harms outcomes, such as diarrhea (3/122 intervention versus 3/132 control),[40] flatulence (5/50 intervention versus 5/50 control),[35] generalized edema (0/40 intervention versus 2/40 control),[36] hyperglycemia (2/40 intervention versus 1/40 control),[36] hypoglycemia (1/40 intervention versus 1/40 control),[36] infection (4/122 intervention versus 1/132 control),[40] myalgia (1/40 intervention versus 1/40 control),[36] and sinusitis (0/40 intervention versus 2/40 control);[36] no statistically significant differences were observed. The RCTs also examined harms outcomes as continuous variables, such as leukopenia,[92] anemia,[92] red blood cell count,[92] hematocrit,[92] glycosylated hemoglobin,[94] and fasting blood glucose;[36,40,44,53,93,94,98] and only one RCT found a statistically significant elevated fasting blood glucose in the omega-3 fatty acids plus statins versus statins alone group.[40]

Figure 20. Forest plot of serious adverse events with statins, with or without omega-3 fatty acids

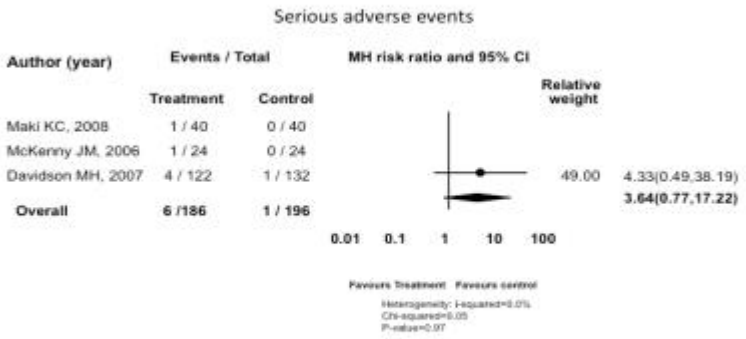


Figure 21. Forest plot of withdrawal due to adverse events with statins, with or without omega-3 fatty acids

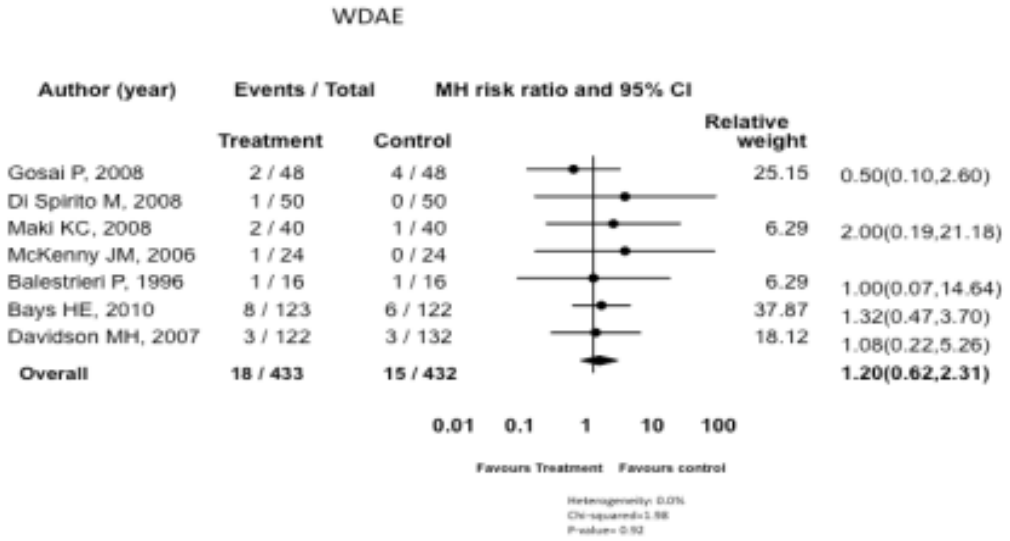


Figure 22. Forest plot of aminotransaminase with statins, with or without omega-3 fatty acids

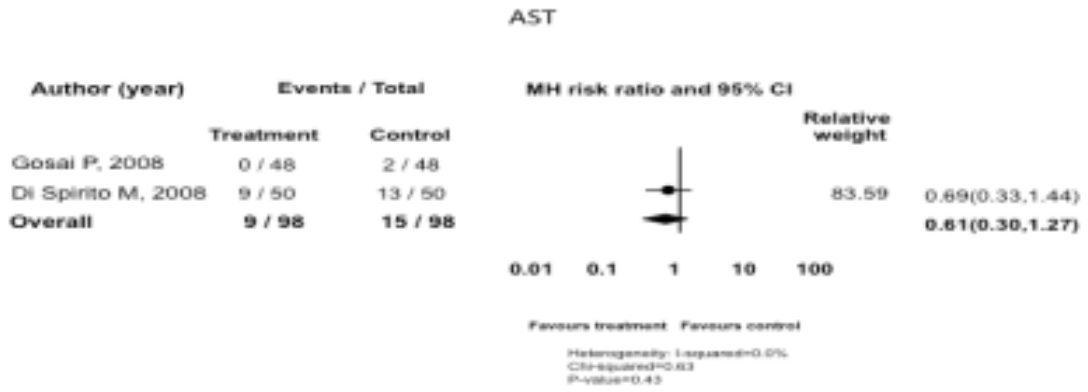


Figure 23. Forest plot of alanine transaminase with statins, with or without omega-3 fatty acids

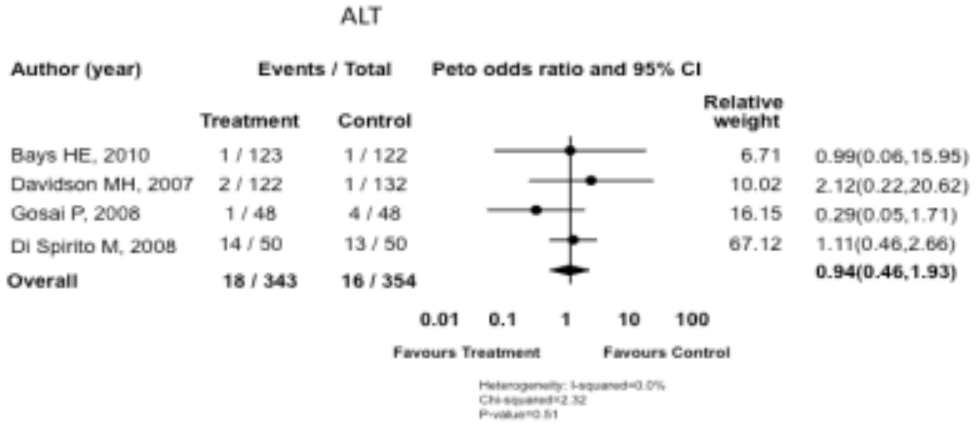


Figure 24. Forest plot of total adverse events with statins, with or without omega-3 fatty acids

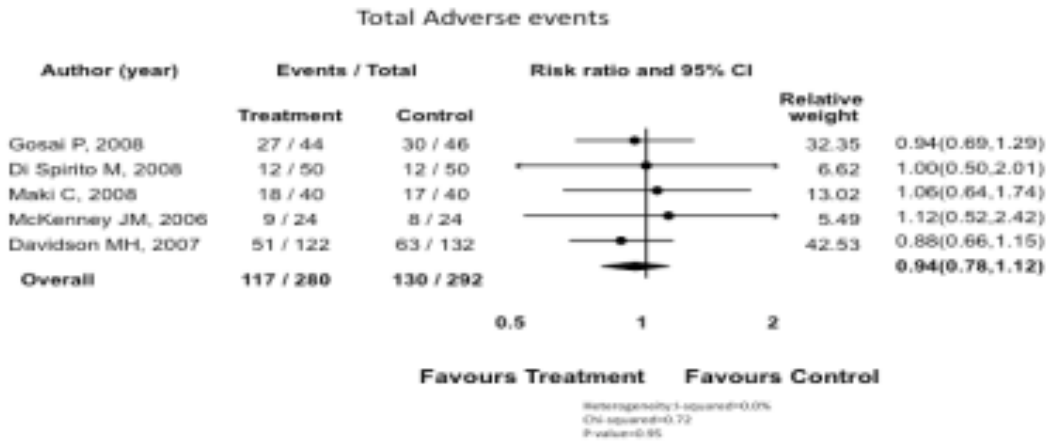


Figure 25. Forest plot of dyspepsia with statins, with or without omega-3 fatty acids

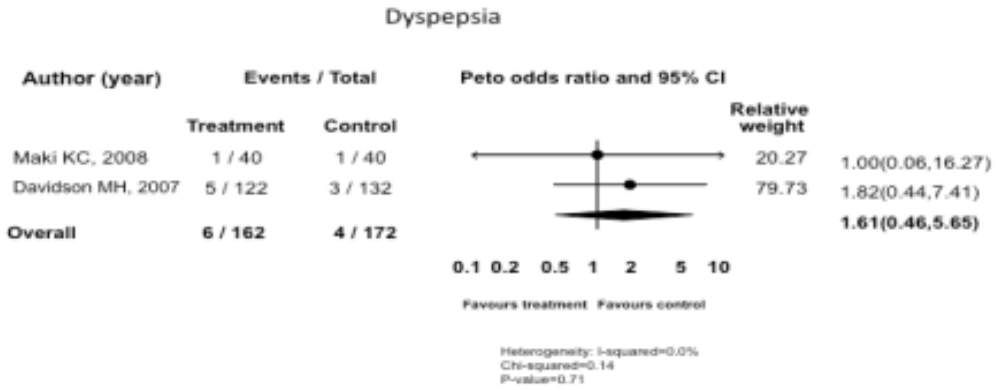


Figure 26. Forest plot of headache with statins, with or without omega-3 fatty acids

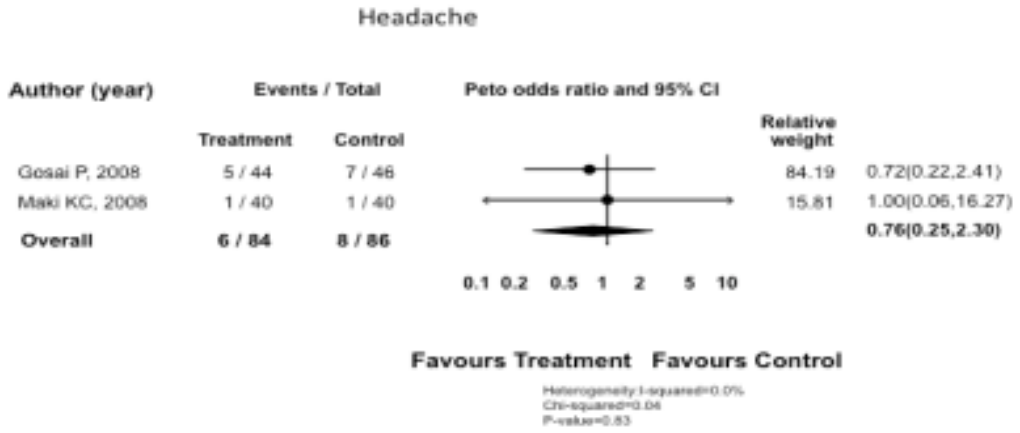


Figure 27. Forest plot of constipation with statins, with or without omega-3 fatty acids

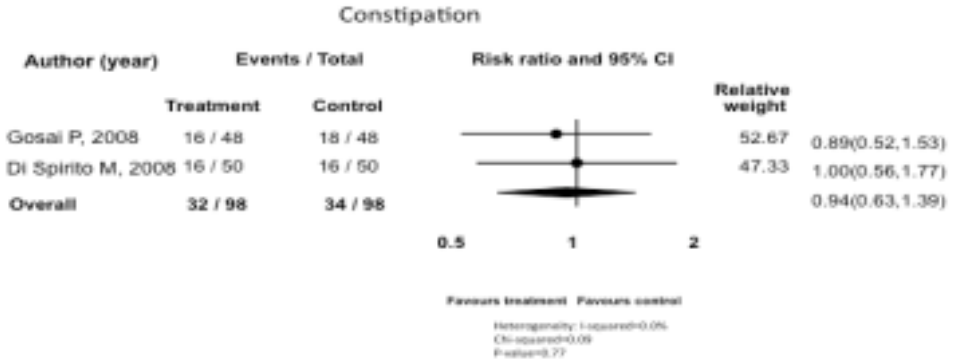


Figure 28. Forest plot of upper respiratory infection with statins, with or without omega-3 fatty acids

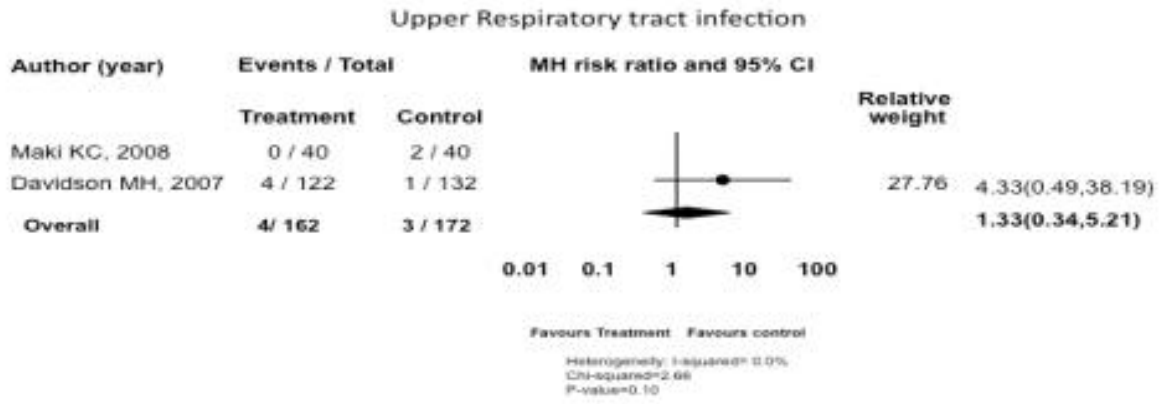
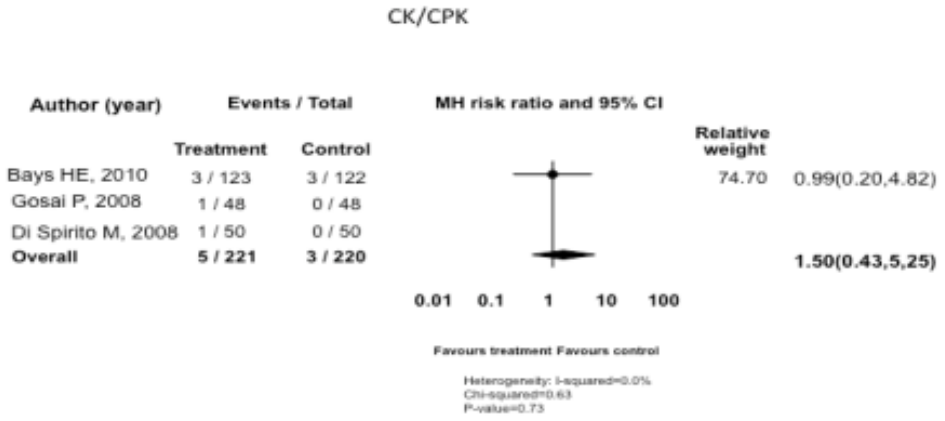


Figure 29. Forest plot of CK/CPK with statins, with or without omega-3 fatty acids



Omega-3 fatty acids/fish oils plus plus aspirin versus aspirin alone

Six RCTs examined omega-3 fatty acids (or fish oils) plus aspirin versus aspirin alone.[47,52,80,90,90,97] Two of these RCTs were conducted among males only.[52,97] Insufficient evidence was noted for all gradable outcomes, including withdrawal due to adverse events[80] and bleeding[47,90](Table 43). Bleeding in one study was defined as those episodes leading to deviation from the protocol.[47] The second study reported bleeding episodes of any type.[90]. None of the included RCTs examined the gradable outcomes serious adverse events, renal dysfunction or hepatotoxicity. No significant differences were observed across all harms, including constipation (1/12 intervention group versus 0/12 control group),[90] diarrhea (0/12 intervention group versus 1/12 control group),[90] fishy taste (4/12 intervention group versus 0/12 control group),[90] gastrointestinal adverse events (7/143 intervention group versus 12/148 control group),[47] flatulence (0/12 intervention group versus 1/12 control group),[90] headache (1/12 intervention group versus 1/12 control group),[90] and nausea (3/12 intervention group versus 3/12 control group).[90] One RCT reported leukopenia as a continuous outcome, with no statistically significant differences observed.[90]

Table 43.Strength of evidence for omega-3 fatty acids plus aspirin versus aspirin alone

	Strength of Evidence						Conclusions
Harms	**Risk of Bias**	**Consistency**	**Directness**	**Precision**	**Additional Domain(s)**	**Strength of Evidence**	
	Low, Moderate, or High	Consistent, Inconsistent, or Not Applicable	Direct, Indirect Surrogate, or Indirect Comparisons	Precise, or Imprecise		High, Moderate, Low, or Insufficient	
Withdrawal due to adverse events [n=1 study]	Moderate	NA	Direct	Imprecise	NA	Insufficient	0 events observed
Bleeding [n=2 studies]	High	NA	Direct	Imprecise	NA	Insufficient	No significant differences: Study 1: 0 events observed Study 2: 3/143 intervention group vs. 2/148 control group

Abbreviation: NA = not applicable.

Omega-3 fatty acids/fish oils plus aspirin and clopidogrel versus aspirin and clopidogrel alone

One retrospective cohort study examined the effect of fish oils in combination with aspirin and clopidogrel in 182 elderly subjects with coronary artery disease.[100] An age and gender matched control group of subjects taking aspirin and clopidogrel alone was selected. Major and minor bleeding episodes were noted after a follow-up of 33 months. Major bleeding was defined as a decrease in haemoglobin of > 2 g, intracerebral hemorrhage, or any bleeding episode that required hospitalization. Minor bleeding was defined as epistaxis, abnormal bruising, and gastrointestinal bleeding that did not require hospitalization or lead to a decrease in haemoglobin > 2 g. No significant differences were found between intervention and control groups. Strength of evidence for bleeding was insufficient (Table 44).

Table 44. Strength of evidence for fish oils plus aspirin and clopidogrel versus aspirin and clopidogrel alone

	Strength of Evidence						Conclusions
Harms	**Risk of Bias**	**Consistency**	**Directness**	**Precision**	**Additional Domain(s)**	**Strength of Evidence**	
	Low, Moderate, or High	Consistent, Inconsistent, or Not Applicable	Direct, Indirect Surrogate, or Indirect Comparisons	Precise, or Imprecise		High, Moderate, Low, or Insufficient	
Bleeding [n=1 studies]	Moderate	NA	Direct	Imprecise	NA	Insufficient	No significant differences: Major Bleeding: 1/182 intervention vs. 0/182 control group Minor Bleeding: 4/182 intervention vs. 7/182 control group

Omega-3 fatty acids/fish oils plus aspirin, dipyridamole, and calcium channel blockers versus aspirin, dipyridamole, and calcium channel blockers

One RCT also examined the effects of omega-3 fatty acids/fish oils plus aspirin, dipyridamole, and calcium channel blockers versus aspirin, dipyridamole, and calcium channel blockers alone.[52] Another RCT with a low risk of bias examined omega-3 fatty acids plus aspirin and calcium channel blockers versus aspirin and calcium channel blockers alone. Insufficient evidence was noted for the gradable outcomes bleeding (described as bleeding complications)[51,52] and withdrawal due to adverse events[51] (Table 45). None of the included RCTs examined serious adverse events, renal dysfunction or hepatotoxicity. No statistically significant differences were observed regarding gastrointestinal events (7/43 intervention group versus 3/39 control group [52]).

Omega-3 fatty acids/fish oils plus warfarin versus warfarin alone

Two RCTs examined the effects of omega-3 fatty acids (or fish oils) plus warfarin versus warfarin alone.[47,55] Insufficient evidence was noted for the gradable outcomes bleeding [47,55] and withdrawals due to adverse events[55] (Table 45). Bleeding in one study was defined as those episodes leading to deviation from the protocol.[47] The other study reported major bleeding (defined as bleeding episodes causing death or requiring hospitalization, vitamin K, or blood transfusion) and minor bleeding (defined as any bleeding episode that did not qualify as a major bleed but that required a change in warfarin dosage or referral).[55] None of the included studies examined the gradable outcomes serious adverse events, renal dysfunction or hepatotoxicity. Furthermore, three patients with an unstable international normalized ratio withdrew but it was not indicated which groups that they belonged to.[55] One of the RCTs reported gastrointestinal events, which did not differ significantly between groups (9/174 intervention vs. 0/145 control).[47]

Omega-3 fatty acids/fish oils plus ramipril and/or Irbesartan versus ramipril and/or Irbesartan alone

One RCT with a moderate risk of bias examined the effects of fish or marine oils 3g/day plus ramipril among patients at low risk of CHD.[79] Insufficient evidence was noted for the gradable outcomes withdrawal due to adverse events, bleeding (erythrocyturia grade 3), and renal dysfunction (glomerular filtration rate) (Table 45). This RCT did not report the results for other gradable harms, such as serious adverse events and hepatotoxicity. Furthermore, zero events was observed for hyperkalcaemia.

Omega-3 fatty acids/fish oils plus fenofibrate versus fenofibrate alone

One RCT with a moderate risk of bias examined the effects of omega-3 fatty acids 4 g/day plus fenofibrate versus corn oil plus fenofibrate among patients with low CHD risk.[56] Insufficient evidence was noted for the gradable harms serious adverse events, withdrawal due to adverse events, and renal dysfunction (elevated creatinine) (Table 45). This RCT did not report results for the gradable harms bleeding or hepatotoxicity. Furthermore, no statistically significant differences were observed for constipation (1/84 intervention group versus 5/83 control group), diarrhea (4/84 intervention group versus 5/83 control group), flatulence (1/84 intervention group versus 3/83 control group), gastrointestinal adverse events (7/84 intervention group versus 5/83 control group) and nausea (5/84 intervention group versus 3/83 control group).

Table 45. Strength of evidence for cardiovascular drugs with or without omega-3 fatty acids/fish oil

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Statins						
Serious adverse events [meta-analysis including 3 studies]	Moderate	Consistent	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; 0/10 intervention group vs. 1/10 control group
Withdrawal due to adverse events [meta-analysis including 7 studies]	Moderate	Inconsistent	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences; RR 3.6 (95% CI 0.8, 17.2)
Renal dysfunction* (creatinine [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; OR 1.2 (95% CI 0.6, 2.4)
Hepatotoxicity: aminotransaminase [meta-analysis including 2 studies]	Moderate	Consistent	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No significant differences
Hepatotoxicity: alanine transaminase [meta-analysis including 4 studies]	Moderate	Inconsistent	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; RR 0.61 (95% CI 0.30, 1.27)
Aspirin + dipridamole + calcium channel blockers						
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences: 3/43 intervention group vs. 1/39 control group
Aspirin+ calcium channel blockers						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Warfarin						
Withdrawal due to adverse events [1study]	High	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Bleeding [2 studies]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences: Study 1: 0 events observed Study 2: 2/174 intervention group vs. 2/145 control group

Ramipril and/or irbesartan						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	0 events observed
Bleeding [1 study](Grade 3 erythrocyturia)	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences: 4/15 intervention group vs. 1/15 control group
Renal dysfunction* [glomerular filtration rate, 1 study]	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	No statistically significant difference
Fenofibrate						
Serious adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences; 3/84 intervention group vs. 4/83 control group
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences 4/84 intervention group vs. 4/83 control group
Renal dysfunction (creatinine [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No significant differences 0/84 intervention group vs. 1/83 control group

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Vitamin E

Ten RCTs examined vitamin E plus aspirin, statins, or furosemide versus these cardiovascular medications alone.[38,46,49,82-85,87-89] The included participants ranged from the elderly with CHD,[83] to those with diabetes,[88] or stroke,[49] to healthy females.[38] The majority of studies were parallel RCTs (with two crossover RCTs [83,87]) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Vitamin E plus aspirin versus aspirin alone

Three RCTs examined vitamin E plus aspirin versus aspirin alone [38,49,89] and insufficient evidence was noted for the gradable harms bleeding (hemorrhagic events) [49] and withdrawals due to adverse events[89] (Table 46). None of the RCTs reported data related to the gradable harms serious adverse events, renal dysfunction or hepatotoxicity. Only one RCT examined the interaction between vitamin supplements and cardiovascular medication by calculating the S-index. This RCT found a positive interaction or synergism between vitamin E and aspirin for withdrawals due to adverse events (S-index=1.11). Antagonistic interactions were found for and headache (S-index=-1.53) and gastrointestinal discomfort (S-index=-0.33).[89] No statistically significant differences were observed in the number of patients experiencing headache (28/121 intervention group versus 20/122 control group), gastrointestinal discomfort (14/121 intervention group versus 10/122 control group) or total adverse events (23/121 intervention group versus

24/122 control group).[89] One RCT examined the occurrence of cancer and no statistically significant differences were observed (716/9966 intervention group versus 722/9968 control group).[38]

Vitamin E plus nifedipine versus nifedipine alone

One crossover RCT examined the effects of vitamin E plus nifedipine versus nifedipine alone, and insufficient evidence was noted across all of the gradable harms, including withdrawal due to adverse events, renal dysfunction, and hepatotoxicity (zero events were observed[83]) (Table 46). This RCT did not report on the gradable outcomes serious adverse events or bleeding. Furthermore, fasting plasma glucose was examined as a continuous outcome and no statistically significant differences were observed.[83]

Vitamin E plus furosemide versus furosemide alone

One parallel RCT examined the effects of vitamin E plus furosemide versus furosemide alone and did not report the results of any of the gradable outcomes. Fasting blood glucose was reported as a continuous outcome; no statistically significant effects were observed.[82]

Vitamin E plus statins versus statins alone

Five RCTs examined the effects of vitamin E plus statins versus statins alone; [46,84,85,87,88] insufficient evidence was noted across the gradable harms including organ toxicity outcomes (raised alanine transaminase,[46,85] aspartate aminotransferase,[46] abnormal alkaline phosphatase,[46] elevated creatinine,[46] abnormal blood urea nitrogen[46]) , and QT intervals (measured as continuous varialble).[84] (Table 46). None of the RCTs reported data on the gradable harms serious adverse events, withdrawal due to adverse events or bleeding. Furthermore, glycosylated hemoglobin,[88] leukopenia,[46] and anemia,[46] were examined as continuous outcomes and no statistically significant differences were observed.

Table 46. Strength of evidence for cardiovascular drugs with or without vitamin E

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Aspirin						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant difference; 29/121 intervention group vs. 19/122 control group
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant difference; 3/52 intervention group vs. 3/48 control group
Nifedipine						
Withdrawal due to adverse events [n=1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Renal dysfunction (creatinine [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed

Hepatotoxicity (alanine transaminase, aspartate aminotransferase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Statins						
Renal dysfunction (creatinine, blood urea nitrogen* [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Hepatotoxicity (alanine transaminase [2 studies], aspartate aminotransferase, alkaline phosphatase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
QT interval (continuous data)	Moderate	NA	Indirect Surrogate	Imprecise	Insufficient	**Inconclusive** No significant difference observed.

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Vitamin K

Two RCTs examined the effects of vitamin K plus phenprocoumon versus phenprocoumon alone or vitamin K plus warfarin versus warfarin alone.[39,41] Both were parallel RCTs of moderate risk of bias.

Vitamin K plus phenprocoumon versus phenprocoumon alone

One RCT examined the effects of vitamin K 100 µg/day plus phenprocoumon versus phenprocoumon alone among patients on long-term oral anticoagulant therapy.[39] Insufficient evidence was observed for the gradable outcome bleeding (Table 47) but none of the other gradable outcomes were reported. Bleeding was reported as major and minor episodes, where a major episode pertained to fatal or intracranial hemorrhage, requirement of transfusion, hospitalization, or surgery, or muscle and joint bleeding.

Vitamin K plu warfarin versus warfarin alone

Another RCT examined the effects of vitamin K 150 µg/day plus warfarin versus warfarin alone among the same population.[41] Insufficient evidence was observed for the gradable harms of bleeding episodes (no further description provided) and withdrawals due to adverse events (Table 47). This RCT did not report the gradable harms serious adverse events, renal dysfunction or hepatotoxicity.

Table 47. Strength of evidence for anticoagulants with or without vitamin K

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Phenprocoumon						
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences for minor bleeding; Minor bleeding: 7/94 intervention group vs. 10/95 control group Major bleeding: 2/94 intervention group vs.0/95 control group
Warfarin						
Withdrawal due to adverse events [n=1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; 0/35 intervention group vs. 2/33 control group
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed

Abbreviation: NA = not applicable.

Summary of Results for Key Question 3

- Fifty-seven randomized controlled trials and one retrospective cohort study contributed evidence to Key Question 3, examining harms outcomes.
- Overall, the studies were generally of moderate risk of bias across all harms, which ranged from minor (e.g., flatulence) to severe (e.g., leukopenia, hemorrhaging).
- Only one RCT examined the interaction between vitamin supplements and cardiovascular medication; there was a positive interaction or synergism between vitamin E and aspirin for withdrawals due to adverse events and headache but an antagonism interaction was observed for gastrointestinal discomfort.[89]
- Meta-analysis was not possible due to the low event rate across all of the harms outcomes for all supplements examined except for omega-3 fatty acids.
- A majority of the studies reported 0 events or no statistically significant differences across all harms and all supplements, including echinacea (n=1 study), garlic (n=4 studies), gingko biloba (n=7 studies), ginseng (n=2 studies), hawthorne (n=1 study), oral magnesium (n=3 studies), niacin (n=1 study), omega-3 fatty acids (n=22 studies), vitamin E (n=10 studies), vitamin K (n=3 studies).
- Five RCTs examined the effects of coenzyme Q10 plus statins, fenofibrate or ACE-inhibitors versus these medications alone. One uncontrolled RCT reported a greater proportion of patients experiencing decreased myalgia in the group administered coenzyme Q10 plus statins compared with the group administered statins alone (relative risk [RR] 4.18 [95 percent confidence interval (CI) 1.50, 11.46]), as well as lower pain severity (mean difference [MD] -1.76 [95 percent CI -2.93, -0.58]), and decreased pain interference (MD -1.43 [95 percent CI -2.76, -0.10]).[62] However, another RCT did not observe a statistically significant difference in myalgia between patients receiving coenzyme Q10 plus statins versus patients receiving statins alone.[37]
- For all gradable outcomes for which evidence was found, the strength of evidence was graded insufficient because type II error could not be excluded because of low power of studies for harms outcomes.
- Insufficient evidence was noted across the serious adverse events meta-analysis, withdrawal due to adverse events meta-analysis, aminotransaminase meta-analysis, and alanine transaminase meta-analysis for omega-3 fatty acids plus statins versus statins alone. Meta-analysis was also possible for total adverse events (n=5 studies, RR 0.94, 95% CI: 0.78-1.12), dyspepsia (n=2 studies, odds ratio [OR] 1.61, 95% CI: 0.46-5.55), headache (n=2 studies, OR 0.76, 95% CI: 0.25-2.30), constipation (n=2 studies, RR 0.94, 95% CI: 0.63-1.39), upper respiratory infection (n=2 studies, RR 1.33, 95% CI: 0.34-5.21), and creatine kinase (n=3 studies, RR 1.50, 95% CI: 0.43-5.25); no statistically significant effects were observed. We were unable to discern the effects of sex, ethnicity or age on the results, as these were not examined in the RCTs for which meta-analysis was deemed appropriate.
- None of the other omega-3 fatty acids RCTs found statistically significant results across all harms, except for one RCT that found a statistically significant elevated fasting blood glucose level in the omega-3 fatty acids plus statins versus statins alone group,[40] yet 6 other RCTs did not observe a statistically significant difference for omega-3 fatty acids plus statins versus statins alone.[36,44,53,93,94,98]

Key Question 4

In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on pharmacokinetic outcomes (e.g., half-life [$t_{1/2}$], area under the concentration curve [AUC]) of cardiovascular drugs of interest?

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

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

Overview

A total of 14 unique studies were screened in. [35,63,65,67,71,73-75,95,96,99,132,133,135] Three studies were removed from evidence synthesis because the dose of the dietary supplement was not reported,[133] a cardiovascular drug was used that is not marketed in the United States,[132] and finally a poorer study design sequential, single group before-after Ginkgo Biloba and ticlopidine interaction study did not add to the available randomized controlled trial (RCT) evidence.[135] Thus, a total of 11 studies contributed evidence on exposure and pharmacokinetic outcomes (Table 48). Generally, these studies were open-label, crossover, RCTs, of moderate risk of bias for outcomes of interest, and included between 8 and 50 healthy volunteers (Table 48).

Six studies investigated cardiovascular drug kinetics following a single dose.[63,65,67,71,74,99] In keeping with the United States Food and Drug Adminstration guidance,[30] seven studies reported pharmacokinetic outcomes potentially indicating cardiovascular drug interactions such as the area under the concentration curve (AUC) and maximum concentration (C_{max})as geometric mean ratios (dietary supplement plus cardiovascular drug: drug alone) with corresponding 90 percent confidence intervals.[35,63,65,67,71,74,95] Others reported data as post-treatment means or median changes from baseline. Carryover effects in these crossover trials was not a major concern because all study designs incorporated adequate washout periods, that were well over five times the half-lives of the drugs and supplements under investigation. Detailed study characteristics and data are tabulated in Appendix C. Statistical analyses were undertaken to compare the combination of dietary supplement plus cardiovascular drug with the cardiovascular drug alone. No evidence addressing Key Question 4 subquestions (a) or (b) was identified. No data were available on bioavailability and volume of distribution.

Table 48. Overview of included studies addressing Key Question 4

Dietary supplement	N of studies included for KQ 4	Cardiovascular drug(s)	Study design(s)	Participants	Study region	Race/Ethnicity	Overall risk of bias for pharmacokinetic outcomes	Industry funding or potential for conflict of interest
Coenzyme Q10	0	-	-	-	-	-	-	-
Echinacea	1[63]	Warfarin	Crossover RCT	Healthy non-smoking males	Australia/New Zealand	Mixed – Caucasians and Asians/South Asians	Moderate	Yes
Garlic	1[65]	Warfarin	Crossover RCT	Healthy non-smoking males	Australia/New Zealand	Mixed – Caucasians and Asians	Moderate	No
Ginger	1[67]	Warfarin	Crossover RCT	Healthy non-smoking males	Australia/New Zealand	Mixed – Caucasians and Asians	Moderate	No
Ginkgo biloba	3[67,71,99]	Ticlopidine, digoxin, and warfarin	Crossover RCT	Healthy adults	East Asia, North America and Australia/New Zealand	Asians, NR, and Mixed – Caucasians and Asians	Moderate	Yes[71] Unclear[99] No[67]
Ginseng	2[73,74]	Warfarin	1 crossover 1 parallel RCT	Healthy adults	Australia/New Zealand and North America	Mixed – Caucasians Asians and Hispanics	Moderate	No
Hawthorne	1[75]	Digoxin	Crossover RCT	Healthy non-smoking adults	North America	NR	Moderate	Unclear
Magnesium (oral)	0	-	-	-	-	-	-	-
Niacin (≤ 250 mg/d)	0	-	-	-	-	-	-	-
omega-3 fatty acids fatty acids/Fish oils	3[35,95,96]	Rosuvastatin, atorvastatin, and simvastatin	Crossover RCT	Healthy adults	North America	Mostly Caucasians, or mostly Hispanics	Moderate	Yes
Red yeast rice extract	0	-	-	-	-	-	-	-
Resveratrol	0	-	-	-	-	-	-	-
Vitamin A		-	-	-	-	-	-	-
Vitamin D with Calcium	0	-	-	-	-	-	-	-
Vitamin D	0	-	-	-	-	-	-	-

Dietary supplement	N of studies included for KQ 4	Cardiovascular drug(s)	Study design(s)	Participants	Study region	Race/Ethnicity	Overall risk of bias for pharmacokinetic outcomes	Industry funding or potential for conflict of interest
without Calcium								
Vitamin E	0	-	-	-	-	-	-	-
Vitamin K	0	-	-	-	-	-	-	-

Abbreviations: NR = not reported; RCT = randomized controlled trial.

Table 49. Risk of bias of studies

All RCTs (N=11)			
Items	Yes	No	Unclear
Adequate generation of allocation sequence	18%	0%	82%
Allocation concealment	0%	0%	100%
Comparability of groups	91%	0%	9%
Purity of supplement	82%	18%	0%
Blinding of allocated intervention	100%	0%	0%
Adequately addressed missing data	55%	9%	36%
Freedom from potential for conflict of interest	36%	45%	18%
Crossover RCTs (N=10)			
Suitability of crossover design for the study condition	100%	0%	0%
Free of carryover effect	100%	0%	0%
Appropriateness of statistical analysis for crossover design	20%	10%	70%
Comparability of groups between periods 1 and 2	0%	0%	100%
Freedom from bias introduced by dropouts	60%	10%	20%

Abbreviations: RCTs = randomized controlled trials.

Echinacea

A randomized open-label crossover trial investigated exposure and pharmacokinetic 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 two weeks, with a single dose of 25 mg warfarin versus warfarin alone.[63] Both S- and R-warfarin enantiomer specific pharmacokinetic parameters were reported, including AUC_{∞}, C_{max} , half-life, clearance and volume of distribution in 12 healthy males of known CYP2C9 and VKORC1 genotype. The 90 percent CIs for the geometric means of all parameters were all within the bioequivalence range of 80 percent to 125 percent. Although not considered to be clinically significant, a statistically significant decrease in S-warfarin $AUC_{\infty,}$ and increases in drug clearance and apparent volume of distribution were noted with coadministration of the supplement (GMRs [90 percent CIs]: 0.92 [0.85, 0.99]; 1.09 [1.01, 1.18]; and 1.09 [1.03, 1.18] respectively).[63] Strength of evidence is summarized in Table 50.

Table 50. Strength of evidence for warfarin with or without *Echinacea*

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
AUC_{∞}, C_{max} , half-life, and clearance for S- and R-warfarin	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions

Abbreviations: AUC_{∞} = area under the concentration curve extrapolated to infinity; C_{max}= maximum concentration; NA = not applicable.

Garlic

An open-label, randomized, crossover trial of 7.4 mg per day of allicin pre-treatment for two weeks plus a single dose of 25 mg warfarin versus a single dose of warfarin alone was conducted in 16 healthy males.[65] Four participants were lost to followup or withdrew, so only 12 participants completed the study. GMRs of S- and R-warfarin AUC_{∞}, C_{max} , half-life and clearance for S- and R-warfarin were not statistically different; however, the 90% CIs went beyond the 0.8 to 1.25 clinical bioequivalence boundaries for Cmax of both S- and R-warfarin (GMR [90 percent CI] S-warfarin 1.06 [0.77, 1.47]; R-warfarin 1.02 [0.8, 1.4]).[65] Strength of evidence is summarized in Table 51.

Table 51. Strength of evidence for warfarin with or without garlic

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
AUC_{∞}, half-life, and clearance for S- and R-warfarin	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions
C_{max} S- and R-warfarin	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Clinically significant interactions could not be ruled out in either direction

Abbreviations: AUC_{∞} = area under the concentration curve extrapolated to infinity; C_{max}= maximum concentration; NA = not applicable.

Ginkgo biloba

Three studies examined pharmacokinetic interaction of *Ginkgo biloba* and specific cardiovascular drugs.[67,71,99] All three studies were randomized crossover trials in healthy adults.

In a study of young healthy Korean males, single doses of ticlopidine (250 mg) were coadminstered with *G. biloba* (80 mg), or ticlopidine were administered alone. [71] GMRs of AUC_{∞} and C_{max} of ticlopidine were not statistically different from unity, and were clinically nonsignificant (Appendix C). Ticlopidine mean half-life and median t_{max} were not significantly affected by coadministration with *G. biloba*.[71]

In eight healthy adults, digoxin mean AUC_{∞}, C_{max}, clearance, elimination rate constant, t_{max} and half-life showed statistically nonsignificant changes between 7 day treatment with 240 mg/day of *G. biloba* plus a single dose of 0.5 mg of oral digoxin on the last day, and a single dose of 0.5 mg digoxin alone.[99] GMRs were not reported, nor could we calculate them in the absence of individual patient data; therefore, we could not rule out clinical interaction based on the predefined GMR margins of bioequivalence.[99]

In 12 healthy male participants, no statistically or clinically significant differences were noted in geometric mean ratios of AUC_{∞}, Cmax, half-life, clearance and volume of distribution of warfarin when administered as a 25 mg single dose with 7 day pre-treatment with *Ginkgo biloba* (12 g/day) or alone. [67] However, there was significant reduction in t_{max} of both S- and R-warfarin enantiomers (GMR [90 percent CI]: 0.68 [0.63, 0.73]; 0.72 [0.67, 0.77], respectively). Based on the available data by group, we estimated that this decrease amounted to approximately 33 percent and 23 percent decreases in t_{max} arithmetic means for S- and R-warfarin enantiomers respectively. [67]

Strength of evidence is summarized in Table 52.

Table 52. Strength of evidence for ticlopidine with or without *G. biloba*

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Ticlopidine						
AUC_∞, Half-life and C_{max}	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions
Clearance	-	-	-	-	Insufficient	Data not reported
Digoxin						
AUC_∞, C_{max}, half-life, and clearance	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Inconclusive results because type II error could not be excluded
Warfarin						
AUC_∞, C_{max} , half-life, and clearance for S- and R-warfarin	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions

Abbreviations: AUC_∞ = area under the concentration curve extrapolated to infinity; C_{max}= maximum concentration; NA = not applicable.

Ginseng

Interactions between American ginseng (*Panax quinquefolius*, 2 g/day from weeks 2 to 4)and warfarin (5 mg/day for 3 consecutive days of weeks 1 and 4) given over 4 weeks were investigated in a parallel randomized double blind placebo controlled trial in 20 healthy volunteers.[73] Compared with controls administered warfarin alone, a statistically significant reduction in the warfarin AUC was noted when ginseng was coadministered (between group difference in median change from week 4 to week 1 -0.64µg/mL per day [95 percent CI, -1.25, -0.13]).[73] The clinical significance of this finding is unclear because analysis was not based on geometric mean ratios.

A second open-label randomized crossover trial in 12 healthy males of a single dose of 25 mg warfarin coadminstered with a 7 day pretreatment with Korean ginseng (2 capsules 3 times a day, each capsule containing 0.5 g *Panax ginseng* root and 8.93 mg ginsenosides) or alone, found clinically interpretable results.[74], The geometric mean ratios of S- and R-warfarin AUC_∞, Cmax, half-life, clearance and volume of distribution were neither statistically nor clinically different, indicating no interaction. The GMR for t_{max} of both S- and R-warfarins showed statistically nonsignificant results, but the lower and upper bounds of the 90 percent CI crossed the predefined bioequivalence boundaries (S- and R-warfarin t_{max} GMR [90 percent CI]: 1.20 [0.77, 1.62]; 1.11 [0.78, 1.44], respectively).[74]

Strength of evidence is summarized in Table 53.

Table 53. Strength of evidence for warfarin with or without ginseng

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Cmax , half-life, and clearance for S- and R-warfarin	Moderate	Not applicable	Indirect surrogate	Precise	Low	No clinically significant interactions
AUC_{∞}	Moderate	Inconsistent	Indirect surrogate	Imprecise	Insufficient	The evidence of ginseng and warfarin interaction is unclear because with American ginseng, statistically significant reduction in AUC of warfarin was noted, but clinical significance is unclear. Korean ginseng demonstrated no clinically significant interactions

Hawthorne

Pharmacokinetic interactions between hawthorne (*Craetagus oxycantha*) and digoxin were investigated in eight healthy male volunteers in an open-label, randomized crossover trial of digoxin 0.25 mg/day for a 10 day period plus 900 mg/day of extract of hawthorne leaves with flowers standardized to 84.3 mg of oligomeric procyanidins for a 21 day period, versus digoxin alone for ten days.[75] Using a paired analysis, the differences in means of AUC_{∞}, Cmax , t_{max}, half-life, and clearance did not reach statistical significance.

Strength of evidence is summarized in Table 54.

Table 54. Strength of evidence for digoxin with or without hawthorne

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Digoxin AUC_{∞}, Cmax , half-life, and clearance	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** type II error could not be excluded

Abbreviations: AUC_{ss} = steady state area under the concentration curve;NA = not applicable.

Omega-3 Fatty Acids/Fish Oil

Three open-label randomized crossover studies in 24 to 50 healthy adult volunteers investigated interactions between ω-3 fatty acids and various statins.[35,95,96] Each study compared statin (rosuvastatin 40 mg/day, atorvastatin 80mg/day, or simvastatin 80 mg/day) coadministered with 4 g/day of ω-3 fatty acids, with statin alone over a 14 day period. Due to the differences in first pass metabolism between various statins,[155] we did not conduct meta-analysis of outcomes data. No statistically or clinically significant differences were noted for steady state AUC and C_{max} GMRs for rosuvastatin, atorvastatin, 2- hydroxyatorvastatin, and 4-hydroxyatorvastatin. No statistically significant changes were observed in steady state β-hydroxysimvastatin arithmetic means of AUC, C_{max}, t_{max}, clearance and half-life.[35,95,96]

Strength of evidence is summarized in Table 55.

Table 55. Strength of evidence for statins with or without omega-3 fatty acids

Cardiovascular drugs(s) / Harm	Risk of bias	Consistency	Directness	Precision	Grade	Conclusion Treatment effect
Rosuvastatin, atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin AUC_{ss}, Cmax	Moderate	Not applicable	Indirect surrogate	Precise	Low	No clinically significant interactions
Half-life, and clearance of rosuvastatin, atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin Beta-hydroxy-simvastatin AUC_{ss}, Cmax , half-life, and clearance	Moderate	Not applicable	Indirect surrogate	Imprecise	Insufficient	Inconclusive results because type II error could not be excluded

Abbreviations: AUC_{ss} = steady state area under the concentration curve; C_{max}= maximum concentration; NA = not applicable.

Applicability. Evidence of interaction affecting pharmacokinetic outcomes may not translate into altered clinical effectiveness or harms. Evidence originating in healthy young adults is not representative of older patients taking cardiovascular drugs. Metabolism of cardiovascular drugs may differ between the populations studied in these trials and CVD patients.

Summary of Results for Key Question 4

- Eleven randomized controlled trials contributed evidence on pharmacokinetic outcomes.
- No data was available from observational studies.
- All trials were conducted in small numbers of healthy participants.
- Interactions between a dietary supplement and cardiovascular drugs were investigated by comparing pharmacokinetics of the cardiovascular drug when coadministered with a supplement versus the drug alone. Clinical significance of interaction was evaluated using the United States Food and Drug Administration (FDA) guidance. According to the guidance, statistically significant interactions alone could not determine clinical significance of interactions unless the 90 percent confidence intervals of the geometric mean ratios fell well within the default *no effect* boundary of 0.80 to 1.25.
- No studies were found examining pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (less than or equal to 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, vitamin K and a cardiovascular drug.
- A paucity of studies of supplement-drug combinations for which data was available precluded exploration of heterogeneity in terms of pre-identified subgroups such as age and gender. Statistical interaction was not investigated in any pharmacokinetic study.
- No clinically significant interactions were noted when *Echinacea*, ginger, ginkgo biloba were coadministered with warfarin and when *Ginkgo biloba* was coadministered with ticlopidine. The strength of evidence for these finding was graded as low because of single pharmacokinetic studies with moderate risk of bias. Available evidence was insufficient precluding meaningful conclusions about interactions between garlic and warfarin, ginkgo biloba and digoxin, omega-3 fatty acids and simvastatin and hawthorne and digoxin. Interactions between ginseng and warfarin, and ω-3 fatty acids and rosuvastatin or atorvastatin are unclear because for some of the pharmacokinetic outcomes there was low strength of evidence suggesting no clinically relevant interactions but insufficient for others.
- Evidence of pharmacokinetic interactions may not translate into altered clinical effectiveness or harms.
- Evidence originating in healthy young adults may not be applicable to older CVD patients taking cardiovascular drugs due to possible differences in metabolism.

Discussion

Key Findings and Strength of evidence

Billions of dollars are spent annually in the United States on complementary and alternative medicine (CAM) and a large portion of this expenditure is spent directly on dietary supplements (DS).[8] Given the high prevalence of cardiovascular disease and frequency of polypharmacy in this population, the risk of drug-supplement interactions deserves serious consideration primarily to avoid potential harm; either as a result of decreasing clinical effect of drugs, or increased toxicity. A more thorough understanding and knowledge of potential drug-supplement interactions is important to provide specific evidence-based recommendations that do not call for universal avoidance of all dietary supplements in conjunction with pharmaceutical treatments to treat or to prevent cardiovascular disease. Without such precision, recommendations may result in the avoidance of potentially beneficial supplements or more importantly might be more readily ignored, leading to greater likelihood for harm through negative interaction.

This systematic review identifies a considerable knowledge gap regarding the safety of combining DSs with cardiovascular drugs in patients with cardiovascular disease. We sought to identify the direct and indirect evidence for cardiovascular drug-DS interactions and their outcomes, and found 168 records that addressed at least some aspects of this issue. After identifying companion papers and articles with useful data 69 unique studies contributed evidence for synthesis. With few exceptions there is insufficient evidence to draw any strong conclusions on particular interactions between dietary supplements and cardiovascular drugs. In addition to an overall lack of evidence, the studies that were included were often grossly underpowered to adequately assess clinically relevant outcomes. In addition, many of the studies had important methodological limitations or were poorly generalizable to the population of relevance. The strength of the evidence found was frequently compromised by poor allocation concealment and issues related to blinding, study reporting, and potential for conflict of interest.

In order to comment on clinically important sequelae of drug-supplement interactions we identified gradable outcomes of clinical significance based on consultation with key informants and clinical experts (the Technical Expert Panel). These outcomes included mortality, myocardial ischemic events, cerebrovascular events, quality of life, hospitalization, arrhythmia and peripheral vascular disease. Twenty-two randomized controlled trials reported direct evidence of drug-supplement interactions on predetermined gradable clinical outcomes. As noted however, most of the trials were grossly underpowered to demonstrate any real effect, and often were of moderate risk of bias, leading to insufficient grades for strength of evidence. The only exception to the lack of a signal for clinical outcomes came from studies that evaluated two non-gradable outcomes. In one randomized controlled trial (RCT) post-angiography restenosis rates were improved through consumption of 3.2 grams of eicosapentanoic acid taken along with aspirin, dipyridamole, and calcium channel antagonists for a duration of six months.[52] This finding was not supported by a similar but lower quality trial in India.[51] The second non-gradable clinical outcome of note came from a large long-term pragmatic trial in which 19,934 women were randomized to 600 IU of vitamin E plus 100 mg/day of aspirin versus aspirin taken alone for 10 years. In this trial, no significant differences occurred between either group in the composite outcome consisting of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95 [95 percent confidence interval (CI) 0.79, 1.13]).[38]

Anticipating a paucity of evidence describing the influence of cardiovascular drug-DS interaction on meaningful clinical outcomes, indirect evidence was also sought. Gradable intermediate outcomes (with strong epidemiological links to meaningful clinical outcomes) relevant to cardiovascular patients included blood pressure, lipid profile, International Normalized Ratio (INR), metabolic syndrome, change in 10-year Framingham risk profile, and QT prolongation. Fifty-nine studies were identified that addressed intermediate cardiovascular outcomes. Again, these were mostly underpowered studies of highly selected individuals, with considerable risk of study bias attributed to inadequate blinding, and allocation concealment. As a result, the most frequently graded strength of the evidence was "insufficient," with a few outcomes graded as "low."

The inclusion of coenzyme Q10 with statin drugs seems to have no significant effect on any parameter of lipid profile predetermined to be a gradable outcome (high- or low-density lipoprotein-cholesterol (HDL-C or LDL-C), triglycerides, and non-HDL-C). Only one study explored the effect of coenzyme Q10 with fenofibrate on cholesterol levels and hypertension.[60] Although the trial failed to demonstrate any interaction, the RCT was underpowered to find any significant results. A similar situation applies to a small sized RCT comparing the inclusion of coenzyme Q10 with an angiotensin-converting enzyme (ACE) inhibitor on ejection fraction among patients with heart failure.[54] One RCT of 60 patients with coronary artery disease (CAD) suggests that the combination of 4 grams of garlic oil taken with nitrates has a positive effect on HDL-C levels compared with nitrates taken alone.[58] This result likely does not reflect an interaction between the two agents so much as an isolated effect of garlic since nitrates are not known to affect HDL-C.

In this review we found some of the richest evidence on the combination of omega-3 fatty acids with cardiovascular drugs. Out of a total of 23 RCTs that measured both gradable and non-gradable surrogate outcomes, 12 assessed the combination of omega-3 fatty acids with statins (atorvastatin, simvastatin, lovastatin). From pooled results of six trials[40,44,53,91,139,141] and five trials[40,44,53,91,139] respectively, no beneficial or harmful effect on HDL-C or LDL-C was found (low strength of evidence). While results were inconclusive, there appeared to be an indication of improvement in patient profiles of total cholesterol and triglycerides from taking omega-3 fatty acids with statins, which might not have attained statistical significance due to low power of evidence despite meta-analysis. Results regarding non-HDL-C and total cholesterol/HDL-C ratio were inconsistent across studies. In addition, there is evidence of low strength from one parallel arm RCT[93] and one cross-over RCT[36] that systolic blood pressure is improved when statins are taken with omega-3 fatty acids.

The addition of omega-3 fatty acids to the combination of aspirin and a calcium channel blocker with or without dipyridamole appears to reduce triglyceride levels but not HDL-C or LDL-C.[51,52] It is likely that the triglyceride drop reflects the activity of omega-3 fatty acids alone rather than a synergistic or additive effect in combination with antiplatelet agents and calcium channel blockers. The combination of omega-3 fatty acids with ACE-inhibitors appears to have no significant effect on blood pressure and also demonstrates evidence consistent with omega-3 fatty acids having an independent benefit for triglyceride.[140] In patients with biopsy proven IgA nephropathy, a single 6-month duration RCT found that the inclusion of omega-3 fatty acids with renin–angiotensin system blockers reduced the degree of proteinuria in comparison to the cardiovascular drugs.[79] In the only trial that assessed for pharmacodynamic interaction between warfarin and omega-3 fatty acids, there was no evidence of differences in coagulation based on

INR, however this was a very small study (n=11) and neither data nor confidence intervals were provided to evaluate this further.[55]

In a single RCT conducted in an elderly population (at least 65 years), platelet adhesion, (a non-gradable outcome) decreased significantly through concomitant use of vitamin E with aspirin.[49] In another RCT, supplementation with vitamin E in patients taking nifedipine led to a significant beneficial change in LDL-C (low strength of evidence). Again, we suspect this is an isolated effect of the dietary supplement rather than reflective of an interaction between vitamin E and nifedipine itself. Finally, supplementation with low doses of vitamin K (0.1-0.15 mg/day) in patients anticoagulated with warfarin or coumarin derivatives appeared to provide stability to INR titration and increase time within the therapeutic range based on two studies.[39,41] The stabilizing effect of vitamin K was independent of pre-specified subgroup status including gender (male/female) and age (younger or older than 65 years) in one of the studies where this was evaluated.[143] However, a particular limitation of these studies, is that one trial only involved Caucasian participants,[39] whereas in the other ethnicity was not reported.[41]

Outcomes related to harms associated with drug interactions between dietary supplement and cardiovascular drugs were reported in 57 unique studies, most of which were considered to be at moderate risk of bias. Gradable harms outcomes included serious adverse events, withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity. Of the studies that assessed for harms outcomes, reported adverse events ranged from mild (e.g., flatulence) to severe (e.g., leucopenia, major bleeding) but for all the gradable outcomes for which evidence was found, the strength of evidence was judged insufficient primarily due to a lack of power contributing to the possibility of a type II error. Furthermore, very few studies systematically screened for pre-defined adverse events. With respect to non-gradable harms outcomes, results from one RCT indicated that coenzyme Q10 (200mg/day) may be efficacious in treating myalgias associated with statin therapy.[62] In another RCT a significantly elevated fasting blood glucose occurred in the omega-3 fatty acids plus statins group versus the statins alone group.[40]

Finally, evidence for interactions between cardiovascular drugs and dietary supplements was sought from studies that assessed for direct changes in drug pharmacokinetics when combined with any of the supplements in question. Gradable pharmacokinetic outcomes included area under the concentration curve (AUC), maximum concentration (Cmax), clearance, and drug half-life. Eleven studies contributed pharmacokinetic evidence, all of which had moderate risk of bias. We found no clear evidence of drug-supplement interaction. Evidence was either insufficient to rule in or out clinically important pharmacokinetic interactions or showed no clinically important interactions. No studies examined pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (up to 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D (with or without calcium supplementation), vitamin E, and vitamin K with any of the cardiovascular drugs. The following findings were graded as having low strength of evidence. Coadministration of *Echinacea* with warfarin may reduce the AUC of warfarin with statistical significance, but warfarin was still within the range of clinical bioequivalence. Supplementation with *Gingko biloba*, garlic, *Panax ginseng* or ginger extracts in patients taking warfarin does not appear to change measurably any clinically relevant warfarin pharmacokinetics. American ginseng demonstrated a shift in AUC of warfarin, however the clinical significance of this shift is not clear. No pharmacokinetic interaction between *Ginkgo biloba* and ticlopidine was identified. Finally, evidence of no significant interaction (graded as insufficient to low strength of evidence) was obtained from three trials investigating the combination of omega-3 fatty acids and statins (rosuvastatin, simvastatin, and atorvastatin).

Clinical Context and applicability of evidence for decision-making

Most of the studies included in this review that measured clinical outcomes provided inconclusive findings primarily due to limitations in study design (underpowered) and risk of bias (allocation concealment, randomization). The weakness of the evidence itself and its clinical relevance is compounded by a general lack of evidence on dietary supplement-cardiovascular drug interactions in the literature overall. Ultimately this limited information makes it impossible to translate our findings into clear advice and tools for clinical decision-making. Without an adequate evidence-base from the literature, variability in effects across clinically important subgroups (i.e., stratified by age, ethnicity, gender or health status) could not be assessed. The evidence on clinical outcomes is generally inconclusive and applicability of inconclusivity is meaningless. The trials were generally efficacy studies in highly selected cardiovascular populations lasting for a short period of observation, along with some single-dose studies in healthy individuals. As such we are unfortunately left with the unsatisfying yet fundamentally important call for more research with focused consideration and evaluation of dietary supplement-drug interaction in both clinical and observational studies.

The limit of good clinical outcomes data on which to base recommendations, leads to predicting hypothetical interactions wherein indirect evidence is the most prevalent albeit least reliable information source. The study of pharmacokinetic outcomes and changes in these outcomes are best suited to address this area. However, evidence of pharmacokinetic alterations due to interaction may not translate into altered clinical effectiveness or harms even if well characterized. Pharmacokinetic studies are generally conducted in healthy volunteers and as such the evidence may not reflect the compromised physiologic processes of the elderly and the diseased.

With relatively limited findings given its scope, the value in this review is that it points out the need for further consideration of the question of interactions and comparative effectiveness for dietary supplements when considered in conjunction with cardiovascular drugs. Aside from further research in the area of dietary supplement-drug interactions, better documentation of supplement use by cardiovascular patients is critical to define better where interactions may result in clinically relevant sequelae.

Review of other Systematic Reviews

Recent systematic reviews related to the topic of dietary supplement-drug interactions have been published but do not address the same scope, are not comprehensive, or involve different populations of interest. Mills and colleagues published a systematic review in 2005 focused on the effect of natural health products on the metabolism of conventional medicines.[107] Their focus was not cardiovascular drugs or patients in particular and describes the evidence for dietary supplement–drug interactions for any conventional drug category. The evidence in the review is compiled from 41 pharmacokinetic studies. Mills' review identified a lack of evidence supporting any interaction between coenzyme Q10 and warfarin, *Gingko biloba* and warfarin, and *G. biloba* and digoxin. These finding are consistent with those in our review. Both reviews identified a shift in AUC of INR when American ginseng was taken in conjunction with warfarin; however, we question the clinical significance of this finding.

Also in 2005, Desai and colleagues published a review of interactions between dietary supplements and antiplatelet agents.[156] The review included both clinical trials and case reports.

With respect to the dietary supplements considered in our review, Desai concluded that omega-3 fatty acids given in conjunction with aspirin led to comparatively significant reductions in ADP induced platelet aggregation, blood platelet count, thromboxane B2, and restenosis rates, and also led to a prolongation in bleeding time. The addition of vitamin E to aspirin led to comparatively significant reductions in platelet adhesion, ischemic stroke, recurrent episodes of TIA, and prolonged dental bleeding time. Unlike our review, the Desai review did not attempt to grade the outcomes extracted and while findings are largely consistent, the graded evaluation we completed did not allow the same confidence in conclusions regarding the interactions from these agents based on the directness and overall strength of evidence.

In one of the more relevant reviews published by Izzo and colleagues in 2005, Pubmed was searched to Feb 2003 for drug interactions with cardiovascular drugs and included evidence from case reports (n=43) and clinical trials (n=8).[108] This review did not systematically evaluate the quality of evidence, nor was there any grading for the strength of their recommendations. For example, drug interactions between *Gingko*, garlic, and ginseng were identified based on few or single case reports while our review found low or insufficient evidence of any interaction from trials of both direct and indirect evidence. In a 2009 review by Izzo and Ernst, the evidence was again extracted from case reports (n=41) and clinical studies (n=17) but did not focus on drug interactions with cardiovascular drugs.[113] None of their 17 clinical studies provided evidence for dietary supplement-cardiovascular drugs within the scope of our review.

Skalli and colleagues published a review in 2007, wherein the majority of evidence for supplement-drug interactions was generated from case reports, and there was no focus on cardiovascular drugs.[157] The authors identified interactions between warfarin and all of the following: ginger; *Ginkgo*; garlic; and ginseng. This was again primarily from single case reports or case series. Our review found no evidence of such interactions from clinical trials providing direct or indirect evidence (insufficient or low levels of evidence). The reviewers also suggest that *Ginkgo biloba* can counteract the effect of thiazide diuretics by increasing blood pressure (based on case report data). We found insufficient evidence to support this claim.

The most recent systematic review on dietary supplement-drug interactions was published in 2010 by Kennedy and Seely, and examined herb-drug interactions identified from trials whereby herbal impact on hepatic metabolism via cytochrome P450 isoenzymes could be ascertained.[115] In this review, the target population was not specific to cardiovascular patients or drugs, and the review evaluated indirect evidence limited to herbs metabolized via the cytochrome P450 system. While the information from this review provides an evaluation of primarily indirect data regarding possible pharmacokinetic interactions, the results do not overlap meaningfully with the findings from our review which addresses only direct evidence for pharmacokinetic interaction.

Limitations of the Review process

There were a number of pre-identified limitations to the review process that constrained the scope of the review to a manageable yet relevant synthesis overall. The most obvious limitation was restricting the number of dietary supplements considered to the sixteen that were included. The process to decide on this subset of supplements was based on surveys from the literature regarding usage, and a consensus process of selection that included the Technical Experts Panel (TEP) members. Limiting the review to the most commonly used and relevant dietary supplements in the context of cardiovascular disease allowed us to maintain as broad an approach as possible in exploring both direct and indirect evidence for interactions with cardiovascular drugs.

An additional limitation in this review comes from not including all possible indirect evidence that addressed the potential for pharmacodynamic or pharmacokinetic dietary supplement-drug interactions. We limited our review to direct evidence of pharmacokinetic interactions by assessing for changes in parameters of drug clearance in humans when a dietary supplement was coadministered with cardiovascular drug(s). This approach omits an exploration of possible hypothetical interactions derived from assessing alterations in probe drugs or other surrogates that speak to changes in enzymes involved in drug metabolism.[115] In addition, potentially useful additional evidence could come from signals related to changes in drug transport proteins that may lead to localized shifts in drug concentration as well as altered rates of drug clearance. For instance, P-glycoprotein and other membrane bound drug efflux transporters are found in numerous tissues and biological filters including the intestines, liver, kidneys, and blood brain barrier.[158] Like the cytochrome P450 enzymes, P-glycoprotein is susceptible to inhibition and induction.[115,159] The evidence of drug transport and more indirect evidence of pharmacokinetic alteration was not considered in our review so as to best allocate resources to the most direct, clinically relevant, and ultimately gradable evidence.

The review process did not allow the inclusion of combinations of multiple dietary supplements with cardiovascular drugs, in order to make causal inference possible. This limitation has negative implications for external validity due to the fact that the way in which people self-prescribe likely includes combinations of numerous dietary supplements with cardiovascular drugs. Somewhat related, excluding studies where proportions of populations taking cardiovascular drugs was less than 80 percent resulted in missing data from individuals from studies in over 102 otherwise evaluable reports. This exclusion criterion, which is important to ensure the rigor of the review process and to prevent inaccurate analyses, still resulted in omission of data from a number of otherwise relevant studies.

A further limitation of the review process employed is the emphasis on the environment for cardiovascular treatment relevant to North America. This emphasis comes from limiting the drugs in question to those used in North America, thereby leaving out drugs from other jurisdictions, and the data obtainable from additional, international sources of research. Finally, we only included publications where English or German was the language of publication.

Conclusions

With limited data to give a clear signal on dietary supplement-drug interactions, it is difficult to provide clear guidance to clinicians and patients regarding advice on the choices to be made in this area. Drug interactions that may result in positive or negative outcomes likely exist, and occur, but the evidence available and identified in this review is insufficient to provide clinical recommendations with confidence. The strength of evidence that we did find was low at best, with poor grading resulting from risks of bias, and small sample sizes greatly increasing the risk of type II error. In addition, the etiology for results are difficult to determine effectively as changes in a measured outcome could be due to either a real therapeutic effect that comes from the dietary supplement itself or is due to an interaction between the drug and the supplement in question.

With these caveats in mind, and the fact that the most reliable data comes from indirect intermediate outcomes associated with clinical results, the following is a summary of the clearer signals from the evidence reviewed:

- Coenzyme Q10 (100 to 200 mg per day) taken in combination with statin drugs likely does not interfere with efficacy and possibly provides benefit for statin induced myalgia.

- Omega-3 fatty acids (2 to 4 grams per day) from fish and/or supplements likely do not interfere with the efficacy of statin therapy or calcium channel blockers in presence of antiplatelet agents, and may provide independent benefit in resolving hypertriglyceridemia.
- Vitamin K (0.1-0.15 mg/day) may help to stabilize INR when given with warfarin.
- Garlic (4-10 grams/day) may not interact negatively with nitrates and warfarin and may confer independent benefit in improving HDL and total cholesterol.

Our confidence, however, in the validity and reproducibility of these findings is low.

Limitations of the Evidence Base

The literature search applied in this review was comprehensive in exploring multiple sources for human level evidence, yet despite this, there was a decided lack of relevant evidence available. The available literature comes primarily from small trials of highly selected patients and subjects, that limits external validity. While there is data from which we can derive a sense of lack of interaction in many cases, the small size of the trials makes it impossible to ascertain the potential for a true clinical interaction if the trials had been adequately powered to see evidence of harm or interaction.

The internal validity of most trials was compromised due to flawed designs, lack of appropriate allocation concealment, and risk of bias. There are very few examples where a formal assessment of statistical interaction was completed. One notable exception comes from a trial whereby a decrease in triglyceride levels due to combination of omega-3 fatty acids with niacin led to twice the additive effect of the each therapy alone, indicating the possibility for synergy through concurrent use.[80] In the absence of corroborating pharmacokinetic evidence or assessment for interaction, it is often impossible to determine whether a difference in outcome is due to true pharmacological interaction, or due to more independent combined, or possibly counteracting therapeutic effects. As the goal of this synthesis work was not to complete a comparative effectiveness analysis of dietary supplement versus drugs for cardiovascular disease we did not formally assess for these comparative therapeutic effects.

In terms of the pharmacokinetic evidence assessing Key Question 4, most of the research was conducted on healthy young adults. Thus this level of evidence may not be applicable to older patients taking cardiovascular drugs due to possible differences in metabolism and the existence of comorbidities.

One of the principal limitations of the trials we evaluated was the fact that they were very small and thus susceptible to type II error. A slimly reassuring corollary to this is that if there was a real and dramatic clinical impact due to an interaction then some clinical effect would likely have shown up despite being underpowered for smaller effect sizes. Of more concern are possible interactions that could arise through polypharmacy of prescription drugs, a situation all too common, in particular for the elderly population.

Future Research Recommendations

Given the important gap in research in the area of dietary supplement-drug interactions there should be a strategic investment in building research capacity to address relevant questions. With the continued burden of cardiovascular disease in North America, this issue is not going to go away and will likely increase in magnitude if the public continues to increase their use of dietary supplements for self-care.

A focused research strategy regarding dietary supplement-cardiovascular drugs could consider a number of recommendations arising from this review:

1) Future trials should focus on meaningful clinical outcomes, be appropriately powered and rigorously conducted and reported, and provide precise measurements of both clinical outcomes and harms outcomes;

2) Trials should be representative of the population taking cardiovascular drugs in terms of comorbidities, setting, and racial distribution. They should also consider subgroup analysis for age, gender, race, comorbidities (e.g. liver or renal compromise), and genotypic polymorphisms of the cytochrome P450 enzyme;

3) Pharmacokinetic studies should follow Food and Drug Administration guidance for conduct and reporting so comparison between trials can be carried out more effectively;

4) Pharmacokinetic studies should present interpretation of statistically significant outcomes in terms of clinical significance;

5) Clinical trials and observational studies that explore the effect of cardiovascular drugs should assess the use of dietary supplements, and include this in the reporting of results;

6) Phase I trials of cardiovascular drugs should include older populations, and if possible a pharmacokinetic assessment that includes dietary supplement usage

7) Future studies should examine vulnerable subgroups such as the elderly, those with compromised renal and liver functions, and patients with multiple comorbidities;

8) Where possible, comparative effectiveness studies should include a statistical analysis for interactions, and the trials should be powered accordingly; and

9) Until well powered experimental studies are conducted to examine dietary supplement-drug coadministration, evidence from well-conducted prospective observational studies should be sought. Electronic health record linkages between databases of dietary supplement use and cardiovascular drug prescription may also add to the equipoise that has been so insufficiently addressed.

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. What is complementary and alternative medicine?[website]. National Center for Complementary and Alternative Medicine. http://nccam.nih.gov/health/whatiscam/. Last Accessed: 20-6-2011
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. [Review] [88 refs]. 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. [Review] [125 refs]. 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. [Review] [1359 refs]. 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.] Draft posted Oct. 2007. http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf. Last Accessed: 14-7-2011
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 8 (1) , 2008 Article Number: 4 Date of Publication: 08 Feb 2008 2008;(1):
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 and Raina, P. McMaster Quality Assessment Scale of Harms (McHarm) for primary studies: Manual for use of the McHarm [website]. http://hiru.mcmaster.ca/epc/mcharm.pdf. Last Accessed: 22-12-2010
26. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009 Oct;62(10):1013-20. [PMID: 19230606].
27. 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].
28. U.S. Food and Drug Administration. What is a Serious Adverse Event?[website]. http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm. Last Accessed: 7-8-2011
29. Atkins D, Chang S, Gartlehner G, et al. Assessing applicability when comparing medical interventions: Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2011 Apr 2. [PMID: 21463926].
30. Approved drug products with therapeutic equivalence evaluations. Rockville (MD): U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Office of Pharmaceutical Science. Office of Generic Drugs.; 2011. 31st ed.
31. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986 Sep;7(3):177-88. [PMID: 3802833].
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 Apr 6. [PMID: 21477993].
33. 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].
34. 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].
35. 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].
36. 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].
37. 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].
38. 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].
39. Rombouts EK, Rosendaal FR, van der Meer FJ. Daily vitamin K supplementation improves anticoagulant stability. J Thromb Haemost 2007 Oct;5(10):2043-8. [PMID: 17666020].
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, nseth 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. Subramanian S, Kalyanaraman B, Migrino RQ. Mitochondrially targeted antioxidants for the treatment of cardiovascular diseases. [Review] [133 refs]. Recent Patents Cardiovasc Drug Discov 2010 Jan 1;5(1):54-65. [PMID: 19807685].
58. 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].
59. 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].
60. 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].
61. 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].
62. 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].
63. 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].
64. 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].
65. 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].
66. 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].
67. 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].
68. 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].
69. 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].
70. 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].

71. 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].
72. 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].
73. 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].
74. 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].
75. 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].
76. 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].
77. 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.
78. 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].
79. 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].
80. 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.
81. 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].
82. 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].
83. 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].
84. 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].
85. 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].
86. 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].
87. 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].
88. 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].
89. 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].
90. 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].
91. 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].
92. 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].
93. 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.
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. 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].
96. 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].
97. 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].
98. 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].
99. 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].
100. 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].
101. Leading causes of death[website]. Centers for Disease Control and Prevention. http://www.cdc.gov/nchs/fastats/lcod.htmLast Accessed: 20-6-2011
102. Leading causes of death[website]. Statistics Canada. http://www40.statcan.gc.ca/l01/cst01/hlth36a-eng.htmLast Accessed: 20-6-2011
103. Trifiro G, Spina E. Age-related Changes in Pharmacodynamics: Focus on Drugs Acting on Central Nervous and Cardiovascular Systems. Curr Drug Metab 2011 Apr 18. [PMID: 21495972].
104. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem 2010;17(6):571-84. [PMID: 20015034].
105. Ramsay NA, Kenny MW, Davies G, et al. Complimentary and alternative medicine use among patients starting warfarin. Br J Haematol 2005 Sep;130(5):777-80. [PMID: 16115136].
106. Coxeter PD, McLachlan AJ, Duke CC, et al. Herb-drug interactions: an evidence based approach. Curr Med Chem 2004 Jun;11(11):1513-25. [PMID: 15180581].
107. Mills E, Wu P, Johnston BC, et al. Natural health product-drug interactions: A systematic review of clinical trials. Ther Drug Monit 2005;27(5):549-57.
108. Izzo AA, Di Carlo G, Borrelli F, et al. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. [Review] [81 refs]. Int J Cardiol 2005 Jan;98(1):1-14. [PMID: 15676159].
109. Mas E, Mori TA. Coenzyme Q(10) and statin myalgia: what is the evidence? Curr Atheroscler Rep 2010 Nov;12(6):407-13. [PMID: 20725809].
110. Whayne TF, Jr. Statin Myopathy: Significant Problem With Minimal Awareness by Clinicians and no Emphasis by Clinical Investigators. Angiology 2011 Jul;62(5):415-21. [PMID: 21421631].
111. Mannel M. Drug interactions with St John's wort : mechanisms and clinical implications. Drug Saf 2004;27(11):773-97. [PMID: 15350151].
112. Caccia S, Gobbi M. St. John's wort components and the brain: uptake, concentrations reached and the mechanisms underlying pharmacological effects. Curr Drug Metab 2009 Nov;10(9):1055-65. [PMID: 20214594].
113. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. [Review] [189 refs]. Drugs 2009;69(13):1777-98. [PMID: 19719333].
114. Flattery M. Herbal therapies and cardiac side effects. Prog Cardiovasc Nurs 2008;23(4):187-90. [PMID: 19067984].
115. Kennedy DA, Seely D. Clinically based evidence of drugherb interactions: A systematic review. Expert Opin Drug Saf 2010;9(1):79-124. [PMID: 20021292].
116. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009 Aug 18;151(4):264-9, W64. [PMID: 19622511].
117. Ahlbom A, Alfredsson L. Interaction: A word with two meanings creates confusion. Eur J Epidemiol 2005;20(7):563-4. [PMID: 16119427].
118. Sampson M, McGowan J, Cogo E, et al. An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009 Sep;62(9):944-52. [PMID: 19230612].

119. Reference Manager 12 [computer program]. Thomson Reuters. 2011.
120. DistillerSR [computer program]. 2011.
121. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. www.cochrane-handbook.org.
122. Struijk-Mulder MC, Ettema HB, Verheyen CC, et al. Comparing consensus guidelines on thromboprophylaxis in orthopedic surgery. [Review] [31 refs]. J Thromb Haemost 2010 Apr;8(4):678-83. [PMID: 20040041].
123. 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].
124. Peters JL, Sutton AJ, Jones DR, et al. Assessing publication bias in meta-analyses in the presence of between-study heterogeneity. Journal of the Royal Statistical Society: Series A (Statistics in Society) 2010;173(3):575-91.
125. 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].
126. Rowland M, Tozer TN. Absorption and disposition kinetics. In: 3rd ed Philadelphia, PA: Lippincott Williams & Wilkins; 1995. p. 11-52.
127. Lazzarin N, Vaquero E, Exacoustos C, et al. Low-dose aspirin and omega-3 fatty acids improve uterine artery blood flow velocity in women with recurrent miscarriage due to impaired uterine perfusion. Fertil Steril 2009 Jul;92(1):296-300. [PMID: 18692841].
128. Ghatak A, Brar MJ, Agarwal A, et al. Oxy free radical system in heart failure and therapeutic role of oral vitamin E. Int J Cardiol 1996 Dec 6;57(2):119-27. [PMID: 9013263].
129. Eritsland J, Seljeflot I, Arnesen H, et al. Effect of long-term, moderate-dose supplementation with omega-3 fatty acids on monocyte procoagulant activity and release of interleukin-6 in patients with coronary artery disease. Thromb Res 1995 Feb 15;77(4):337-46. [PMID: 7740525].
130. Chan DC, Watts GF, Barrett PH, et al. Mechanism of action of a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor on apolipoprotein B-100 kinetics in visceral obesity. J Clin Endocrinol Metab 2002 May;87(5):2283-9. [PMID: 11994377].
131. Jonkers IJ, Smelt AH, Princen HM, et al. Fish oil increases bile acid synthesis in male patients with hypertriglyceridemia. J Nutr 2006 Apr;136(4):987-91. [PMID: 16549462].
132. Fan L, Tao GY, Wang G, et al. Effects of Ginkgo biloba extract ingestion on the pharmacokinetics of talinolol in healthy Chinese volunteers. Ann Pharmacother 2009 May;43(5):944-9. [PMID: 19401473].
133. Ratanabanangkoon P, Guzman H, Almarsson O, et al. A high-throughput approach towards a novel formulation of fenofibrate in omega-3 oil. Eur J Pharm Sci 2008 Apr 23;33(4-5):351-60. [PMID: 18313905].
134. Bargossi AM, Grossi G, Fiorella PL, et al. Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors. Mol Aspects Med 1994;15 Suppl:s187-s193 . [PMID: 7752830].
135. Lu WJ, Huang JD, Lai ML. The effects of ergoloid mesylates and ginkgo biloba on the pharmacokinetics of ticlopidine. J Clin Pharmacol 2006 Jun;46(6):628-34. [PMID: 16707409].
136. Lankin VZ, Tikhaze AK, Kukharchuk VV, et al. Antioxidants decreases the intensification of low density lipoprotein in vivo peroxidation during therapy with statins. Mol Cell Biochem 2003 Jul;249(1-2):129-40. [PMID: 12956408].
137. Sharma M, Ansari MT, Abou-Setta AM, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. [Review] [51 refs]. Ann Intern Med 2009 Nov 3;151(9):622-30. [PMID: 19884623].
138. Rombouts EK, Rosendaal FR, van der Meer FJ. Influence of dietary vitamin K intake on subtherapeutic oral anticoagulant therapy. Br J Haematol 2010 May;149(4):598-605. [PMID: 20151978].
139. Meyer BJ, Hammervold T, Rustan AC, et al. Dose-dependent effects of docosahexaenoic acid supplementation on blood lipids in statin-treated hyperlipidaemic subjects. Lipids 2007 Mar;42(2):109-15. [PMID: 17393216].
140. Howe PR, Lungershausen YK, Cobiac L, et al. Effect of sodium restriction and fish oil supplementation on BP and thrombotic risk factors in patients treated with ACE inhibitors. J Hum Hypertens 1994 Jan;8(1):43-9. [PMID: 8151606].
141. Davidson MH, Macariola-Coad JR, McDonald AM, et al. Separate and joint effects of marine oil and simvastatin in patients with combined hyperlipidemia. Am J Cardiol 1997 Sep 15;80(6):797-8. [PMID: 9315596].
142. Lungershausen YK, Howe PR. Improved detection of a blood pressure response to dietary intervention with 24-hour ambulatory monitoring. Am J Hypertens 1994 Dec;7(12):1115-7. [PMID: 7702808].
143. Maki KC, Dicklin MR, Davidson MH, et al. Baseline lipoprotein lipids and low-density lipoprotein cholesterol response to prescription omega-3 acid ethyl ester added to Simvastatin therapy. Am J Cardiol 2010 May 15;105(10):1409-12. [PMID: 20451686].
144. Chan DC, Watts GF, Barrett PHR, et al. Effect of atorvastatin and fish oil on plasma high sensitive c-reactive protein, interleukin-6 and tumor necrosis factor-alpha levels in obese subjects. Atherosclerosis 2002;3(2):87
145. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular

disease and cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294(1):56-65.
146. Chan DC, Watts GF, Nguyen MN, et al. Factorial study of the effect of n-3 fatty acid supplementation and atorvastatin on the kinetics of HDL apolipoproteins A-I and A-II in men with abdominal obesity. Am J Clin Nutr 2006 Jul;84(1):37-43. [PMID: 16825679].
147. Chan DC, Watts GF, Mori TA, et al. Randomized controlled trial of the effect of n-3 fatty acid supplementation on the metabolism of apolipoprotein B-100 and chylomicron remnants in men with visceral obesity. Am J Clin Nutr 2003 Feb;77(2):300-7. [PMID: 12540386].
148. Chan DC, Nguyen MN, Watts GF, et al. Effects of atorvastatin and n-3 fatty acid supplementation on VLDL apolipoprotein C-III kinetics in men with abdominal obesity. Am J Clin Nutr 2010 Apr;91(4):900-6. [PMID: 20181806].
149. Chan DC, Watts GF, Barrett PH, et al. Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity. Clin Chem 2002 Jun;48(6 Pt 1):877-83. [PMID: 12029003].
150. Nordøy A, Bonaa KH, Nilsen H, et al. Effects of Simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med 1998;243(2):163-70.
151. Nordøy A, Hansen JB, Brox J, et al. Effects of atorvastatin and omega-3 fatty acids on LDL subfractions and postprandial hyperlipemia in patients with combined hyperlipemia. Nutrition, metabolism, and cardiovascular diseases : NMCD 2001;11(1):7-16. [PMID: 11383326].
152. Bays HE, Maki KC, Doyle RT, et al. The effect of prescription omega-3 fatty acids on body weight after 8 to 16 weeks of treatment for very high triglyceride levels. Postgrad Med 2009 Sep;121(5):145-50. [PMID: 19820283].
153. Budoff M. Aged garlic extract retards progression of coronary artery calcification. J Nutr 2006 Mar;136(3 Suppl):741S-4S. [PMID: 16484554].
154. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circ Cardiovasc Qual Outcomes 2002 Dec 17;106(25):3143-421. [PMID: 12485966].
155. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. Pharmacol Ther 2006 Oct;112(1):71-105. [PMID: 16714062].
156. Desai D, Hasan A, Wesley R, et al. Effects of dietary supplements on aspirin and other antiplatelet agents: An evidence-based approach. Thromb Res 2005;117(1-2):87-101.
157. Skalli S, Zaid A, Soulaymani R. Drug interactions with herbal medicines. Ther Drug Monit 2007 Dec;29(6):679-86. [PMID: 18043467].
158. Glaeser H. Importance of P-glycoprotein for drug-drug interactions. Handb Exp Pharmacol 2011;(201):285-97. [PMID:21103973].
159. Inui H, Ohkawa H. Herbicide resistance in transgenic plants with mammalian P450 monooxygenase genes. Pest Manag Sci 2005 Mar;61(3):286-91. [PMID:15660356].