CRD summary
The authors concluded that low-strength evidence supported the benefits of omega-3 fatty acids and of garlic co-administered with statin and nitrate therapy for specific intermediate outcomes, but safety concerns persisted. These conclusions reflect the findings presented but, as the authors pointed out, are based on small underpowered studies for most outcomes and supplements.

Authors' objectives
To examine the benefits, harms and pharmacokinetic interactions arising from the co-administration of commonly used dietary supplements with cardiovascular drugs.

Searching
Five databases including EMBASE, MEDLINE and The Cochrane Library were searched to October 2011 for studies in English and German. Search terms were reported in an appendix. Trial registries were searched and individuals at the Technology Enhancement Programme and Agency for Healthcare Research and Quality were contacted for further studies.

Study selection
Eligible studies compared a dietary supplement co-administered with a cardiovascular drug versus the drug alone or co-administered with another dietary supplement. Study design was restricted to randomised controlled trials (RCTs), non-randomised trials and observational studies with a control group of at least five participants. Eligible outcomes included clinical or surrogate cardiovascular efficacy or harms and pharmacokinetic outcomes in any adult population. Only studies with more than 80% of participants taking cardiovascular drugs that were marketed in the United States were included.

Most participants had various cardiovascular-related conditions or were at high risk for coronary heart disease; other participants were healthy volunteers. Mean participant age ranged from 44 to 63 years (where reported); most study samples were mixed gender. Dietary supplements administered included coenzyme Q-10, echinacea, garlic, ginkgo biloba, omega-3 fatty acids, vitamin E and American ginseng. Cardiovascular drugs investigated were mainly aspirin, statins, warfarin, fenofibrate, nitrates, calcium channel blockers and angiotensin-converting-enzyme (ACE) inhibitors.

One reviewer screened titles and abstracts of retrieved records for eligibility; exclusions were checked by a second reviewer. Two reviewers independently assessed the full publications retrieved; any discrepancies were resolved through consensus.

Assessment of study quality
Study quality was assessed according to risk of bias per outcome using generic items for confounding and types of bias (such as selection, performance, detection and attrition bias). Some items were specific to particular study designs, for example assessment of allocation sequence generation and concealment for RCTs. Overall risk of bias per study was rated as low, moderate or high.

One reviewer performed the quality assessment; a second reviewer independently verified the assessment.

Strength of evidence for pre-specified primary outcomes was assessed as being high, moderate, low or insufficient based on overall risk of bias, consistency, directness and precision.

Strength of evidence was graded by a methodologist and a content expert.

Data extraction
Data were extracted for outcomes and categorised into four groups: clinical, intermediate, harms and pharmacokinetic.
One reviewer with a clinical background rated study populations’ 10-year coronary heart disease risk according to National Cholesterol Education Program Adult Treatment Panel III guidelines.

One reviewer extracted the data; a second reviewer independently verified data for a 10% random sample of the included studies.

Methods of synthesis

Only RCTs with similar populations that compared the same dietary supplement and cardiovascular drug in intervention and control groups and reported identical outcome measures in the same statistical formats were pooled in a meta-analysis. Continuous and binary outcome data (except rare events) were pooled using a random-effects DerSimonian and Laird method; binary outcome data for rare events (with an event rate of less than 1%) were pooled as Peto odds ratios in a fixed-effect model. Results from trials with zero events in one of the arms were pooled using the fixed-effect Mantel-Haenszel method. Trials with zero events in both arms were not pooled.

Statistical heterogeneity was assessed using Cochran’s Q ($\alpha=0.10$) and the $I^2$ statistical tests ($I^2$ of more than 50% indicated significance).

All other study findings were presented as a narrative synthesis. The authors followed the US Food and Drug Administration guidance for analysis and interpretation of drug interaction pharmacokinetic studies.

Results of the review

Sixty-eight studies were included in the review (exact number uncertain, figure and text differ): 65 RCTs, two controlled clinical trials and one observational study. Most RCTs were at moderate risk of bias: 25% reported adequate sequence generation and 9% reported allocation concealment.

Gradable primary outcomes for dietary supplements plus cardiovascular drugs:

Evidence was insufficient for all predefined gradable clinical efficacy and harms outcomes because only a small number of underpowered studies were available per supplement.

The largest trial (19,934 healthy female participants) reported the longest treatment duration (10 years) and showed no benefit from co-administering vitamin E with aspirin on a composite cardiovascular outcome (RR 0.95, 95% CI 0.79 to 1.13).

Gradable secondary outcomes for dietary supplements plus cardiovascular drugs: Evidence for most secondary outcomes was insufficient or of low strength. Incremental benefits were observed for triglyceridemia with omega-3 fatty acid plus statins and for levels of high-density lipoprotein cholesterol with garlic plus nitrates.

Authors’ conclusions

Limitations of the evidence precluded meaningful conclusions across most supplement-drug combinations. Low-strength evidence supported the benefits of omega-3 fatty acids and of garlic co-administered with statin and nitrate therapy for specific intermediate outcomes. Safety concerns persisted.

CRD commentary

The review question was clear. Inclusion criteria appeared sufficiently replicable. There was an extensive search of relevant data sources. Efforts were made to reduce the risk of error and bias during the review stages of study selection, data extraction and quality assessment. Criteria used to assess quality of studies seemed suitable, but the brevity of the authors’ description of items used for specific study designs made this judgement uncertain. The grading approach for overall quality of evidence per outcome was commendable because it reduced the risk of reliance on poor-quality evidence for main conclusions. Study details and their findings were not clearly presented in the paper, but full details were available in the main report (see Other Publications of Related Interest). Some studies included healthy participants so their results may not be generalisable to a population with cardiovascular conditions.

The authors’ conclusions reflect the findings presented but, as the authors pointed out, are based on small underpowered studies for most outcomes and supplements.
Implications of the review for practice and research

Practice: The authors stated that precise recommendations were needed to guide the use of dietary supplements in disease prevention and management.

Research: The authors stated that future research should address relevant questions in appropriate populations according to disease, genetic makeup, age and so on. This includes well-conducted prospective observational studies and adequately powered intervention trials to investigate meaningful clinical outcomes.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.