Authors' objectives
To determine the association of beta-blockers with depressive symptoms, fatigue and sexual dysfunction by performing a quantitative review of randomised trials that tested beta-blockers in myocardial infarction, heart failure and hypertension.

Searching
MEDLINE (via OVID) was searched from January 1966 to December 2001 using the keywords 'myocardial infarction', 'heart failure' or 'hypertension' in combination with 'adrenergic beta antagonists' and 'trial'. The reference lists of published trials and overviews of beta-blockers were searched for additional studies. The searches were limited to publications in the English language. The US Food and Drug Administration (FDA) website (http://www.fda.gov) was checked for reports of adverse effects in trials of beta-blockers, and principal investigators were contacted if necessary.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) that were placebo-controlled, of a non-crossover design, with at least 100 participants enrolled and a follow-up of a minimum of 6 months, were included.

Specific interventions included in the review
The inclusion criteria specified comparisons of any beta-blocker with placebo. The included interventions were timolol, oxprenolol, propranolol, sotalol, metoprolol, atenolol, pindolol, acebutamol, carvedilol and bucindolol, compared with placebo. The follow-up time of the studies was 6 to 59 months. Dosages were not reported.

Participants included in the review
The authors do not state the inclusion criteria. The included studies involved male and female participants with a mean age of between 45 and 76 years, who were taking beta-blockers and had a diagnosis of myocardial infarction, hypertension or congestive heart failure.

Outcomes assessed in the review
The outcomes to be assessed were the frequency of depressive symptoms, fatigue or sexual dysfunction. The withdrawal of medication for depressive symptoms, fatigue or sexual dysfunction was also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
For each trial, one author abstracted the frequency of adverse events in the beta-blocker and placebo groups, and the number of patients randomised to the treatment groups. Two other authors verified the counts of events, and all authors adjudicated any discrepancies. Two different types of information on adverse events were abstracted: patient-reported symptoms and withdrawal of therapy due to a specified symptom. The tested beta-blockers were categorised according to generation (early versus late) and lipid solubility (high versus low-to-moderate).
Methods of synthesis  
How were the studies combined?  
The combined risk ratio and 95% confidence intervals (CIs) were calculated using a random-effects model. The pooled incidence risk differences and numbers-needed-to-treat (NNT) per year were calculated. This was used as an estimate of absolute risk (NNTs) of beta-blocker therapy on adverse effects.

How were differences between studies investigated?  
The chi-squared statistic was used to test for heterogeneity. A subgroup analysis was performed excluding 3 trials that tested beta-blockers not currently approved by the FDA. Studies were also stratified according to the use of early versus late generation beta-blockers and high versus low-to-medium lipid solubility.

Results of the review  
Fifteen studies involving 42,409 participants were included. Not all studies reported on all outcomes.

Overall, beta-blocker therapy was not associated with a significant absolute annual increase in risk of reported depressive symptoms (6 per 1,000 patients, 95% CI: -7, 19). Beta-blockers were associated with a small significant annual increase in risk of reported fatigue (18 per 1,000 patients, 95% CI: 5, 30), equivalent to one additional report of fatigue for every 57 patients treated per year with beta-blockers. Beta-blockers were also associated with a small, significant annual increase in risk of reported sexual dysfunction (5 per 100 patients, 95% CI: 2, 8), equivalent to one additional report for every 1,999 patients treated per year. None of the risks of adverse effects differed significantly by degree of beta-blocker lipid solubility. The risk associated with reported fatigue was significantly higher for early generation than for late generation beta-blockers (p=0.04). Significant variation was found across the studies.

Authors' conclusions  
The conventional wisdom that beta-blocker therapy is associated with substantial risks of depressive symptoms, fatigue and sexual dysfunction is not supported by the data from clinical trials. There is no significant increased risk of depressive symptoms and only small increased risks of fatigue and sexual dysfunction. The risks of these adverse effects should be put in the context of the documented benefits of these medications.

CRD commentary  
The aims of this review were clearly stated. Only one electronic database was searched and the search terms were limited. It is possible, therefore, that studies were missed. The methods of the review were not fully reported, e.g. the authors do not state how decisions were made on the relevance of the primary studies and study validity was not assessed. However, the authors' conclusion appears to follow from the results.

Implications of the review for practice and research  
Practice: The authors state that given the survival benefit associated with beta-blocker therapy, concerns about the development of these adverse effects should not deter physicians from initiating long-term treatment when indicated, although surveillance for adverse effects remains prudent.

Research: The authors did not state any implications for further research.

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Other publications of related interest
These additional published commentaries may also be of interest. Swann AC. Review: beta-blockers increase fatigue and sexual dysfunction but not depression after myocardial infarction. ACP J Club 2003;138:4. Swann AC. Review: beta-blockers increase fatigue and sexual dysfunction but not depression after myocardial infarction. Evid Based Med 2003;8:15.

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