Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis

CRD summary
This review assessed the clinical evidence for the comparison of generic and brand-name drugs used in cardiovascular disease. The authors concluded that the evidence does not support the superiority of either drug class with both yielding comparable results. The review had a number of methodological shortcomings which might impinge upon the reliability of the authors’ conclusions.

Authors’ objectives
To assess the clinical evidence comparing generic and brand-name drugs used in cardiovascular disease.

Searching
MEDLINE, EMBASE and International Pharmaceutical Abstracts were searched from 1984 to August 2008, The search terms were reported. Additional studies were sought through reference mining of articles, letters and commentaries. The search was restricted to English-language studies.

Study selection
Studies were eligible for inclusion if they reported a comparative evaluation of a brand-name drug approved by the Food and Drug Administration (FDA), or an identical formulation of it, and at least one generic version produced by a distinct manufacturer. The evaluation was required to include the measurement of at least one clinical efficacy or safety endpoint, including a vital sign, clinical laboratory study, patient morbidity or mortality or health system utilisation. Both randomised clinical trials (RCTs) and observational studies were eligible for inclusion. Over half of the RCTs were cross-over designs. The included studies assessed generic and brand-name versions of β-blockers, diuretics and calcium channel blockers. Drugs were grouped according to whether that had a narrow therapeutic index (NTI) or not. The interventions were administered at varying doses and for varying durations. The included studies were undertaken in a variety of populations, mostly non-USA.

The authors did not state how the papers were selected for review or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed RCTs for quality using the 5 point Jadad scale and nonrandomised trials using the 9 point Newcastle-Ottawa scale. Disagreements were resolved through consensus.

Data extraction
Effect sizes (ESs) and 95% confidence intervals (CI) were calculated for each study. An ES of <0.2 was considered to be very small, 0.2-0.5 was small, 0.5-0.8 was medium and >0.8 was large.

One reviewer carried out the data extraction which was checked by the second reviewer and any disagreements resolved through consensus.

Methods of synthesis
Meta-analysis was conducted to obtain pooled ESs. The studies were grouped for each cardiovascular drug class. It was not stated whether a fixed-effect or random-effects model was used. Statistical heterogeneity does not appear to have been assessed by the authors and it was unclear how the cross-over trials were incorporated.

Results of the review
A total of 47 studies covering nine different subclasses of cardiovascular drugs were included in the review, 38 of which were RCTs. The sample sizes ranged from 5 to 49,673 patients.
For the 38 RCTs study quality (on a scale of 1-5) was scored as 1 (four studies), 2 (13 studies), 3 (11 studies), 4 (six studies) and 5 (one study); three studies were scored as 0 but the implications of this score were unclear. For the nine nonrandomised trials study quality (on a scale of 1-9) was scored as 3 (one study), 4 (two studies), 5 (four studies), 6 (one study) and 8 (one study).

There were no statistically significant differences between the groups for any of the intervention types considered.

The ES for all drug classes (30 studies, n=837) was -0.03 (95% CI: -0.15, 0.08), favouring brand-name drugs.

ESs which favoured brand-name drugs included: diuretics (10 studies, n=135) ES -0.03 (95% CI: -0.28, 0.22); angiotensin converting enzyme (ACE) inhibitors (1 study, n=23) ES -0.09 (95% CI: -0.68, 0.50); statins (2 studies, n=71) ES -0.25 (95% CI: -0.62, 0.12); and warfarin (4 studies, n=138) ES -0.09 (95% CI: -0.33, 0.15).

ESs which favoured generic drugs included antiplatelet agents (2 studies, n=50) ES 0.21 (95% CI: -0.19, 0.61) and α-blockers (1 study, n=43) ES 0.06 (95% CI: -0.37, 0.50).

Those which favoured neither (ES = 0) included β-blockers (6 studies, n=135) (95% CI: -0.24, 0.25) and calcium channel blockers (4 studies, n=242) (95% CI: -0.53, 0.53).

Authors’ conclusions
The evidence does not support the superiority of either drug class over the other, with both brand-name and generic drugs used in cardiovascular disease yielding comparable results.

CRD commentary
The review addressed a clear question and undertook an adequate search for studies. Studies were restricted to those published in the English language which means that the review was prone to language bias. It does not appear that any attempts were made to retrieve unpublished studies, so some data might have been missed. No formal assessment of publication bias was reported. The authors did not state how the papers were selected for review or how many reviewers performed the selection, which may mean that the selection process was subject to bias. Methods to reduce reviewer bias and error were applied during the review process with respect to study quality and data extraction. The authors did not state what method they used to pool the data but they did undertake an assessment of the methodological differences between studies. Most of the studies had small sample sizes and different settings but there does not appear to have been an exploration of heterogeneity between studies by the authors. Also, it was unclear how cross-over trials were dealt with. The authors’ conclusions reflect the pooled results of a large number of studies, but the lack of exploration of potential clinical and methodological heterogeneity, together with other limitations of the review process and reporting, might impinge upon the reliability of their conclusion.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

Funding
The Attorney General Prescriber and Consumer Education Grant Program; Agency for Healthcare Research and Quality Post-Doctoral Fellowship in Health Services Research; National Institute on Aging, grant number AG027400; National Heart, Lung, and Blood Institute, grant number K23HL090505-01.

Bibliographic details

PubMedID
19050195

DOI
10.1001/jama.2008.758

Original Paper URL
http://jama.ama-assn.org/cgi/reprint/300/21/2514

Indexing Status
Subject indexing assigned by NLM

MeSH
Cardiovascular Agents /pharmacokinetics; Drugs, Generic /pharmacokinetics; Humans; Therapeutic Equivalency

AccessionNumber
12008107780

Date bibliographic record published
03/02/2009

Date abstract record published
31/03/2009

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.