Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Systematic Review and Meta-analysis

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The problem of rising prescription drug costs has emerged as a critical policy issue, straining the budgets of patients and public/private insurers and directly contributing to adverse health outcomes by reducing adherence to important medications. The primary drivers of elevated drug costs are brand-name drugs, which are sold at high prices during a period of patent protection and market exclusivity after approval by the Food and Drug Administration (FDA). To control spending, many payers and providers have encouraged substitution of inexpensive bioequivalent generic versions of these drugs, which can legally be marketed by multiple manufacturers after the brand-name manufacturer’s market exclusivity period ends.

Generic drugs are chemically equivalent to their brand-name counterparts in terms of active ingredients but may differ in peripheral features, such as pill color or shape, inert binders and fillers, and the specific manufacturing process. The 1984 Hatch–Waxman Act first authorized the FDA to approve generic drugs demonstrated to be “bioequivalent,” which is defined as absence of a significant difference in the availability of the active ingredient at the site of drug action. Bioequivalency can be established on the basis of the maximum serum concentration of the active ingredient.

**Context** Use of generic drugs, which are bioequivalent to brand-name drugs, can help contain prescription drug spending. However, there is concern among patients and physicians that brand-name drugs may be clinically superior to generic drugs.

**Objectives** To summarize clinical evidence comparing generic and brand-name drugs used in cardiovascular disease and to assess the perspectives of editorialists on this issue.

**Data Sources** Systematic searches of peer-reviewed publications in MEDLINE, EMBASE, and International Pharmaceutical Abstracts from January 1984 to August 2008.

**Study Selection** Studies compared generic and brand-name cardiovascular drugs using clinical efficacy and safety end points. We separately identified editorials addressing generic substitution.

**Data Extraction** We extracted variables related to the study design, setting, participants, clinical end points, and funding. Methodological quality of the trials was assessed by Jadad and Newcastle-Ottawa scores, and a meta-analysis was performed to determine an aggregate effect size. For editorials, we categorized authors’ positions on generic substitution as negative, positive, or neutral.

**Results** We identified 47 articles covering 9 subclasses of cardiovascular medications, of which 38 (81%) were randomized controlled trials (RCTs). Clinical equivalence was noted in 7 of 7 RCTs (100%) of β-blockers, 10 of 11 RCTs (91%) of diuretics, 5 of 7 RCTs (71%) of calcium channel blockers, 3 of 3 RCTs (100%) of antplatelet agents, 2 of 2 RCTs (100%) of statins, 1 of 1 RCT (100%) of angiotensin-converting enzyme inhibitors, and 1 of 1 RCT (100%) of α-blockers. Among narrow therapeutic index drugs, clinical equivalence was reported in 1 of 1 RCT (100%) of class 1 antiarrhythmic agents and 5 of 5 RCTs (100%) of warfarin. Aggregate effect size (n=837) was −0.03 (95% confidence interval, −0.15 to 0.08), indicating no evidence of superiority of brand-name to generic drugs. Among 43 editorials, 23 (53%) expressed a negative view of generic drug substitution.

**Conclusions** Whereas evidence does not support the notion that brand-name drugs used in cardiovascular disease are superior to generic drugs, a substantial number of editorials counsel against the interchangeability of generic drugs.

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GENERIC DRUGS IN CARDIOVASCULAR MEDICINE

We used 3 main subject heading domains: terms relating to the type of study (for example, clinical study, crossover, equivalence, effect, and outcome), terms relating to the products of interest (for example, brand-name, nonproprietary, generic, innovator, patent, and pharmaceutical drug), and terms relating to cardiovascular medicine. Cardiovascular disease was defined as any condition affecting the heart or blood vessels, including myocardial infarction, hypertension, cardiac arrhythmias, peripheral vascular disease, and heart failure. Under the cardiovascular category, we used search terms addressing general terms (eg, cardiovascular, heart, hematologic), cardiovascular disease (eg, atherosclerosis, hyperlipid, ischemia), and classes of pertinent drugs (eg, β-agonist, anticoagulant). Articles containing at least 1 search term in each of the 3 main categories met criteria for the title/abstract review.

Search terms and parameters were adjusted for each database while maintaining a common overall architecture. Search results from MEDLINE and EMBASE were combined and screened for duplicate entries. Search results from IPA were handled separately because of differences in output organization.

Study Selection
Studies were included if they reported on a comparative evaluation of 1 brand-name drug and at least 1 generic version produced by a distinct manufacturer (biologic products, which are regulated differently, were excluded). The comparative evaluation had to include measurement of at least 1 clinical efficacy or safety end point, including a vital sign (eg, heart rate, blood pressure, urine output), a clinical laboratory study (eg, international normalized ratio [INR], low-density lipoprotein, urine electrolytes), patient morbidity or mortality, or health system utilization. “Clinical laboratory studies” did not include specialized assays of concentrations of the drug or its metabolites used in pharmacokinetic evaluation.

We included both randomized controlled trials (RCTs) and observational studies. We excluded case studies as well as qualitative analyses of effectiveness, pharmacoeconomic evaluations, or surveys. For this part of the study, we also excluded commentaries, essays, legal analyses, consensus statements, and letters to the editor. Studies were excluded if they were written in a language other than English or were conducted in vitro or in animals. Although the study could take place in any location, the brand-name drug used (or an identical formulation of it) must have been approved by the FDA. Manual reference mining of articles, letters, and commentaries supplemented the search results.

Data Extraction and Synthesis
Data were extracted (A.S.K.) and checked (W.H.S.), with disagreements resolved by consensus. We assessed a number of variables related to the organization and outcome of the studies: the study design, listed source of funding, the setting (US vs non-US), the characteristics of the population studied, the number of participants, the mean age (or age range) of the participants, the clinical end points, and the self-identified source of funding (where listed). The methodological quality of the randomized clinical trials (RCTs) was assessed using the 5-point scale developed by Jadad et al. The methodological quality of nonrandomized trials was assessed using the 9-star Newcastle-Ottawa scale. This was done independently by 2 of us (A.S.K. and W.H.S.), with differences resolved by consensus.

Drugs were further subdivided based on whether they had a wide therapeutic index (WTI) or NTI. The federal definition of an NTI drug follows: “(a) There is less than a 2-fold difference in median lethal dose (LD$_{50}$) and median effective dose (ED$_{50}$) values, or (b) There is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and (c) Safe and effective use of the drug, the time until maximum concentration is reached, or the area under the curve based on serum concentration as a function of time.

Some physicians and patients have expressed concern that bioequivalent generic and brand-name drugs may not be equivalent in their effects on various clinical parameters, including physiological measures such as heart rate or blood pressure, important laboratory measurements, and outcomes such as health system utilization or mortality. Of particular concern are narrow therapeutic index (NTI) drugs, which are drugs whose effective doses and toxic doses are separated by a small difference in plasma concentration. Brand-name manufacturers have suggested that generic drugs may be less effective and safe than their brand-name counterparts. Anecdotes have appeared in the lay press raising doubts about the efficacy and safety of certain generic drugs.

Little empirical evidence has been assembled to assess clinical differences resulting from the use of generic medications, so we sought to systematically evaluate comparisons of generic and brand-name drugs on these outcomes. We focused on drugs used primarily to treat cardiovascular disease, which as a group make up the largest portion of outpatient prescription drug spending. We reviewed studies published from 1984 to 2008 comparing clinical characteristics of generic and brand-name drugs in this field and pooled available results. To determine the concurrent expert opinion on the subject of generic substitution, we also systematically reviewed the content of editorials published during this time.

METHODS
Data Sources
We performed a systematic search of articles published in peer-reviewed health care–related journals between January 1984 and August 2008 using MEDLINE, EMBASE, and International Pharmaceutical Abstracts (IPA) with the help of a professional librarian. Data were extracted (A.S.K.) and checked (W.H.S.), with disagreements resolved by consensus. We assessed a number of variables related to the organization and outcome of the studies: the study design, listed source of funding, the setting (US vs non-US), the characteristics of the population studied, the number of participants, the mean age (or age range) of the participants, the clinical end points, and the self-identified source of funding (where listed). The methodological quality of the randomized clinical trials (RCTs) was assessed using the 5-point scale developed by Jadad et al. The methodological quality of nonrandomized trials was assessed using the 9-star Newcastle-Ottawa scale. This was done independently by 2 of us (A.S.K. and W.H.S.), with differences resolved by consensus.

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of the drug products require careful titration and patient monitoring. The FDA does not formally designate the therapeutic index of drugs, but according to this definition (confirmed with review of the cardiovascular literature), relevant drugs with an NTI include the anticoagulant warfarin (Coumadin; DuPont Pharmaceuticals, Wilmington, Delaware) and antiarrhythmic drugs affecting the sodium and potassium channels (class I and class III).

To conduct a meta-analysis of included studies, we identified those RCTs where means and standard deviations for clinical outcomes were presented or could be derived from the published results. If the correlation was not reported for a crossover design, we assumed a coefficient of 0.5. We calculated a Cohen D effect size for each study with a 95% confidence interval (CI) according to established methods from information provided in the article. The effect sizes compare the difference in effect between the study groups divided by the standard deviation of this difference. We considered an effect size of less than 0.2 to be very small, an effect size of 0.2 to 0.5 to be small, an effect size of 0.5 to 0.8 to be medium, and an effect size of greater than 0.8 to be large. Since this measure is independent of the measurement used, sample size, and standard deviation of the outcome measure, we aggregated different end points across studies to obtain effect sizes with 95% CIs for each cardiovascular drug class as well as an aggregate effect size for all studies included in the meta-analysis.

Review of Editorials
We assessed the perspectives presented in editorials about the appropriateness of using generic drugs in treating cardiovascular disease during the same time period covered by our systematic review of the data. We repeated the MEDLINE and EMBASE searches using the same criteria. Two of us (A.S.K. and A.S.M.) then reviewed each title and abstract. Editorials were defined as articles expressing perspectives or viewpoints that did not include direct pharmacokinetic or clinical comparisons of generic and brand-name drugs. We also excluded systematic literature reviews, reports of surveys, case reports without substantial additional discussion, and letters to the editor.

Using content analysis, 2 of us (A.S.K. and W.H.S.) then coded themes in the editorials. We focused on the examples used (if any), sources cited (if any), and ultimate conclusions reached to categorize the editorial viewpoint within 1 of 3 main categories: (1) those presenting a generally negative opinion discouraging generic drug substitution, (2) those presenting a generally positive opinion encouraging generic drug substitution, and (3) those presenting a neutral analysis or that otherwise made no recommendations on the issue. We determined whether the editorial addressed generic and/or cardiovascular drugs broadly or focused on a subset of drugs, such as NTI drugs or drugs in a particular class. Investigators reconciled differences in coding by consensus.

RESULTS
The search done in September 2008 identified 8556 records, 3932 records from EMBASE, 2848 records from MEDLINE, and 1776 records from IPA. After removing overlapping citations and applying our exclusion criteria, 71 articles were prioritized from those 3 sources. We added 2 studies from evaluation of citations from prioritized articles. A total of 26 citations were excluded after full review. In total, our review identified 47 articles for detailed analysis (Figure 1), covering 9 different subclasses of cardiovascular drugs.

Nearly half of included studies (23/47, 49%) were primarily bioequivalency studies, in which pharmacokinetic comparisons occurred along with clinical end points, and more than a third (18/47, 38%) involved only healthy, young subjects. Less than half of the articles (21/47, 45%) were published since 2000 and only 17 (36%) were conducted in the United States. Table 1, Table 2, Table 3, and...
TABLE 4 include all categories of WTI cardiovascular drugs while TABLE 5 highlights the 2 NTI categories, warfarin (Coumadin) and class I antiarrhythmic drugs.

**WTI Drugs**

Nearly all trials (31/34, 91%) comparing generic and brand-name cardiovascular drugs with a WTI were RCTs with a crossover design. These articles encompassed 7 different drug classes, although more than three-fourths (27/34, 79%) involved β-blockers, diuretics, or calcium channel blockers.

### Table 1. Studies Involving β-Blockers

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studieda</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Population (Setting)</th>
<th>Jadad or Newcastle-Ottawa Scoreβ</th>
<th>Results</th>
<th>Listed Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahrens et al.25, 2007</td>
<td>Toprol XL vs 8 versions of long-acting metoprolol</td>
<td>49 (673 (56)/4 y</td>
<td>Retrospective cohort study</td>
<td>Patients affiliated with 3 German health insures (non-US)</td>
<td>8</td>
<td>No excess risk of hospitalization for cardiovascular events after adjustment for confounding (OR, 1.04-1.06; 95% CI, 0.89-1.21)</td>
<td>Generic manufacturers</td>
</tr>
<tr>
<td>Portoles et al.26, 2005</td>
<td>Coreg vs carvedilol</td>
<td>24 (22.8)/1 dose each with washout</td>
<td>RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>No significant differences in HR, BP, PR length, tolerability</td>
<td>Not listed</td>
</tr>
<tr>
<td>Mirfasaelian et al.27, 2003</td>
<td>Tenormin vs atenolol</td>
<td>12 (NA)/1 dose each with washout</td>
<td>Bioequivalency study; double-blind RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>No significant differences in reductions of HR, BP</td>
<td>Not listed</td>
</tr>
<tr>
<td>Bongers and Sabin,28 1999</td>
<td>Toprol XL vs long-acting metoprolol</td>
<td>52 (62)/4 wk for each product</td>
<td>Double-blind RCT with crossover</td>
<td>Outpatients with stable angina and 6 proven ST-segment depressions on ambulatory ECG (non-US)</td>
<td>3</td>
<td>Both significantly reduced ischemic events; no significant difference in reductions of HR or BP, signs of ischemia on telemetry (P = .21), anginal attacks (P = .34), nitrate use (P = .13), or adverse events (P = .08); median HR slightly less for brand-name (P = .08)</td>
<td>Brand-name manufacturer</td>
</tr>
<tr>
<td>Chiang et al.29, 1995</td>
<td>Tenormin vs atenolol</td>
<td>23 (58)/4 wk each with washout</td>
<td>Double-blind RCT with crossover</td>
<td>Outpatients with hypertension (non-US)</td>
<td>3</td>
<td>No significant differences in reductions of HR, BP</td>
<td>Not listed</td>
</tr>
<tr>
<td>Sarkar et al.30, 1995</td>
<td>Tenormin vs atenolol</td>
<td>31 (NA)/1 dose each with washout</td>
<td>Bioequivalency study; RCT with crossover</td>
<td>Healthy subjects (US)</td>
<td>2</td>
<td>No significant differences in reductions of HR, BP</td>
<td>Generic manufacturer</td>
</tr>
<tr>
<td>Carter et al.31, 1999</td>
<td>Inderal vs Inderal LA (long-acting) vs propranolol</td>
<td>15 (46)/4 wk each with washout</td>
<td>Single-blind RCT with crossover</td>
<td>Outpatients with hypertension (US)</td>
<td>3</td>
<td>No significant differences in reductions of HR, reductions of BP; tolerability</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>el-Sayed and Davies,32, 1989</td>
<td>Inderal vs propranolol vs placebo</td>
<td>12 (NA)/1 dose each with washout</td>
<td>Double-blind RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>No significant differences in change in resting HR, SBP, postexercise values</td>
<td>Not listed</td>
</tr>
<tr>
<td>Sanderson and Lewis,33, 1986</td>
<td>Inderal vs propranolol</td>
<td>1700 (68)/Half switched to Inderal LA for 4 wk; then all switched for 4 wk</td>
<td>Retrospective cohort study</td>
<td>Outpatients with multiple indications for β-blocker (non-US)</td>
<td>3</td>
<td>Increased incidence of self-reported adverse effects among group taking generic at initiation of study (P &lt; .001) (difference extinguished after all switched to Inderal LA, P = .15)</td>
<td>Not listed</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CI, confidence interval; ECG, electrocardiogram; HR, heart rate; NA, not available; OR, odds ratio; RCT, randomized controlled trial; SBP, systolic blood pressure.

25 Toprol XL and Tenormin are manufactured by AstraZeneca, Wilmington, Delaware; Coreg, GlaxoSmithKline, London, England; and Inderal, Ayerst Laboratories, Radnor, Pennsylvania.

27 The Jadad score range is 1-5 for RCTs; the Newcastle-Ottawa score range, 1-9 stars for observational studies.

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### Table 2. Studies Involving Diuretics

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studieda</th>
<th>No. of Patients (Age Mean or Range, y)/ Duration</th>
<th>Study Design</th>
<th>Population (Setting)</th>
<th>Jadad or Newcastle-Ottawa Scoreb</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al, 1997</td>
<td>Lasix vs 3 versions of furosemide vs intravenous Lasix</td>
<td>17 (65)/1 wk of each product</td>
<td>Bioequivalency study; open-label RCT with crossover</td>
<td>Outpatients with CHF (US)</td>
<td>3</td>
<td>Statistically nonsignificant differences in urine electrolytes (P = .37-.45) but wide intraindividual variability</td>
<td>Brand-name manufacturer</td>
</tr>
<tr>
<td>Awad et al, 1992</td>
<td>Lasix vs furosemide</td>
<td>20 (21-33)/1 dose of each with washout</td>
<td>Bioequivalency study; RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>0</td>
<td>Statistically nonsignificant differences in urine electrolytes, urine volume (P &gt; .05)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Kaojarern et al, 1990</td>
<td>Lasix vs 3 versions of furosemide</td>
<td>8 (25-39)/1 dose of each with washout</td>
<td>Bioequivalency study; RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>1</td>
<td>Statistically nonsignificant differences in 6-h urine output, urine electrolytes (P &gt; .05)</td>
<td>Medical center, brand-name manufacturer</td>
</tr>
<tr>
<td>Sharoky et al, 1989</td>
<td>Dyazide vs triamterene-hydrochlorothiazide</td>
<td>30 (55)/3 wk of brand and 3 wk of generic</td>
<td>Bioequivalency study; RCT with crossover</td>
<td>Outpatients with hypertension taking brand-name Dyazide (US)</td>
<td>4</td>
<td>Statistically nonsignificant differences in electrolytes, CBC, BP, tolerability (P &gt; .05)</td>
<td>Generic manufacturer</td>
</tr>
<tr>
<td>Singh et al, 1987</td>
<td>Intravenous Lasix vs intravenous furosemide</td>
<td>5 (20-51)/1 dose of each with washout</td>
<td>Bioequivalency study; double-blind RCT</td>
<td>Inpatients with edema of renal origin (non-US)</td>
<td>2</td>
<td>Statistically nonsignificant differences in urine electrolytes, standing and recumbent BP, urine output, tolerability (P &gt; .05)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Meyer et al, 1985</td>
<td>Lasix vs 3 versions of furosemide</td>
<td>12 (NA)/1 dose of each with washout</td>
<td>Bioequivalency study; double-blind RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>Statistically significant differences in 6-h urine output (P &lt; .05)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Grahnen et al, 1984</td>
<td>Lasix vs furosemide vs intravenous furosemide</td>
<td>8 (26)/2 doses of each with washout</td>
<td>Bioequivalency study; double-blind RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>Statistically nonsignificant differences in urine output (P &gt; .05)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Garg et al, 1984</td>
<td>Lasix vs furosemide</td>
<td>16 (NA)/1 dose of each with washout</td>
<td>Bioequivalency study; double-blind RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>Statistically nonsignificant differences in serum and urine electrolytes, HR, BP, urine output (P &gt; .05)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Pan et al, 1984</td>
<td>Lasix vs furosemide</td>
<td>5 (NA)/2 d of each</td>
<td>Bioequivalency study; double-blind RCT with crossover</td>
<td>Outpatients with CHF (non-US)</td>
<td>1</td>
<td>Statistically nonsignificant differences in electrolytes, urine output, weight, urine electrolytes (P &gt; .2)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Matti et al, 1984</td>
<td>Lasix vs 6 versions of furosemide</td>
<td>6 (NA)/1 dose of each with washout</td>
<td>Bioequivalency study; RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>0</td>
<td>“Acceptable level of diuresis” in self-reported urine output (no statistical tests done)</td>
<td>Government</td>
</tr>
<tr>
<td>Martin et al, 1984</td>
<td>Lasix vs furosemide</td>
<td>12 (18-42)/1 dose of each with washout</td>
<td>Bioequivalency study; RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>0</td>
<td>Statistically nonsignificant trend of lower urine output (P = .07-.08), statistically nonsignificant differences in urine electrolytes</td>
<td>Medical center</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CBC, complete blood count; CHF, congestive heart failure; HR, heart rate; NA, not available; RCT, randomized controlled trial.
aLasix is manufactured by Sanofi-Aventis, Paris, France; Dyazide is manufactured by GlaxoSmithKline, London, England.
bThe Jadad score range is 1-5 for RCTs; the Newcastle-Ottawa score range, 1-9 stars for observational studies.
We identified 9 articles that compared clinical outcomes in generic and brand-name \(\beta\)-blockers.\(^{25-33}\) These studies involved 4 different \(\beta\)-blockers: long-acting metoprolol (Toprol XL; Ayerst Laboratories, Radnor, Pennsylvania), long-acting atenolol (Tenormin; AstraZeneca, Wilmington, Delaware), carvedilol (Coreg; GlaxoSmithKline, London, England), and propranolol (Inderal; Ayerst Laboratories, Radnor, Pennsylvania). Long-acting metoprolol was evaluated in 1 double-blind RCT in outpatients with stable angina and 1 retrospective cohort study involving nearly 50,000 German patients over 4 years.\(^{25}\) The cohort study identified users of \(\beta\)-blockers from provincial administrative data in Germany and found no differences in clinical outcomes after controlling for patient sociodemographic characteristics and their co-

### Table 3. Studies Involving Calcium Channel Blockers

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studied(^a)</th>
<th>No. of Patients (Age Mean or Range, y)/Duration</th>
<th>Study Design</th>
<th>Population (Setting)</th>
<th>Jadad or Newcastle-Ottawa Score(^b)</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al,(^{46}) 2007</td>
<td>Norvasc vs amlodipine camsylate</td>
<td>189 (73)/8 wk with dose increase after 4 wk if BP still elevated</td>
<td>Multicenter double-blind parallel group RCT</td>
<td>Outpatients with uncomplicated essential hypertension (US)</td>
<td>3</td>
<td>Significant BP improvement in both groups; statistically nonsignificant differences in tolerability (P &gt; .05)</td>
<td>Generic manufacturer, government</td>
</tr>
<tr>
<td>Mignini et al,(^{46}) 2007</td>
<td>Norvasc vs amlodipine maleate</td>
<td>24 (34.8)/1 dose of each with washout</td>
<td>Single-blind RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>Decrease in SBP; increase in HR, decrease in PR and QRS intervals, with statistically nonsignificant differences between the 2 groups</td>
<td>Not listed</td>
</tr>
<tr>
<td>Park et al,(^{47}) 2004</td>
<td>Norvasc vs amlodipine camsylate</td>
<td>18 (22)/1 dose of each with washout</td>
<td>Bioequivalence study: open-label RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>4</td>
<td>Significant improvements in BP in both groups; statistically nonsignificant differences in electrolytes, CBC, UA, HR, ECG changes (P &gt; .05)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Sassen et al,(^{46}) 1997</td>
<td>Calan vs verapamil</td>
<td>8 (70)/2 wk of each with washout</td>
<td>Bioequivalence study: double-blind RCT with crossover</td>
<td>Elderly outpatients with hypertension (US)</td>
<td>3</td>
<td>Generic associated with a marginally greater BP reduction than brand; statistically nonsignificant differences in HR, ECG changes (P &gt; .05)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Usha et al,(^{49}) 1997</td>
<td>Cardizem vs long-acting diltiazem</td>
<td>12 (27)/1 dose of each with washout</td>
<td>Bioequivalence study: double-blind RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>3</td>
<td>Statistically nonsignificant differences in BP, HR, ECG changes (P &gt; .05)</td>
<td>Generic manufacturer</td>
</tr>
<tr>
<td>Waldman and Morganroth,(^{30}) 1995</td>
<td>Calan SR or Isoptin SR vs sustained-release verapamil</td>
<td>24 (NA)/1 dose of each with washout</td>
<td>Bioequivalence study (both fasting and after a meal): open-label RCT</td>
<td>Healthy subjects (US)</td>
<td>1</td>
<td>In fasting patients, statistically nonsignificant difference in BP, HR, or ECG changes; in fed patients, increased PR interval on ECG with generic (P &lt; .05)</td>
<td>Brand-name manufacturer; brand-name, industry-affiliated foundation</td>
</tr>
<tr>
<td>Carter et al,(^{31}) 1993</td>
<td>Isoptin vs 1 of 2 versions of verapamil</td>
<td>Youth cohort: 8 (27)/1 wk with washout; elderly cohort: 8 (73)/3 wk with no washout</td>
<td>Double-blind randomized 3-way RCT with crossover</td>
<td>Healthy subjects and elderly outpatients with hypertension (US)</td>
<td>2</td>
<td>Statistically nonsignificant differences in HR, BP, or PR intervals for youth cohort; statistically insignificant differences in elderly cohort also, except 1 generic associated with increased PR interval and (paradoxically) higher supine BP</td>
<td>American College of Clinical Pharmacy, medical center</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CBC, complete blood count; ECG, electrocardiogram; HR, heart rate; NA, not available; RCT, randomized controlled trial; SBP, systolic blood pressure; UA, urinalysis.

\(^{a}\)Norvasc is manufactured by Pfizer, New York, New York; Calan, Searle Pharmaceuticals, Chicago, Illinois; Cardizem, Marion Merrell Dow Inc, Kansas City, Missouri; and Isoptin, Knoll Pharmaceuticals, Whippany, New Jersey.

\(^{b}\)The Jadad score range is 1-5 for RCTs; the Newcastle-Ottawa score range, 1-9 stars for observational studies.
morbidities. In 1 RCT in outpatients with hypertension and 2 bioequivalency studies in healthy volunteers, Tenormin was not found to be superior to the generic version in lowering heart rate and blood pressure.\(^{27,29,30}\) In a retrospective cohort study of patients switching from short- to long-acting \(\beta\)-blocker preparations, self-reported adverse effects occurred more frequently at baseline in patients taking generic propranolol than in those taking Inderal (34.6\% vs 24.8\%, \(P<.001\)), and the difference was noted to be extinguished after all were switched to Inderal LA (Long-Acting) (20.5\% vs 17.6\%, \(P=15\)).\(^{33}\) These patients were not randomly assigned to

### Table 4. Studies Involving Other Non-NTI Cardiovascular Drugs Grouped by Drug Class

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studied(^a)</th>
<th>No. of Patients (Age Mean or Range, y)/Duration</th>
<th>Study Design</th>
<th>Population (Setting)</th>
<th>Jadad or Newcastle-Ottawa Score(^b)</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashraf et al,(^52) 2005</td>
<td>Plavix vs clopidogrel</td>
<td>30 (49)/1 dose of each with washout</td>
<td>Double-blind RCT with crossover</td>
<td>Patients with suspected ischemic heart disease (non-US)</td>
<td>3</td>
<td>Statistically nonsignificant differences in reduction in platelet aggregation blood tests (57.8% vs 80.7%, (P=0.72))</td>
<td>Generic manufacturer, government</td>
</tr>
<tr>
<td>Rao et al,(^53) 2003</td>
<td>Plavix vs clopidogrel</td>
<td>20 (27)/10 d</td>
<td>Bioequivalence study: open-label parallel group RCT</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>Statistically nonsignificant differences in bleeding time, tolerability ((P&gt;.05))</td>
<td>Not listed</td>
</tr>
<tr>
<td>Merali et al,(^54) 1998</td>
<td>Enteric-coated aspirin vs 3 versions of enteric-coated acetylsalicylic acid</td>
<td>12 (18-49)/1 dose of each with washout</td>
<td>Bioequivalence study: RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>2</td>
<td>Statistically nonsignificant differences in platelet function assay ((P&gt;.05))</td>
<td>Internal funding</td>
</tr>
<tr>
<td>Portoles et al,(^55) 2004</td>
<td>Vasotec vs enalapril</td>
<td>24 (23)/1 dose of each with washout</td>
<td>Bioequivalence study: open-label RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>3</td>
<td>Statistically nonsignificant differences in BP reductions, changes in HR, effect on CBC, UA ((P&gt;.05))</td>
<td>Not listed</td>
</tr>
<tr>
<td>Assawawitoontip and Wiwanitkit,(^56) 2002</td>
<td>Zocor vs simvastatin</td>
<td>48 (37)/8 wk of each with washout</td>
<td>Double-blind RCT with crossover</td>
<td>Outpatients with hypercholesterolemia not previously treated (non-US)</td>
<td>4</td>
<td>Reductions in LDL in both groups; statistically nonsignificant differences in cholesterol measurements, LFTs, creatine kinase levels (unpaired t test, (\alpha=.05))</td>
<td>Generic manufacturer</td>
</tr>
<tr>
<td>Wiwanitkit et al,(^57) 2002</td>
<td>Zocor vs simvastatin</td>
<td>43 (49)/16 wk of each with washout</td>
<td>Double-blind RCT with crossover</td>
<td>Outpatients with hypercholesterolemia not previously treated (non-US)</td>
<td>4</td>
<td>Reductions in LDL in both groups; statistically nonsignificant differences in cholesterol measurements, LFTs, adverse effects ((P&gt;.05))</td>
<td>Generic manufacturer</td>
</tr>
<tr>
<td>Tsai et al,(^58) 2007</td>
<td>Hytrin vs terazosin</td>
<td>43 (63)/6 wk of each with washout (dose change allowed at week 2)</td>
<td>Open-label RCT with crossover</td>
<td>Outpatients with hyperprolactinemia (non-US)</td>
<td>3</td>
<td>Improvements in urine flow and quality of life indices in both; statistically nonsignificant differences in effects on BP, HR, CBC, symptom scales ((P&gt;.05))</td>
<td>Generic manufacturer</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; BPH, benign prostatic hypertrophy; CBC, complete blood count; HR, heart rate; LDL, low-density lipoprotein; LFTs, liver function test results; NTI, narrow therapeutic index; RCT, randomized controlled trial; UA, urinalysis.

\(^a\)Plavix is manufactured by Bristol-Myers Squibb, New York, New York; Vasotec and Zocor by Merck, Whitehouse Station, New Jersey; and Hytrin by Abbott Laboratories, Abbott Park, Illinois.

\(^b\)The Jadad score range is 1-5 for RCTs; the Newcastle-Ottawa score range, 1-9 stars for observational studies.
Table 5. Studies Involving Narrow Therapeutic Index Cardiovascular Drugs

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studieda</th>
<th>No. of Patients (Age Mean or Range, y/Duration)</th>
<th>Study Design</th>
<th>Population (Setting)</th>
<th>Jadad or Newcastle-Ottawa Scoreb</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amit et al, 2004</td>
<td>Pronestyl vs procainamide</td>
<td>119 (65)/6 mo each separated by 1 wk of prior therapy</td>
<td>Double-blind RCT with crossover</td>
<td>Elderly outpatients with arrhythmia (US)</td>
<td>3</td>
<td>No significant differences in INR (P = .97), no significant differences in INR measurements or variation (P = .86)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Kasmer et al, 2007</td>
<td>Coumadin vs warfarin</td>
<td>57 (71)/4 wk of Coumadin and then 8 wk of warfarin vs 4 wk of warfarin and then 8 wk of Coumadin</td>
<td>Single-blind crossover</td>
<td>Patients with mechanical heart valves who received Coumadin for ≥2 mo (non-US)</td>
<td>5</td>
<td>No significant changes in INR (P = .97) or hospitalization for hemorrhage (P = .85) or thromboembolism (P = .97)</td>
<td>Government</td>
</tr>
<tr>
<td>Handler et al, 2009</td>
<td>Coumadin vs warfarin</td>
<td>2521 (65)/6 mo before and 6 mo after switch</td>
<td>Retrospective observational study (pre/post design)</td>
<td>Outpatients with numerous indications for anticoagulation taking Coumadin (US)</td>
<td>4</td>
<td>Dose changes were rare; no significant differences in INR or frequency of adverse effects (P &gt; .05)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Witt et al, 2003</td>
<td>Coumadin vs warfarin</td>
<td>2299 (65)/6 mo before and 3 mo after switch</td>
<td>Retrospective cohort study</td>
<td>Outpatients with numerous indications for anticoagulation taking Coumadin (US)</td>
<td>4</td>
<td>More INR values below therapeutic range with generic (P &lt; .001); overall average INR decreased by 0.13 after switch; no significant differences in hospitalizations, ED use, outcomes (bleeding or thromboembolism)</td>
<td>Not listed</td>
</tr>
</tbody>
</table>

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**Table 5. Studies Involving Narrow Therapeutic Index Cardiovascular Drugs (continued)**

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studied</th>
<th>No. of Patients (Age Mean or Range, y)/Duration</th>
<th>Study Design</th>
<th>Population (Setting)</th>
<th>Warfarin Anticoagulant</th>
<th>Jadad or Newcastle-Ottawa Score</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milligan et al, 67 2002</td>
<td>Coumadin vs warfarin</td>
<td>182 (75)/8 mo before and 10 mo after switch</td>
<td>Retrospective cohort study</td>
<td>Outpatients with numerous indications for anticoagulation taking Coumadin (US)</td>
<td>5</td>
<td>No significant differences in INR (P &lt; .001), dose adjustments (P = .15)/H11022</td>
<td>No significant differences in adverse events (P = .24 for hemorrhagic)</td>
<td>Insurance company</td>
</tr>
<tr>
<td>Welb et al, 68 2000</td>
<td>Coumadin vs warfarin</td>
<td>113 (70)/4 wk before and 10 wk after switch</td>
<td>Multicenter double-blind RCT with crossover</td>
<td>Outpatients with atrial fibrillation who received Coumadin for 1 mo (US)</td>
<td>4</td>
<td>No significant differences in daily dose (&lt;0.5 mg/d), average INR difference (P &lt; .08), adverse events (P = .24 for hemorrhagic)</td>
<td></td>
<td>Generics manufacturer</td>
</tr>
<tr>
<td>Swenson and Fundak, 69 2000</td>
<td>Coumadin vs warfarin</td>
<td>210 (78)/8 wk</td>
<td>Prospective observational cohort study</td>
<td>Outpatients with indications for anticoagulation receiving Coumadin for ≥3 mo switched to warfarin (US)</td>
<td>6</td>
<td>No significant differences in INR between groups (P = .19); changes in INR of &gt;1.0 were rare; no adverse effects or adverse events</td>
<td>Not listed</td>
<td></td>
</tr>
<tr>
<td>Neutel and Smith, 70 1998</td>
<td>Coumadin vs warfarin</td>
<td>39 (70)/3 wk of Coumadin and then 6 wk of warfarin vs 3 wk of warfarin and then 6 wk of Coumadin</td>
<td>Single-blind RCT with crossover</td>
<td>Outpatients with arrhythmia stably treated with Coumadin for 6 wk (US)</td>
<td>2</td>
<td>Changes in INR after switching were small and not significant (P &gt; .05); no differences in adverse effect profiles between drugs</td>
<td>Not listed</td>
<td></td>
</tr>
<tr>
<td>Richton-Hewett et al, 71 1988</td>
<td>Coumadin vs warfarin</td>
<td>55 (57)/3 mo of Coumadin and then 4 mo of Coumadin</td>
<td>Retrospective cohort study</td>
<td>Outpatients with indications for anticoagulation switched to warfarin in a single hospital (US)</td>
<td>5</td>
<td>Higher rate of INR out of range (P &lt; .001), dose changes (P &lt; .05), clinic utilization (P &lt; .03) with generic group; no significant differences in morbidity/mortality</td>
<td>Not listed</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ED, emergency department; INR, international normalized ratio; RCT, randomized controlled trial; VPBs, ventricular premature beats.

Different preparations, and recipients of the generic formulation may have been different from recipients of the brand. An RCT later conducted in hypertensive patients found no clinical differences, including rates of observed adverse effects, among these 3 versions of propranolol. 31

Eleven articles compared outcomes among patients using diuretics: 10 with the loop diuretic furosemide (Lasix; Sanofi-Aventis, Paris, France) 34-36,38-44 and 1 with the combination diuretic triamterene-hydrochlorothiazide (Dyazide; GlaxoSmithKline). 37 The furosemide studies were of lower quality, and 7 were bioequivalency studies performed in a total of 82 generally young, healthy subjects who received only 1 dose of each brand-name or generic formulation. 33,36,39-41,43,44 The clinical end points for these studies were primarily urine output and urine electrolytes. However, only 1 study, conducted in South Africa in 1985, found significant differences. 39

*Three studies of furosemide involved patients with volume overload. In these studies, generic and brand-name formulations of furosemide showed no significant clinical differences. 34,36,39* A 1997 open-label RCT with crossover in 17 outpatients with congestive heart failure who received Lasix, 3 versions of generic furosemide, and intravenous furosemide for a week’s time noted wide intrindividual variability in patients’ urine electrolytes that the authors hypothesized might overwhelm any minor differences in bioavailability. 34 The study of triamterene-hydrochlorothiazide was a prospective RCT in 30 patients with hypertension. 37 It demonstrated no statistically significant differences on blood pressure and serum electrolytes in patients using the medication for 3-week blocks.

Seven articles evaluated generic and brand-name versions of calcium channel blockers. 35-38 The largest, a multicenter, double-blind, parallel-group RCT in 189 patients with hypertension, found
improvements in blood pressure and no significant differences between brand-name and generic versions of amlo-
dipine (Norvasc; Pfizer, New York, New York) over 8 weeks.49 Two studies re-
ported slight, but statistically signifi-
cant, differences in 1 measured clinical outcome (the PR interval on electro-
cardiogram), although there were no as-
associated changes in heart rate or other 
cardiogram), although there were no as-
clinical outcomes in either of those 
udies.50,51

The remaining 7 studies evaluated an-
tiplatelet agents (clopidogrel; [Plavix; 
Bristol-Myers Squibb, New York, New 
York] and enteric-coated aspirin [ace-
tylsalylic acid]).52-54 the angiotensin-
converting enzyme (ACE) inhibitor 
enalapril (Vasotec; Merck, Whitehouse 
Station, New Jersey),55 the statin simva-
statin (Zocor; Merck),56,57 and the α-
blocker terazosin (Hytrin; Abbott Labo-
ratories, Abbott Park, Illinois).58 None 
of these studies reported significant clini-
cal differences between the generic and 
brand-name versions. Two longer-term 
RCTs of simvastatin were conducted in 
Thailand. Both of these studies, of high 
methodological quality, showed no sta-
tistically significant differences in low-
ering low-density lipoprotein levels.56,57 
However, there were a number of im-
portant limitations in the studies. The 2 
studies of clopidogrel used clinical out-
comes related to platelet aggregation and 
bleeding time, not incidence of cardio-
vascular disease such as myocardial in-
farction.52,53 The study involving enala-
pril was well designed but measured 
minimal change in 24 healthy subjects 
who received only 1 dose of the generic 
and brand-name forms.55 The terazosin 
study, which was conducted in outpa-
tients with benign prostatic hypertro-
phy, found no significant differences in 
heart rate and blood pressure and was of 
relatively high quality.58

NTI Drugs

Thirteen articles analyzed generic and 
brand-name versions of cardiovascular 
drugs with an NTI. Two addressed clini-
cal end points in treatment with class I 
antiarrhythmic drugs (propafenone 
[Rythmex; Knoll Pharmaceuticals, 
Dellkenheim, Germany] and procain-
amide [Pronestyl; E. R. Squibb & Sons, 
New Brunswick, New Jersey]).59,60 The 
study of propafenone used a pre/post de-
sign of 114 patients with atrial fibrilla-
rion receiving stable doses of brand-
name propafenone for at least 18 months 
who were required by their insurer to 
switch to a generic version of the drug. 
This study, which included no concu-
current controls, found no differences in 
rates of health system utilization such as 
clinical visits, coprescription with other 
medications, or rates of cardiovascular 
in the 18 months after switching to a ge-
neric drug and a slight reduction in emer-
gency department visits with the ge-
neric version (P < .01).59 Procainamide 
was studied in a bioequivalency study of 
patients with ventricular dysrhythmias; 
no differences in telemetry output were 
found between the generic and brand-
name versions.50

The remaining 11 articles studied warfarin (Coumadin).61-71 In 6 RCTs or 
prospective studies, generic and brand-
name warfarin performed similarly with 
respect to clinical end points such as 
INR, frequency of adverse events, and 
number of required dose adjust-
ments.51,62,64,68-70 Five retrospective 
observational studies evaluated patient 
INRs and clinical outcomes in pa-
tients who were required to switch from 
Coumadin to warfarin because of 
changes in coverage in diverse set-
tings: nationwide in Israel, a Cana-
dian province, a staff model health 
maintenance organization (HMO), a 
commercial HMO, and a municipal hos-
pital in the United States. All of these 
used pre/post designs and found 
results similar to the RCTs; no signifi-
cant differences were seen in clinical 
outcomes, including hemorrhagic ad-
verse events or thromboembolic dis-
 ease.61,65-67 One of the cohort studies 
found a small but significant decrease 
in INR in patients using the generic 
drug, although it did not translate into 
differences in morbidity or mortal-
ity.64 A fourth retrospective cohort study 
found increased health care system uti-
ilization in patients not taking Couma-
din (although no differences in mor-
bidity/mortality), but the drug used as 
a comparator in that study was not rated 
as bioequivalent by the FDA.71

Aggregate Effect Sizes

Data from 30 studies contributed to the 
effect sizes of the outcomes. As seen in 
FIGURE 2, when data were pooled by 
drug class, in each case, the 95% CI 
crossed zero, and the effect size was 
“very small” (except for statins and an-
tiplatelet agents, where the effect size 
was “small”). The aggregate effect size 
(n = 837) was −0.03 (95% CI, −0.15 
to 0.08), which indicates nearly com-
plete overlap of the generic and brand-
name distributions. These data sug-
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**Editors Addressing Generic Substitution**

Forty-three editorials and commentaries met our criteria during the study period. The greatest number (19, 44%) were published from 1993 to 1999, while 14 (33%) were published from 2000 to 2008. Twenty-five (58%) discussed cardiovascular and generic drugs broadly, while 18 (42%) focused only on cardiovascular NTI drugs.

Of these editorials, 23 (53%) expressed a negative view of the interchangeability of generic drugs compared with 12 (28%) that encouraged substitution of generic drugs (the remaining 8 did not reach a conclusion on interchangeability). Among editorials addressing NTI drugs specifically, 12 (67%) expressed a negative view while only 4 (22%) supported generic drug substitution.

**COMMENT**

To our knowledge, our analysis is the first comprehensive review of the empirical evidence comparing clinical characteristics of generic and brand-name drugs used in cardiovascular disease. The 47 studies in our sample covered 8 different subclasses of cardiovascular drugs, including 2 types of NTI drugs. Measured clinical outcomes included vital signs; clinical laboratory values such as INR and urine electrolytes; adverse effects or other morbidity; and health care system utilization, including clinic and emergency department visits.

The studies in our sample concluded that generic and brand-name cardiovascular drugs are similar in nearly all clinical outcomes. Among WTI drugs, the best evidence for clinical equivalence emerged from high-quality prospective RCTs in patients with cardiovascular disease involving β-blockers, calcium channel blockers, and statins. Fewer trials compared generic and brand-name diuretics, antiplatelet agents, ACE inhibitors, and α-blockers, limiting our ability to reach similar conclusions in these drug classes.

Among NTI drugs, warfarin was the subject of the most studies addressing therapeutic equivalence. The 6 studies with a prospective design (461 patients) demonstrated similar clinical outcomes with brand-name and generic versions of the drug for multiple different outcomes, including INR, required dose adjustments, and adverse events. Among the retrospective reviews, 2 revealed transient differences in INR after changes from brand-name to generic warfarin without any differences in clinical outcomes. The only study showing specific differences in use of health care resources compared Coumadin with a version of warfarin that was not rated as bioequivalent by the FDA. Taken as a whole, these results suggest that switching from brand-name to generic warfarin products rated as bioequivalent by the FDA is safe, although it may be useful to monitor the INR of higher-risk patients more closely during a switch period.

Even though there is little evidence of important clinical differences between generic and brand-name drugs in cardiovascular disease, many editorials expressed a negative view of generic drug interchangeability and urged heightened concern on the part of physicians and patients. This opinion has not changed substantially over time; among the most recent editorials (published 2000-2008), 6 of 14 (43%) expressed a negative view of substitution. One explanation for this discordance between the data and editorial opinion is that commentaries may be more likely to highlight physicians’ concerns based on anecdotal experience or other nonclinical trial settings. Another possible explanation is that the conclusions may be skewed by financial relationships of editorialists with brand-name pharmaceutical companies, which are not always disclosed.

Approximately half of the trials in our sample (23/47, 49%) and nearly all of the editorials and commentaries, did not identify sources of funding.

Our study has several limitations that reflect the underlying literature. The majority of the studies we identified were bioequivalence studies, which included small populations and were powered to assess differences in pharmacokinetic parameters rather than clinical outcomes. For the smaller studies, only large differences in clinical outcomes would have been statistically significant, although our meta-analysis addresses the limitation of small sample size by pooling results across studies. Most clinical outcomes were evaluated by testing a superiority hypothesis rather than noninferiority hypothesis. Statistical significance in the context of a superiority study does not allow one to conclude that agents are equivalent, only that there is insufficient evidence available to conclude that the agents are different. In addition, many of the bioequivalence studies included disproportionately young and healthy subjects, and there were limited data comparing generic and brand-name medications in patients with multiple morbidities and taking numerous medications. Such patients may be at greater risk of adverse events if modest clinical differences in medication formulations exist.

Most of the studies were conducted in 4 medication classes: β-blockers, calcium channel blockers, diuretics, and warfarin. The small numbers of studies in other classes limited our ability to draw class-specific conclusions about comparative safety or efficacy. Finally, most studies were short-term evaluations and did not collect the data necessary to compare long-term outcomes associated with generic drug use such as rates of myocardial infarction or death. The lack of studies evaluating clinical outcomes in generic drug use is not altogether surprising, as neither generic drug makers nor brand-name manufacturers are likely to make large financial investments over many years to pursue a research initiative that could adversely affect their business model if their hypotheses are not confirmed.

Despite these limitations, we identified numerous studies that evaluated differences in clinical outcomes with generic and brand-name medications. Our results suggest that it is reasonable for physicians and patients to rely on FDA bioequivalence rating as a proxy for clinical...

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Statistical analysis: Kesselheim, Shrank.

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Women’s Hospital and Harvard Medical School), helped
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sign and manuscript. Neither received compensation.

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