Yllescas was strong enough to survive a lengthy medical evacuation which eventually brought him to the National Naval Medical Center in Bethesda, MD. With Dena and other family members at his side, Captain Yllescas underwent almost daily surgeries in the hope of recovery. Dena Yllescas chronicled his hospitalization on an Internet blog which drew tens of thousands of readers. Friends, relatives and total strangers all followed Captain Yllescas's progress and prayed for his recovery. President George W. Bush made a special trip to the medical center and awarded Captain Yllescas the Purple Heart in a brief ceremony on November 10.

Captain Yllescas knew the dangers he faced and the risks he took. He also knew the importance of the work he did in the Army on behalf of his fellow Americans. He risked and ultimately sacrificed his own life so that people a world away could have the chance to enjoy the freedoms he had found in America.

Captain Yllescas is survived by his wife, Dena, and daughters Julia, age 7, and Eva, 10 months; parents, Barbara Yllescas of Lincoln and Otto Yllescas of Guatemala; a brother, Christopher of Columbia, MO; and two sisters, Jennifer Winterbauer of Lincoln and Natalie Yllescas of Guatemala.

The life and service of Captain Yllescas represents an example we can all look up to and seek to emulate. He served his country honorably and made the ultimate sacrifice in furtherance of a much larger goal. Captain Yllescas made the most of his short life, and the greatest tragedy is that now it is impossible to know what more this promising young man might have accomplished. I join all Nebraskans in mourning the loss of Captain Yllescas and in offering my deepest condolences to his family.

GULF WAR ILLNESS RESEARCH FUNDING

Mr. ROCKEFELLER. Madam President, I rise today to urge my colleagues to review the findings of the congressionally mandated Research Advisory Committee on Gulf War Veterans' Illnesses. This report, which was released a few weeks ago, confirms what many veterans of the Gulf War, lawmakers, physicians, and researchers have long suspected that the mysterious illnesses suffered by one in four gulf war veterans are real, and are a result of their exposure to neurotoxic chemicals.

It was not long after the successful conclusion of the gulf war that many of our soldiers returned home with multiple persistent symptoms including headaches, memory loss, gastrointestinal problems, and widespread pain. The symptoms were real, yet the cause and effective treatment have remained frustratingly elusive. As a leading member of the Senate Committee on Veterans' Affairs, I pushed hard for oversight hearings and continued research efforts.

Finally, 17 years after the end of that conflict, this report confirms that veterans' neurotoxin and pesticide exposure during the gulf war has been consistently found to be causally associated with gulf war illness. Unfortunately, this report also concludes that few veterans have recovered from their exposure, and treatments remain ineffective. While it is important that the cause of this illness has been established, it is unacceptable for our veterans to continue to suffer from these wounds of war.

In light of the findings of the Research Advisory Committee on Gulf War Veterans' Illnesses, there must be a continued investment in gulf war illness research. It is estimated that 175,000 to 210,000 gulf war veterans are suffering from the effects of neurotoxin exposure directly related to their time spent in the Gulf. Once again, hundreds of thousands of soldiers find themselves back in the area as part of Operation Iraqi Freedom. Therefore, it is vital that we do all that we can to adequately fund gulf war research.

We also need to learn the lesson of the value of candor and research. DOD and VA must be more open with Congress about the concerns facing our troops, from neurotoxin and pesticide exposures in the gulf war to the troubling issue of suicide, mental health issues, and traumatic brain injury, TBI, in the current conflict. We must address all the wounds of war, both visible and invisible, for our veterans who have served so bravely.

GENERIC MEDICINES

Ms. STABENOW. Madam President, I rise today to bring to my colleagues' attention a recent article in the respected Journal of American Medicine on generic medicines. The article comes at a critical time as we begin to tackle the important issue of health care reform.

There is no doubt that health care reform must include offering solutions that reduce skyrocketing health care costs. One solution to reducing costs is to increase access to generic medicines, which offer savings of up to 80 percent over brand drug costs.

The new JAMA article provides specific evidence on the benefits of generic medicines. The analysis, which included U.S. scientists reviewing more than 20 years of research on generic versus brand name drugs, found that there is no clinical evidence showing that brand name cardiovascular drugs were superior to their generic versions. Moreover, the lead author of the report noted that generics can lead to better outcomes because they cost less, which means patients can afford to take them and stay on them.

As our economy continues to struggle, Americans across the country are looking for ways to make ends meet. We hear too often about older Americans rationing their medicines and even mothers watering down infant formula to make it last longer, not knowing of the dangerous health impact this can have. A recent survey conducted by BearingPoint, Inc., and Zogby found that an alarming number of consumers admitted that they would consider denying themselves or their children health care to save money during this difficult economic time.

As we consider the critical and interrelated issues regarding the economic crisis and reform of national health care, the new JAMA study supports every effort we can make now to increase the use of generic medicines. We should remove the numerous barriers to getting generic medicines to consumers sooner rather than later, and we must prevent the creation of new barriers that will impede greater use of generics. We also should consider how to create a workable pathway for biogenerics, a pathway that actually gets these safe and affordable life-saving medicines to patients in a timely manner.

Generic medicines save consumers and State and Federal governments billions of dollars annually. At the same time, generic medicines are FDA approved, guaranteeing their safety and effectiveness.

When the new Congress tackles the important health care initiatives that lie ahead, the safety and effectiveness of prescription drugs must remain a top priority. As the medical evidence concludes, Congress can have confidence in the fact that increasing access to generic medicines will provide high-quality care at significant cost savings for consumers and the government.

I ask unanimous consent to have the article to which I referred printed in the RECORD.

There being no objection, the material was ordered to be printed in the RECORD, as follows:

Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease

A Systematic Review and Meta-analysis

Aaron S. Kesselheim, MD, JD, MPH
Alexander S. Misono, BA
Joy L. Lee, BA
Margaret R. Stedman, MPH
M. Alan Brookhart, PhD
Niteesh K. Choudhry, MD, PhD
William H. Shrank, MD, MSHS

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 antiplatelet 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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THE PROBLEM OF RISING PRESCRIPTION drug costs has emerged as a critical policy issue, straining the budgets of patients and public/private insurers[1] and directly contributing to adverse health outcomes by reducing adherence to important medications.[2,3] 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).[4] 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.[5]

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.[6] 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.[7] Bioequivalency can be established on the basis of the maximum serum concentration of

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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.[8-10] 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.[11] Anecdotes have appeared in the lay press raising doubts about the efficacy and safety of certain generic drugs.[12,13]

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.[14] 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.

We used 3 main subject heading domains: terms relating to the type of study (for example, *clinical study, crossover, equivalen$, effect$, 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 they 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.[15] The methodological quality of nonrandomized trials was assessed using the 9-star Newcastle-Ottawa scale.[16] 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

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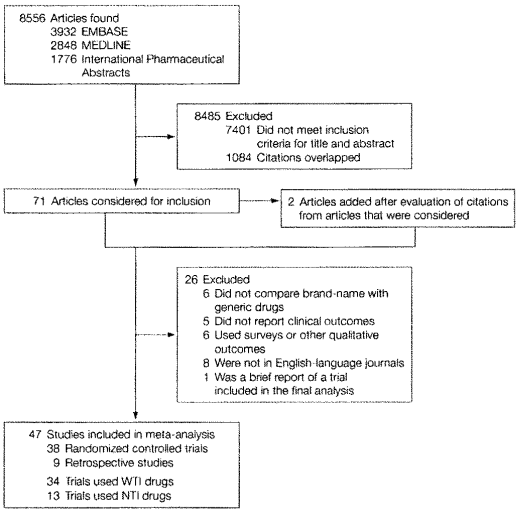
Figure 1. Study Selection



NTI indicates narrow therapeutic index; WTI, wide therapeutic index.

of the drug products require careful titration and patient monitoring."[17,18] 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.[19-22] 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.[23]

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,[24] 2 of us (A.S.K. and W.H.S.) then coded themes in the commentaries. We focused on the examples used (if any), sources cited (if any), and ultimate conclusions reached to categorize the editorial's 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

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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

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/ Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Listed Source of Funding
Ahrens et al,[25] 2007	Toprol XL vs 8 versions of long-acting metoprolol	49 673 (56)/4 y	Retrospective cohort study	Patients affiliated with 3 German health insurers (non-US)	8	No excess risk of hospitalization for cardiovascular events after adjustment for confounding (OR, 1.04-1.06; 95% CI, 0.89-1.21)	Generic manufacturers
Portoles et al,[26] 2005	Coreg vs carvedilol	24 (22.8)/1 dose of each with washout	RCT with crossover	Healthy subjects (non-US)	2	No significant differences in HR, BP, PR length, tolerability	Not listed
Mirfazaelian et al,[27] 2003	Tenormin vs atenolol	12 (NA)/1 dose of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	2	No significant differences in reductions of HR, BP	Not listed
Bongers and Sabin,[28] 1999	Toprol XL vs long-acting metoprolol	52 (62)/4 wk for each product	Double-blind RCT with crossover	Outpatients with stable angina and 6 proven ST-segment depressions on ambulatory ECG (non-US)	3	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 ($P = .05$)	Brand-name manufacturer
Chiang et al,[29] 1995	Tenormin vs atenolol	23 (59)/4 wk of each with washout	Double-blind RCT with crossover	Outpatients with hypertension (non-US)	3	No significant differences in reductions of HR, BP	Not listed
Sarkar et al,[30] 1995	Tenormin vs atenolol	31 (NA)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (US)	2	No significant differences in reductions of HR, BP	Generic manufacturer
Carter et al,[31] 1989	Inderal vs Inderal LA (long-acting) vs propranolol	15 (46)/4 wk of each with washout	Single-blind RCT with crossover	Outpatients with hypertension (US)	3	No significant differences in reductions of HR, reductions of BP, tolerability	National Institutes of Health
el-Sayed and Davies,[32] 1989	Inderal vs propranolol vs placebo	12 (NA)/1 dose of each with washout	Double-blind RCT with crossover	Healthy subjects (non-US)	2	No significant differences in change in resting HR, SBP, postexercise values	Not listed
Sanderson and Lewis,[33] 1986	Inderal vs propranolol	1700 (68)/Half switched to Inderal LA for 4 wk; then all switched for 4 wk	Retrospective cohort study	Outpatients with multiple indications for β-blocker (non-US)	3	Increased incidence of self-reported adverse effects among group taking generic at initiation of study ($P < .001$) (difference extinguished after all switched to Inderal LA, $P = .15$)	Not listed

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.

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

[b] 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

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/ Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Source of Funding
Murray et al,[34] 1997	Lasix vs 3 versions of furosemide vs intravenous Lasix	17 (65)/1 wk of each product	Bioequivalency study: open-label RCT with crossover	Outpatients with CHF (US)	3	Statistically nonsignificant differences in urine electrolytes (P = .37-.45) but wide intraindividual variability	Brand-name manufacturer
Awad et al,[35] 1992	Lasix vs furosemide	20 (21-32)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	0	Statistically nonsignificant differences in urine electrolytes, urine volume (P > .05)	Not listed
Kaojarern et al,[36] 1990	Lasix vs 3 versions of furosemide	8 (25-39)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	1	Statistically nonsignificant differences in 6-h urine output, urine electrolytes (P > .05)	Medical center, brand-name manufacturer
Sharoky et al,[37] 1989	Dyazide vs triamterene-hydrochloro-thiazide	30 (55)/3 wk of brand and 3 wk of generic	Bioequivalency study: RCT with crossover	Outpatients with hyperten-sion taking brand-name Dyazide (US)	4	Statistically nonsignificant differences in electrolytes, CBC, BP, tolerability (P > .05)	Generic manufacturer
Singh et al,[38] 1987	Intravenous Lasix vs intravenous furosemide	5 (20-51)/1 dose of each with washout	Bioequivalency study: double-blind RCT	Inpatients with edema of renal origin (non-US)	2	Statistically nonsignificant differences in urine electrolytes, standing and recumbent BP, urine output, tolerability (P > .05)	Not listed
Meyer et al,[39] 1985	Lasix vs 3 versions of furosemide	12 (NA)/1 dose of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	2	Statistically significant differences in 6-h urine output (P < .05)	Not listed
Grahnen et al,[40] 1984	Lasix vs furosemide vs intravenous furosemide	8 (26)/2 doses of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	2	Statistically nonsignificant differences in urine output (P > .05)	Not listed
Garg et al,[41] 1984	Lasix vs furosemide	16 (NA)/1 dose of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	2	Statistically nonsignificant differences in serum and urine electrolytes, HR, BP, urine output (P > .05)	Not listed
Pan et al[42] 1984	Lasix vs furosemide	5 (NA)/2 d of each	Bioequivalency study: double-blind RCT with crossover	Outpatients with CHF (non-US)	1	Statistically nonsignificant differences in electrolytes, urine output, weight, urine electrolytes (P > .2)	Not listed
Maitai et al,[43] 1984	Lasix vs 6 versions of furosemide	6 (NA)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	0	"Acceptable level of diuresis" in self-reported urine output (no statistical tests done)	Government
Martin et al,[44] 1984	Lasix vs furosemide	12 (18-42)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	0	Statistically nonsignificant trend of lower urine output (P = .07-.08), statistically nonsignificant differences in urine electrolytes	Medical center

Abbreviations: BP, blood pressure; CBC, complete blood count; CHF, congestive heart failure; HR, heart rate; NA, not available; RCT, randomized controlled trial.
[a] Lasix is manufactured by Sanofi-Aventis, Paris, France; Dyazide is manufactured by GlaxoSmithKline, London, England.
[b] The Jadad score range is 1-5 for RCTs; the Newcastle-Ottawa score range, 1-9 stars for observational studies.

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We identified 9 articles that compared clinical outcomes in generic and brand-name β-blockers.[25-33] These studies involved 4 different β-blockers: long-acting metoprolol (Toprol XL; AstraZeneca, Wilmington, Delaware), atenolol (Tenormin; AstraZeneca), 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 β-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

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/ Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Source of Funding
Kim et al,[45] 2007	Norvasc vs amlodipine camsylate	189 (53)/8 wk with dose increase after 4 wk if BP still elevated	Multicenter double-blind parallel group RCT	Outpatients with uncomplicated essential hypertension (non-US)	3	Significant BP improvement in both groups; statistically nonsignificant differences in tolerability ($P > .05$)	Generic manufacturer, government
Mignini et al,[46] 2007	Norvasc vs amlodipine maleate	24 (34.8)/1 dose of each with washout	Single-blind RCT with crossover	Healthy subjects (non-US)	2	Decrease in SBP, increase in HR, decrease in PR and QRS intervals, with statistically nonsignificant differences between the 2 groups	Not listed
Park et al,[47] 2004	Norvasc vs amlodipine camsylate	18 (22)/1 dose of each with washout	Bioequivalency study: open-label RCT with crossover	Healthy subjects (non-US)	4	Significant improvements in BP in both groups; statistically nonsignificant differences in electrolytes, CBC, UA, HR, ECG changes ($P > .05$)	Not listed
Saseen et al,[48] 1997	Calan vs verapamil	8 (70)/2 wk of each with washout	Bioequivalency study: double-blind RCT with crossover	Elderly outpatients with hypertension (US)	3	Generics associated with a marginally greater BP reduction than brand; statistically nonsignificant differences in HR, ECG changes ($P > .05$)	Not listed
Usha et al,[49] 1997	Cardizem vs long-acting diltiazem	12 (27)/1 dose of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	3	Statistically nonsignificant differences in BP, HR, ECG changes ($P > .05$)	Generic manufacturer
Waldman and Morganroth,[50] 1995	Calan SR or Isoptin SR vs sustained-release verapamil	24 (NA)/1 dose of each with washout	Bioequivalency study (both fasting and after a meal): open-label RCT	Healthy subjects (US)	1	In fasting patients, statistically nonsignificant difference in BP, HR, or ECG changes; in fed patients, increased PR interval on ECG with generic ($P < .05$)	Brand-name manufacturer; brand-name, industry-affiliated foundation
Carter et al,[51] 1993	Isoptin vs 1 of 2 versions of verapamil	Youth cohort: 8 (27)/1 wk of each with washout; elderly cohort: 8 (73)/3 wk of each with no washout	Double-blind randomized 3-way RCT with crossover	Healthy subjects and elderly outpatients with hypertension (US)	2	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	American College of Clinical Pharmacy, medical center

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.

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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 β-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

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/ Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Source of Funding
				Antiplatelet Agents			
Ashraf et al,[52] 2005	Plavix vs clopidogrel	30 (49)/1 dose of each with washout	Double-blind RCT with crossover	Patients with suspected ischemic heart disease (non-US)	3	Statistically nonsignificant differences in reduction in platelet aggregation blood tests (57.8% vs 60.7%, $P = .72$)	Generic manufacturer, government
Rao et al,[53] 2003	Plavix vs clopidogrel	20 (27)/10 d	Bioequivalency study: open-label parallel group RCT	Healthy subjects (non-US)	2	Statistically nonsignificant differences in bleeding time, tolerability ($P > .05$)	Not listed
Merali et al,[54] 1996	Enteric-coated aspirin vs 3 versions of enteric-coated acetylsalicylic acid	12 (18-45)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	2	Statistically nonsignificant differences in platelet function assay ($P > .05$)	Internal funding
				Angiotensin-Converting Enzyme Inhibitors			
Portoles et al,[55] 2004	Vasotec vs enalapril	24 (23)/1 dose of each with washout	Bioequivalency study: open-label RCT with crossover	Healthy subjects (non-US)	3	Statistically nonsignificant differences in BP reductions, changes in HR, effect on CBC, UA ($P > .05$)	Not listed
				Statins			
Assawawitoontip and Wiwanitkit,[56] 2002	Zocor vs simvastatin	48 (37)/8 wk of each with washout	Double-blind RCT with crossover	Outpatients with hypercholesterolemia not previously treated (non-US)	4	Reductions in LDL in both groups; statistically nonsignificant differences in cholesterol measurements, LFTs, creatine kinase levels (unpaired t test, $\alpha = .05$)	Generic manufacturer
Wiwanitkit et al,[57] 2002	Zocor vs simvastatin	43 (49)/16 wk of each with washout	Double-blind RCT with crossover	Outpatients with hypercholesterolemia not previously treated (non-US)	4	Reductions in LDL in both groups; statistically nonsignificant differences in cholesterol measurements, LFTs, adverse effects ($P > .05$)	Generic manufacturer
				α-Blockers			
Tsai et al,[58] 2007	Hytrin vs terazosin	43 (63)/6 wk of each with washout (dose change allowed at week 2)	Open-label RCT with crossover	Outpatients with BPH (non-US)	3	Improvements in urine flow and quality of life indices in both; statistically nonsignificant differences in effects on BP, HR, CBC, symptom scales ($P > .05$)	Generic manufacturer

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.

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Table 5. Studies Involving Narrow Therapeutic Index Cardiovascular Drugs

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Source of Funding
			Antiarrhythmic Agents				
Amit et al,[59] 2004	Rythmex vs propafenone	119 (65)/18 mo	Retrospective cohort study (pre/post design without concurrent controls)	Patients with atrial fibrillation stable while receiving brand for ≥18 mo switched to generic (non-US)	4	Generic use associated with slight reduction in total ED discharges and ED visits for chest pain ($P < .01$); no significant differences in clinic visits, admissions, cardioversions, and rate of use of other cardiovascular medications ($P > .05$)	Generic manufacturer
Kasmer et al,[60] 1987	Pronestyl vs procainamide	10 (62)/6 doses of each separated by 1 wk of prior therapy	Bioequivalence study: single-blind RCT with crossover	Patients with ventricular dysrhythmias (US)	1	No significant change in type or frequency of VPBs on telemetry ($P > .05$)	Generic manufacturer, National Institutes of Health
			Warfarin Anticoagulant				
Handler et al,[61] 1998	Coumadin vs warfarin	57 (71)/4 wk of Coumadin and then 8 wk of warfarin vs 4 wk of warfarin and then 8 wk of Coumadin	Double-blind RCT with crossover	Outpatients with arrhythmia (US)	5	No significant differences in INR ($P = .40$), dose adjustments, adverse events ($P > .05$)	Generic manufacturer
Pereira et al,[62] 2005	Coumadin vs warfarin	7 (63)/Five 3-wk periods of each	Double-blind RCT with crossover	Outpatients with indications for anticoagulation (US)	4	No significant differences in INR measurements or variation ($P = .98$)	Not listed
Paterson et al,[63] 2006	Coumadin vs 1 of 2 versions of warfarin	36 724 (≥66)/40 mo before, 1 mo of transition, and 9 mo following switch	Population-based, cross-sectional time-series analysis	Elderly outpatients with numerous indications for anticoagulation taking Coumadin (non-US)	5	No significant differences in INR testing ($P = .93$) or hospitalization for hemorrhage ($P = .89$) or thromboembolism ($P = .97$)	Government
Lee et al,[64] 2005	Coumadin vs warfarin	35 (52)/4 wk of Coumadin and then 8 wk of warfarin vs 4 wk of warfarin and then 8 wk of Coumadin	Single-blind RCT with crossover	Patients with mechanical heart valves who received Coumadin for ≥2 mo (non-US)	3	Dose changes were rare; no significant differences in pooled INRs or frequency of adverse effects ($P > .05$)	Unknown
Halkin et al,[65] 2003	Coumadin vs warfarin	975 (70)/6 mo before and 6 mo after switch	Retrospective observational study (pre/post design)	Outpatients with numerous indications for anticoagulation taking Coumadin (non-US)	5	After the switch, INR values were lower and warfarin doses prescribed were higher, especially in those who were subtherapeutic when receiving Coumadin ($P < .01$)	Not listed
Witt et al,[66] 2003	Coumadin vs warfarin	2299 (69)/3 mo before and 3 mo after switch	Retrospective cohort study	Outpatients with numerous indications for anticoagulation taking Coumadin (US)	4	More INR values below therapeutic range with generic ($P < .001$); overall average INR decreased by 0.13 after switch; no significant differences in hospitalizations, ED use, outcomes (bleeding or thromboembolism)	Not listed

(continued)

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

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/ Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Source of Funding
				Warfarin Anticoagulant			
Milligan et al,[67] 2002	Coumadin vs warfarin	182 (75)/8 mo before and 10 mo after switch	Retrospective cohort study	Outpatients with numerous indications for anticoagulation taking Coumadin (US)	5	No significant differences in INR (P = .3), dose adjustments (P = .41), adverse events	Insurance company
Weibert et al,[68] 2000	Coumadin vs warfarin	113 (70)/4 wk before and 10 wk after switch	Multicenter double-blind RCT with crossover	Outpatients with atrial fibrillation who received Coumadin for 1 mo (US)	4	No significant differences in daily dose (<0.5 mg/d), average INR difference (P < .08), adverse events (P = .24 for hemorrhagic)	Generic manufacturer
Swenson and Fundak,[69] 2000	Coumadin vs warfarin	210 (78)/8 wk	Prospective observational cohort study	Outpatients with indications for anticoagulation receiving Coumadin for ≥3 mo switched to warfarin (US)	6	No significant differences in INR between groups (P = .15); changes in INR of >1.0 were rare; no adverse effects or adverse events	Not listed
Neutel and Smith,[70] 1998	Coumadin vs warfarin	39 (70)/3 wk of Coumadin and then 6 wk of warfarin vs 3 wk of warfarin and then 6 wk of Coumadin	Single-blind RCT with crossover	Outpatients with arrhythmia stably treated with Coumadin for 6 wk (US)	2	Changes in INR after switching were small and not significant (P > .05); no differences in adverse effect profiles between drugs	Not listed
Richton-Hewett et al,[71] 1988[c]	Coumadin vs warfarin	55 (57)/3 mo of warfarin and then 4 mo of Coumadin	Retrospective cohort study	Outpatients with indications for anticoagulation switched to warfarin in a single hospital (US)	5	Higher rate of INR out of range (P < .001), dose changes (P < .05), clinic utilization (P < .03) with generic group; no significant differences in morbidity/mortality	Not listed

Abbreviations: ED, emergency department; INR, international normalized ratio; RCT, randomized controlled trial; VPBs, ventricular premature beats.
[a] Rythmex is manufactured by Knoll Pharmaceuticals, Delkenheim, Germany; Pronestyl, E. R. Squibb & Sons, New Brunswick, New Jersey; and Coumadin, DuPont Pharmaceuticals, Wilmington, Delaware.
[b] The Jadad score range is 1-5 for RCTs; the Newcastle-Ottawa score range, 1-9 stars for observational studies.
[c] Although conducted in the United States, this study did not involve a bioequivalent generic.

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.[35,36,39-41,43,44] 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.[34,38,42] 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 intraindividual 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.[45-51] The largest, a multicenter, double-blind, parallel-group RCT in 189 patients with hypertension, found

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improvements in blood pressure and no significant differences between brand-name and generic versions of amlodipine (Norvasc; Pfizer, New York, New York) over 8 weeks.[45] Two studies reported slight, but statistically significant, differences in 1 measured clinical outcome (the PR interval on electrocardiogram), although there were no associated changes in heart rate or other clinical outcomes in either of those studies.[50,51]

The remaining 7 studies evaluated antiplatelet agents (clopidogrel; [Plavix; Bristol-Myers Squibb, New York, New York] and enteric-coated aspirin [acetylsalicylic acid]),[52-54] the angiotensin-converting enzyme (ACE) inhibitor enalapril (Vasotec; Merck, Whitehouse Station, New Jersey),[55] the statin simvastatin (Zocor; Merck),[56,57] and the α-blocker terazosin (Hytrin; Abbott Laboratories, Abbott Park, Illinois).[58] None of these studies reported significant clinical 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 statistically significant differences in lowering low-density lipoprotein levels.[56,57] However, there were a number of important limitations in the studies. The 2 studies of clopidogrel used clinical outcomes related to platelet aggregation and bleeding time, not incidence of cardiovascular disease such as myocardial infarction.[52,53] The study involving enalapril was well designed but measured bioequivalency in 24 healthy subjects who received only 1 dose of the generic and brand-name forms.[55] The terazosin study, which was conducted in outpatients with benign prostatic hypertrophy, found no significant differences in heart rate and blood pressure and was of relatively high quality.[58]

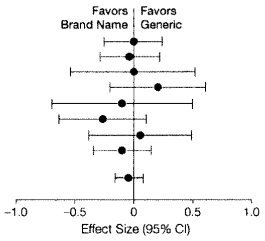
NTI Drugs

Thirteen articles analyzed generic and brand-name versions of cardiovascular drugs with an NTI. Two addressed clinical end points in treatment with class I antiarrhythmic drugs (propafenone [Rythmex; Knoll Pharmaceuticals, Delkenheim, Germany] and procainamide [Pronestyl; E. R. Squibb & Sons, New Brunswick, New Jersey]).[59,60] The study of propafenone used a pre/post design of 114 patients with atrial fibrillation 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 concurrent controls, found no differences in rates of health system utilization such as clinic visits, coprescription with other medications, or rates of cardioversion in the 18 months after switching to a generic drug and a slight reduction in emergency department visits with the generic 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.[60]

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 adjustments.[61,62,64,68-70] Five retrospective observational studies evaluated patient INRs and clinical outcomes in patients who were required to switch from Coumadin to warfarin because of changes in coverage in diverse settings: nationwide in Israel, a Canadian province, a staff model health maintenance organization (HMO), a commercial HMO, and a municipal hospital in the United States. All of these studies used pre/post designs and found results similar to the RCTs; no significant differences were seen in clinical outcomes, including hemorrhagic adverse events or thromboembolic disease.[63,65-67] 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 mortality.[66] A fourth retrospective cohort study found increased health care system utilization in patients not taking Coumadin (although no differences in morbidity/mortality), but the drug used as a comparator in that study was not rated as bioequivalent by the FDA.[71]

Figure 2. Drug Class and Aggregate Meta-analyses of Trials Comparing Generic and Brand-Name Drugs Used in Cardiovascular Disease

Drug Class	No. Studies	No. Subjects	Effect Size (95% CI)
β-Blockers	6	135	0.00 (-0.24 to 0.25)
Diuretics	10	135	-0.03 (-0.28 to 0.22)
Calcium channel blockers	4	242	0.00 (-0.53 to 0.53)
Antiplatelet agents	2	50	0.21 (-0.19 to 0.61)
ACE inhibitors	1	23	-0.09 (-0.68 to 0.50)
Statins	2	71	-0.25 (-0.62 to 0.12)
α-Blockers	1	43	0.06 (-0.37 to 0.50)
Warfarin	4	138	-0.09 (-0.33 to 0.15)
Overall	30	837	-0.03 (-0.15 to 0.08)



ACE indicates angiotensin-converting enzyme; CI, confidence interval.

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 antiplatelet 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 complete overlap of the generic and brand-name distributions. These data suggest no evidence of superiority of brand-name to generic drugs in measured clinical outcomes among these studies.

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Editorials 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[9,72-89] while 14 (33%) were published from 2000 to 2008.[90-103] 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.[114] 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 insignificance 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 clini-

*References 72, 76, 77, 80-84, 86, 87, 90, 93-95, 97, 101-110.
†References 9, 73-75, 78, 79, 85, 88, 89, 91, 92, 96, 98-100, 111-113.

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cal equivalence among a number of important cardiovascular drugs, even in higher-risk contexts such as the NTI drug warfarin. These findings also support the use of formulary designs aimed at stimulating appropriate generic drug use. To limit unfounded distrust of generic medications, popular media and scientific journals could choose to be more selective about publishing perspective pieces based on anecdotal evidence of diminished clinical efficacy or greater risk of adverse effects with generic medications. Such publications may enhance barriers to appropriate generic drug use that increase unnecessary spending without improving clinical outcomes.

Author Contributions: Dr Kesselheim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kesselheim, Misono, Shrank.
Acquisition of data: Kesselheim, Misono, Lee, Shrank.
Analysis and interpretation of data: Kesselheim, Misono, Stedman, Brookhart, Choudhry, Shrank.
Drafting of the manuscript: Kesselheim, Misono, Lee, Shrank.
Critical revision of the manuscript for important intellectual content: Kesselheim, Misono, Stedman, Brookhart, Choudhry, Shrank.
Statistical analysis: Stedman, Brookhart, Choudhry.
Obtained funding: Kesselheim, Shrank.
Administrative, technical, or material support: Kesselheim, Misono, Lee, Shrank.
Study supervision: Kesselheim, Shrank.
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Additional Contributions: Paul Shekelle, MD, PhD (Veterans Affairs Greater Los Angeles Health Care System and RAND Corp), provided comments on an earlier version of the manuscript. Jerry Avorn, MD (Brigham and Women's Hospital and Harvard Medical School), helped conceive the study and provided comments on the design and manuscript. Neither received compensation.

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