You have been assigned to literature critique session #2, Tuesday, 12/1/09, at 3:00 p.m. Individual paper assignments are given below. Electronic versions of the papers can be found on the course website under the heading of “TA Handouts.” Remember, in addition to organizing and writing a critique of your assigned paper, you must come prepared to discuss all of the papers that will be presented during your session - at the very least, you must read all four papers included in this packet. If you have any questions, please let me know.

Best regards,
John

Samit Shah -
“Association Between Tamsulosin and Serious Ophthalmic Adverse Events in Older Men Following Cataract Surgery”

Elio Beta -
“Hormone Therapy and Ovarian Cancer”

Vincent Pureza -
“Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients with Type 2 Diabetes: A Randomized Controlled Trial”

Christine Yang -
“Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Systematic Review and Meta-analysis”
Association Between Tamsulosin and Serious Ophthalmic Adverse Events in Older Men Following Cataract Surgery

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Context Both benign prostatic hyperplasia (BPH) and cataract formation are common in older men. The α-adrenergic receptor blocker tamsulosin is frequently prescribed to treat BPH, and research suggests this drug may increase the intraoperative difficulty of cataract surgery. No studies have documented whether use of tamsulosin or other α-blocker drug therapies affect the risk of serious postoperative adverse events.

Objective To assess the risk of adverse events following cataract surgery in older men prescribed tamsulosin or other α-blocking drugs used to treat BPH.

Design, Setting, and Patients Nested case-control analysis of a population-based retrospective cohort study using linked health care databases from Ontario, Canada. We included all men aged 66 years or older who had cataract surgery between 2002 and 2007 (N=96,128).

Main Outcome Measures A composite of procedures signifying retinal detachment, lost lens or lens fragment, or endophthalmitis occurring within 14 days after cataract surgery. The risk of these adverse events was compared between men treated with tamsulosin or other α-blockers and men with no exposure to these medications in the year prior to cataract surgery. We separately examined the association of drug exposure that was either recent (within the 14 days before surgery) or previous (15-365 days before surgery).

Results Overall, 3,550 patients (3.7%) in the cohort had recent exposure to tamsulosin and 7,426 patients (7.7%) had recent exposure to other α-blockers. Two hundred eighty-four patients (0.3%) had an adverse event. We randomly matched 280 of the cases to 1102 controls according to their age, surgeon, and year of surgery. Adverse events were significantly more common among patients with recent tamsulosin exposure (7.5% vs 2.7%; adjusted odds ratio [OR], 2.33; 95% confidence interval [CI], 1.22-4.43) but were not associated with recent exposure to other α-blockers (7.5% vs 8.0%; adjusted OR, 0.91; 95% CI, 0.54-1.54) or to previous exposure to either tamsulosin (≤1.8% vs 1%; adjusted OR, 0.94; 95% CI, 0.27-3.34) or other α-blockers (2.9% vs 2.1%; adjusted OR, 1.08; 95% CI, 0.47-2.48). This corresponds to an estimated number needed to harm (NNH) of 255 (95% CI, 99-1666).

Conclusions Exposure to tamsulosin within 14 days of cataract surgery was significantly associated with serious postoperative ophthalmic adverse events. There were no significant associations with exposure to other α-blocker medications used to treat BPH.


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IFIS for patients taking tamsulosin and undergoing cataract surgery. However, the warnings and noted precautions in reference materials focused only on the added intraoperative difficulty associated with tamsulosin and did not mention postoperative adverse events.

Each year, approximately 5% of elderly US residents undergo cataract procedures. Because 1% to 5% of male patients are taking tamsulosin at the time of surgery, a sizable proportion of patients may experience IFIS. However, few studies have been large enough to assess the connection between tamsulosin exposure and postoperative complications. In addition, it is unclear whether proximity of therapy to the surgery is important or whether complications are equally likely with α-blockers other than tamsulosin.

Accordingly, we undertook a large, population-based analysis of postoperative adverse events experienced by patients who were prescribed tamsulosin or other α-blockers at the time of cataract surgery. To assess specificity of effect, we also studied exposure to proton pump inhibitors—drugs for which an increased risk of adverse events would not be expected.

**METHODS**

**Overview**

We used several linked administrative databases and a nested case-control design to study serious ophthalmic adverse events experienced by Ontario residents who underwent cataract surgery between 2002 and 2007. Cases were those who experienced an adverse ophthalmic surgical outcome within 14 days of cataract surgery. Controls were selected from those patients who had cataract surgery but who had no such adverse event. The study protocol was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto. The analysis was performed at the Institute for Clinical Evaluative Sciences, which has statutory authority to conduct health services research without consent using anonymized administrative data.

**Data Sources**

The province of Ontario has a universal health insurance program that covers all 12 million residents. Records from 3 health administrative databases were linked using encrypted unique identifiers. The Ontario Drug Benefit database contains highly accurate records of all outpatient prescriptions dispensed to patients aged 65 years or older. The Ontario Health Insurance Plan database contains information on inpatient and outpatient physician services. This database has excellent reliability for surgical procedures. The Ontario Registered Persons database contains demographic and vital status information on all residents. All 3 databases are virtually complete for the variables used in this research.

**Cohort Identification**

We used the Ontario Health Insurance Plan database to identify patients aged 66 years or older who had cataract surgery between April 1, 2002, and June 16, 2007. For those who had multiple procedures over the accrual period, we studied the first. Because BPH was the only indication for tamsulosin for formulary coverage in Ontario and it is the only US Food and Drug Administration–labeled indication, women were excluded. We also excluded those who had other eye procedures in combination with their cataract surgery, those who had eye procedures other than cataract surgery in the preceding 5 years, those prescribed topical cyclosporine within 90 days of surgery, those who died within 14 days of surgery, and those who had a second cataract surgery within 14 days.

**Postoperative Adverse Events: Case Ascertainment**

Case patients had a physician service claim for any 1 of 4 procedures (vitrectomy, vitreous aspiration or injection, dislocated lens extraction, or air or fluid exchange) between 1 and 14 days after cataract surgery. Procedures occurring on the same day as the surgery were not included. These procedures were a composite outcome for serious postoperative ophthalmic adverse events and served as indicators of retinal detachment, lost lens or lens fragment, and suspected endophthalmitis.

Lost lens or lens fragment was defined as any patient on whom the procedure for dislocated lens extraction was performed. Retinal detachment was defined as any patient on whom an air or fluid exchange was performed. Suspected endophthalmitis was defined as any patient on whom a vitrectomy or vitreous aspiration or injection was performed, which was not in tandem with a lost lens or lens fragment or air or fluid exchange. Outcomes were recorded regardless of who patients saw for their postoperative care.

**Selecting Controls**

From the subgroup of patients who did not experience an adverse ophthalmic event, we selected up to 9 controls per case. Controls were randomly selected and matched to cases according to the patient’s year of birth (within 3 years of case’s birth), the surgeon who performed the cataract procedure, and the year the cataract surgery was performed (within 1 year of the case’s surgery). This approach minimized bias due to patient age, surgeon volume and complication rates, and changes in surgical technique over time.

**Assessing Exposure to α-Blockers**

The drug exposure of primary interest was the relatively selective α1a-receptor blocker, tamsulosin. We also assessed exposure to other, less selective α-blocking agents: alfuzosin, doxazosin, prazosin, and terazosin. All of these drugs were covered by the Ontario Drug Benefit Program during the period of study and were identified using specific drug identification numbers recorded on paid claims in the Ontario Drug Benefit Database. Alfuzosin, doxazosin, and terazosin all had indications for BPH. Doxazosin, prazosin, and terazosin all had indications for hypertension.

We created 3 mutually exclusive exposure groups: (1) the recent-exposure group were individuals whose most re-
recent prescription for an α-blocker included the period of the 14 days before cataract surgery, incorporating a 20% grace period to accommodate nonadherence. This period was based on previous observations, (2) the previous-exposure group were those who filled a prescription in the year prior to surgery but who did not qualify for the recent-exposure group (ie, those whose drug supply [plus a 20% grace period] ended between 15 and 365 days before cataract surgery); and (3) the no-exposure group were patients who had no exposure to an α-blocking drug in the 365 days before surgery.

Because some patients received more than 1 study drug before surgery, we used a hierarchical approach to the exposures. We considered a recent exposure to a medication to be more important than a previous exposure, and exposure to tamsulosin (the drug of primary interest) to be more important than exposure to another α-blocker. For example, a patient who satisfied the criteria for recent tamsulosin exposure could have a prior or overlapping prescription for another α-blocker but would remain in the recent-tamsulosin category.

**Covariates**

Our analysis adjusted for several potential confounders (Table 1). Individual-level income status was based on the Ontario Drug Benefit program’s income test for prescription copayment. A count of the number of medications dispensed in the year prior to surgery was used as a validated measure of comorbidity. Those prescribed an anti-diabetic medication in the year before surgery were defined as having diabetes. We also adjusted for topical eye medications prescribed within 90 days of cataract surgery. These drugs were grouped according to indication or mechanism of action to avoid overfitting the statistical model.

**Statistical Analysis**

We used descriptive statistics to characterize cases and controls. Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between adverse events and the following: recent tamsulosin exposure, recent exposure to another α-blocker, previous tamsulosin exposure, and previous exposure to another α-blocker. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). For the study’s case-control ratio of 4, independence in the probability of exposure among cases and controls, and a type I error probability of 0.05, our study had 88% power to reject the null hypothesis of an OR of 1 for a clinically significant unadjusted odds ratio of 2.5. This was based on a cataract surgery cohort of approximately 100 000 men, 3% taking tamsulosin at the time of surgery, and 0.3% experiencing a postoperative adverse event. We used a 2-sided test of significance at the P < .05 level.

**Test for Specificity**

We assessed specificity of effect using proton pump inhibitors as a tracer exposure, an exposure for which we would not expect an association with serious ophthalmic adverse events from cataract surgery. Those analyses excluded patients who had any exposure to tamsulosin or another α-blocker in the 365 days preceding cataract surgery.

### Table 1. Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Characteristicsa</th>
<th>Case (n = 280)</th>
<th>Control (n = 1102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>77.1 (6.6)</td>
<td>76.9 (6.3)</td>
</tr>
<tr>
<td><strong>Diabetes, No. (%)b</strong></td>
<td>79 (28.2)</td>
<td>232 (21.1)</td>
</tr>
<tr>
<td><strong>Low income status, No. (%)</strong></td>
<td>73 (26.1)</td>
<td>241 (21.9)</td>
</tr>
<tr>
<td><strong>No. of drugs in previous y, mean (SD)</strong></td>
<td>10.6 (6.1)</td>
<td>9.4 (5.5)</td>
</tr>
<tr>
<td><strong>Topical eye treatment within 90 d, No. (%)</strong></td>
<td>219 (78.2)</td>
<td>906 (82.2)</td>
</tr>
<tr>
<td><strong>Glaucoma treatment</strong></td>
<td>171 (61.1)</td>
<td>702 (63.7)</td>
</tr>
<tr>
<td><strong>Antibiotics or antiviral treatment</strong></td>
<td>35 (12.5)</td>
<td>139 (12.6)</td>
</tr>
<tr>
<td><strong>Combination treatment with steroids and antibiotics, No. (%)</strong></td>
<td>42 (15)</td>
<td>128 (11.6)</td>
</tr>
</tbody>
</table>

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

*Users of antiallergy and mydriatic drugs were not listed for confidentiality purposes because the cell sizes included fewer than 6 persons.

**Diabetes is defined as prescription for an antidiabetic medication in the year prior to surgery.**

### Estimate of Absolute Risk of Recent Tamsulosin Exposure

We calculated the event rate for our composite end point over the 5-year study period for all patients undergoing cataract surgery to estimate the absolute risk associated with recent tamsulosin exposure. We applied the estimated adjusted OR for recent tamsulosin exposure from the nested case-control analysis to the baseline event rate in the cohort to estimate the number needed to harm (NNH, for which, NNH = 100 × [1/absolute risk increase], and absolute risk increase = estimated absolute risk [OR × baseline event rate] – baseline event rate).

### RESULTS

We identified 96 128 older men who had cataract surgery over the 5-year study period. There were 3550 patients (3.7%) who had recent exposure to tamsulosin and 1006 (1.1%) who had previous exposure to tamsulosin. There were 7426 patients (7.7%) who had recent exposure to other α-blocking medications and 1683 (1.1%) who had previous exposure. We identified 284 case patients (0.3%) who experienced an adverse event in the 14 days after surgery. Of these 284 cases, 175 had a procedure for lost lens or lens fragment, 35 for retinal detachment, and 26 had both. One hundred had suspected endophthalmitis. Of the 284 cases, 280 were matched to 1102 control patients; more than 96% of cases...
were matched to 4 controls. The average age of cases and controls was 77 years, and both groups were dispensed an average of approximately 10 medications in the year preceding cataract surgery. Over one-fifth of the sample had diabetes and low-income status, respectively (Table 1).

In our primary analysis of adverse events following cataract surgery, 21 case patients (7.5%) and 30 control patients (2.7%) received tamsulosin in the 14 days before surgery. This resulted in an adjusted OR of 2.33 (95% CI, 1.22-4.43; Table 2) For patients prescribed other α-blockers (7.5%) and 88 control patients (8.0%) received the medication in the 14 days preceding surgery (adjusted OR, 0.91; 95% CI, 0.54-1.54).

Those who had previous exposure to tamsulosin were not at elevated risk for complications (≤5% case patients [≤1.8%] vs 11 control patients [1.0%]; adjusted OR, 0.94; 95% CI, 0.27-3.34). Previous exposure to other α-blockers also was not associated with elevated risk (8 case patients [2.9%] vs 23 control patients [2.1%]; adjusted OR, 1.08; 95% CI, 0.47-2.48). For our test of specificity, neither recent nor previous exposure to proton pump inhibitors was associated with increased risk for a postoperative adverse event (Table 2).

Our findings are strengthened by the inclusion of consecutive surgeries, the population-based nature of the sample, and the negative finding within the tracer population of proton pump inhibitor users. Because the cataract surgery and adverse outcomes were linked regardless of what physician the patients saw postoperatively, cases were lost to follow-up only when patients sought postoperative care outside the province—an extremely infrequent occurrence. The case-control design is well-suited to this question because serious cataract surgical complications are rare, and nesting the analysis within a predefined cohort helped to identify suitable controls. Furthermore, matching according to age, surgeon, and year of surgery served to minimize bias.

Our overall adverse event rate is comparable with those from other studies. However, most studies examining the effect of tamsulosin have been small and have focused on the intermediate measure of IFIS. Furthermore, few have studied the effect of timing of tamsulosin therapy or controlled for potential confounders, such as surgeon volume and ocular and disease comorbidity. Thus, our study contributes on several fronts.

Why did we find an effect with tamsulosin but not with other α-blocking drugs? This may relate to differences in receptor affinity between tamsulosin and other related medications. It is believed that tamsulosin is more highly selective for α1a-adrenergic receptors than other α-blocker drugs. These particular receptors are present in bladder-neck smooth muscle and in the iris dilator muscle. Blockage of the iris dilator allows unopposed action of the parasympathetically innervated iris constrictor muscle and loss of iris tone, resulting in the clinical syndrome of IFIS. In contrast, the design of the study and the hierarchical method of ascribing medication exposure precluded us from fully evaluating the effect of other α-blocking drugs. In many cases, those prescribed tamsulosin were previously prescribed another α-blocking drug so disentan-
TAMSULOSIN AND SERIOUS OPHTHALMIC ADVERSE EVENTS

Our study has several important limitations. First, we used administrative health data, which lacks clinical information for detailed case-mix adjustment. Noting the difficulty of the cataract surgery using clinical records may explain some of the observed differences in patient outcomes. However, our analysis did account for patient age, sex, and many potential confounders that could complicate cataract surgery such as diabetes and other eye diseases.

Second, our claims data confirm only that prescriptions were filled; not whether the drugs were ingested. Third, although our study included 96,128 consecutive cataract surgeries, the small number of patients in our subgroup analyses may have limited power to detect significant effects. Fourth, many study patients were accrued after published evidence of an association between tamsulosin and IFIS.7 We could not determine whether surgeons anticipated IFIS or used medical or surgical interventions such as iris expansion hooks, intracameral phentolamine, or preoperative atropine.34,36 Such interventions might reduce risks for complications. Furthermore, a knowledge of tamsulosin exposure might lead to closer postoperative scrutiny, thereby increasing the diagnosis of adverse events. However, our study period also included several years prior to the first description of IFIS in 2005, and data from this earlier era would not be subject to increased surveillance and ascertainment bias. Moreover, the adverse events we selected are usually dramatic, quickly present to medical attention, and require procedural interventions.

Fifth, we did not assess whether high doses of the individual α-blocking drugs were associated with changes in risk. Again, these types of subgroup analyses would have limited power due to the low adverse event rates in cataract surgery. Sixth, we excluded adverse events occurring more than 2 weeks after surgery, which may underestimate the true adverse event rate. However, most such cases would usually present within this time frame.

Seventh, our estimate of retinal detachment may be an underestimate because we captured retinal detachments repaired via vitrectomy and air or fluid exchange but not those repaired by scleral buckling. Similarly, our estimate of lost lens or lens fragment may be an underestimate because the procedure of dislocated lens extraction may not be performed if the lost lens or lens fragment is not considered to compromise visual outcome. Eighth, our hierarchical approach to drug exposure assessment did not account for possible interaction or additive effects of α-blocking medications. Ninth, since we did not measure IFIS directly, we are unable to definitively connect the adverse outcomes with IFIS. Tenth, our study was restricted to men older than 65 years. The findings may still pertain to younger individuals, although they may have a lower absolute risk of adverse events.

Finally, because our data sources do not specify which eye underwent cataract surgery, it is possible that we captured postoperative complications occurring in the contralateral (nonoperative) eye. However, requiring such care within 2 weeks of surgery should be extraordinarily rare. Similarly, the procedures counted as adverse events can sometimes be unrelated to cataract surgery (eg, macular pathology from diabetes and macular degeneration). Still, it is unlikely that procedures for these conditions would be performed in the nonoperative or fellow eye within 2 weeks of cataract surgery. On balance, we believe it unlikely that any of these limitations would invalidate our principal finding of an increased risk of adverse events in patients dispensed tamsulosin in the weeks immediately preceding surgery.

Our finding that tamsulosin exposure is associated with an increased risk of postoperative complications concurs with prior studies of intraoperative adverse events. We believe that this is the first large study with an adequate study design to describe this effect and provide a population-based risk estimate (something that can only be done using population-based observational research). It is unclear whether drug discontinuation prior to surgery reduces this risk. Because the combination of cataract surgery and tamsulosin exposure is relatively common, patients should be properly appraised of the risks of drug therapy and preoperative systems should focus on the

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identification of tamsulosin use by patients. In this way, surgeons can plan and prepare for a potentially more complicated procedure or refer to someone with more experience.

Author Contributions: Dr Bell 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: Bell, Hatch, Fischer, Paterson, Gill, Anderson, Rochon.

Acquisition of data: Bell, Cernat.

Analysis and interpretation of data: Bell, Hatch, Fischer, Paterson, Gill, Gruneir, Bronskill, Anderson, Rochon.

Drafting of the manuscript: Bell, Hatch, Fischer, Paterson.

Critical revision of the manuscript for important intellectual content: Bell, Hatch, Fischer, Cernat, Paterson, Gill, Bronskill, Anderson, Rochon.

Statistical analysis: Bell, Cernat.

Obtained funding: Bell, Gill, Bronskill, Anderson, Rochon.

Administrative, technical, or material support: Fischer, Cernat.

Study supervision: Anderson, Rochon.

Financial Disclosures: Dr Hatch has been employed by the University of Toronto and the Toronto Western Hospital to coordinate clinical trials sponsored by Alcon and Novartis. Dr Fischer was last employed by Bayer Inc in 2004. No other authors have any potential or real conflicts of interest to declare. Dr Cernat performed the statistical analysis for this study and declares no conflicts of interest.

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Institute of Aging. Dr Bell is supported by a New Investigator Award from the CIHR Institute of Aging. Dr Bell CM, Hatch VW, Cernat G, Urbach DR. Surgeon volumes and selected patient outcomes in cataract surgery: a population-based analysis. Ophthalmology. 2007;114(3):405-410.
Hormone Therapy and Ovarian Cancer

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Context  Studies have suggested an increased risk of ovarian cancer among women taking postmenopausal hormone therapy. Data are sparse on the differential effects of formulations, regimens, and routes of administration.

Objective  To assess risk of ovarian cancer in perimenopausal and postmenopausal women receiving different hormone therapies.

Design and Setting  Nationwide prospective cohort study including all Danish women aged 50 through 79 years from 1995 through 2005 through individual linkage to Danish national registers. Redeemed prescription data from the National Register of Medicinal Product Statistics provided individually updated exposure information. The National Cancer Register and Pathology Register provided ovarian cancer incidence data. Information on confounding factors and effect modifiers was from other national registers. Poisson regression analyses with 5-year age bands included hormone exposures as time-dependent covariates.

Participants  A total of 909,946 women without hormone-sensitive cancer or bilateral oophorectomy.

Main Outcome Measure  Ovarian cancer.

Results  In an average of 8.0 years of follow-up (7.3 million women-years), 3068 incident ovarian cancers, of which 2681 were epithelial cancers, were detected. Compared with women who never took hormone therapy, current users of hormones had incidence rate ratios for all ovarian cancers of 1.38 (95% confidence interval [CI], 1.26-1.51) and 1.44 (95% CI, 1.30-1.58) for epithelial ovarian cancer. The risk declined with years since last use: 0 to 2 years, 1.22 (95% CI, 1.02-1.46); more than 2 to 4 years, 0.98 (95% CI, 0.75-1.28); more than 4 to 6 years, 0.72 (95% CI, 0.50-1.05), and more than 6 years, 0.63 (95% CI, 0.41-0.96). For current users the risk of ovarian cancer did not differ significantly with different hormone therapies or duration of use. The incidence rates in current and never users of hormones were 0.52 and 0.40 per 1000 years, respectively, i.e., an absolute risk increase of 0.12 (95% CI, 0.01-0.17) per 1000 years. This approximates 1 extra ovarian cancer for roughly 8300 women taking hormone therapy each year.

Conclusion  Regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increased risk of ovarian cancer.

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National Register of Medicinal Product Statistics, which includes information on all redeemed prescriptions at Danish pharmacies since January 1994; (3) the Danish Cancer Register, which includes all cancer cases since 1943; (4) the Pathology Register, which includes information on all histological examinations performed at Danish pathology departments since 1978, however, complete since 1997; (5) the National Register of Patients, which comprises information on discharge diagnoses and surgical codes on all somatic hospitalizations since 1976 and information on births since 1960; (6) the Cause of Death Register, which comprises information on causes of death from death certificates; and (7) Statistics Denmark, which provides a yearly update on the education and employment status on all Danish citizens based on the integrated database for labor market research. Because the National Register of Medicinal Product Statistics is considered complete as of January 1, 1995, this was the date of study start.

Study Population
The present study includes women from the DaHoRS restricted to all Danish women who were at least 50 years by January 1, 1995, through December 31, 2005 (n = 960,887; Figure 1).

The study was approved by the Danish Data Protection Agency and the Danish Medicinal Agency (Lægemiddelstyrelsen). The Danish Ethical Committee takes no interest in Danish Register studies and informed consent is not required.

Exclusion Criteria and Censoring
From the initial 960,887 women, we excluded women registered in the Danish Cancer Register with a diagnosis of ovarian cancer prior to entry (1943-1995 or after January 1, 1995, but prior to their 50th birthday). This was to ensure that all the women in the analysis had not ever had ovarian cancer.

Because the National Register of Patients was updated until December 31, 2005, we used this register for censoring during follow-up of other cancers that potentially would have caused a change in ordination of HT in Denmark. The same register was used for exclusion of these cancers prior to entry (1980-1995 or after January 1, 1995, but prior to their 50th birthday). The cancers were specified by the World Health Organization International Classification of Diseases (ICD) codes version ICD-8 for the years 1980-1993 and ICD-10 from 1994 to present (ICD-8/ICD-10).

Figure 1. Flow Diagram of Study Participants

- 2,067,135 Women aged >15 y in the Civil Registration System
- 960,887 Aged 75.0-80 y between 1995 and 2005
- 34,827 Excluded (had previous cancer)
- 926,000 Had no hormone-related cancers before study entry
- 107,054 Had no bilateral oophorectomy or salpingo-oophorectomy before study entry
- 1,018 Excluded 107 y aged >38.0 y 1. Ovarian cancer at study entry
- 909,946 Included in the analysis
- 575,883 Never used hormone therapy
- 334,063 Used hormone therapy

Because the National Register of Patients, prior to entry (1980-1995 or after January 1, 1995, but prior to their 50th birthday) had bilateral oophorectomy (surgical code, 60120 or KLAE20/21) or bilateral salpingo-oophorectomy (60320 or KLAF10/11) were excluded (n = 16,006).

Women who were 80 years or older (n = 107) or had a diagnosis of ovarian cancer on the day of study entry (n = 1) were excluded. This left a total of 909,946 women at study entry.

Censoring was made at time of death, emigration, event of other cancers known to influence hormone use, at time of bilateral oophorectomy or salpingo-oophorectomy, at 80 years, or at the end of the study period.

Identification of Exposure (Postmenopausal Hormone Use)
The study cohort was linked to the National Register of Medicinal Product Statistics using the personal identification number as the key identifier. The register includes information on the date of the redeemed prescription, the specific Anatomical Therapeutical Chemical code, dose, number of packages, defined daily doses, and route of administration (tablet, patch, gel, etc). The included codes have been previously described. Briefly, prior to data retrieval, detailed rules were used to allocate the different subgroups of hormone use and for shift between different groups. The prescribed defined daily doses determined the length of use, and combination therapy trumped single-preparation therapy in the case of contemporary prescriptions even though the estrogen dose was upgraded.

The information on initiation of hormone use (ie, redeemed prescriptions) was updated daily for each individual during the study period. All the records of hormone exposure were prolonged by 4 months at the expiration of the prescription to account for delay in the recorded diagnoses in Danish registers, prolonged HT for those taking less than the defined daily dose prescribed, and a minor latency time. Thus, gaps between prescriptions were filled prospectively if not longer than 4 months.

Because HT probably acts as a promoter of the ovarian cancer carcinogenesis with a minor latency time, women currently taking hormones were allocated to the hormone type taken for the longest period during the study period. However, these variables were time dependent, ie, a change in HT type would recategorize a woman...
into a new category of HT, if at the time she was taking a new HT longer than the former HT.

Exposure to hormones before age 50 years, but within the 11-year study period, was added to the hormone status and duration of use. This allowed for sensitivity analyses on the effect of less complete exposure history among women entering the cohort at older ages.

To account for women redeeming only 1 prescription (nonadherence), a category of less than a year of use was included in the duration variable. Hormone therapy was categorized according to HT status, which includes never, past, current nonvaginal HT, current vaginal estrogen (0.25 mg/d typically taken over 2-3 days) or hormone intrauterine device (IUD); hormone formulation, which includes never, past, estrogen only, estrogen/progestin, progestin only, tibolone and raloxifene, hormone IUD, or vaginal estrogen; hormone regimen, which includes never, past, cyclic combined EPT, long-cycle combined EPT (ie, simultaneous redemption 7-14 days), or hormone intrauterine device (IUD); hormone formulation, which includes never, past, estrogen only, estrogen/progestin, progestin only, tibolone, raloxifene, hormone IUD, or vaginal estrogen; route of administration, which includes never, past, oral estrogen, dermal estrogen, oral combined estrogen plus progestin, dermal combined estrogen plus progestin, hormone IUD, or vaginal estrogen; estrogen type, which includes never, past, norethisterone acetate, medroxyprogesteron, levonorgestrel, cyproterone acetate, estrogen only, tibolone, raloxifene, hormone IUD, or vaginal estrogen; estrogen dose, which includes never, past, high (>2 mg/d of estradiol), middle (1-2 mg/d), low (<1 mg/d), tibolone, raloxifene, hormone IUD, or vaginal estrogen; duration of HT, which includes never, past, current, <1, 1 to 4, >4 to 7, and >7 years, hormone IUD, or vaginal estrogen; and time since last use in years among former users, which includes current, 0 to 2, >2 to 4, >4 to 6, and >6 years, hormone IUD, or vaginal estrogen).

Identification of Ovarian Cancer Cases
The Danish Cancer Register was used until December 31, 2002, for identification of primary invasive ovarian cancer using the ICD for oncology topography code 183.0 and morphology codes ending with a 3. At the time of this study, information from January 2003 was not updated in the Danish Cancer Register. Thus, from 2003 the Pathology Register was used for case finding until December 31, 2005. The Systemized Nomenclature of Medicine topography codes were between 87 000-87 800 and the morphology codes ending with a 3.

Information on the histology of tumors was obtained from the Danish Cancer Register until 2003 and from the Pathology Register from 2003. The tumors were classified as either epithelial tumors (ie, clear cell, endometroid, mucinous, serous, adenocarcinoma not otherwise specified, and epithelial or nonepithelial tumors (ie, sex cord stromal, germinal cell, and tumors not otherwise specified or other morphology codes ending with a 3). Borderline tumors were not included. No histology information was available for 8 women with ovarian cancer. These women were excluded from the analyses of the associations between HT and epithelial ovarian cancer but were included in the overall ovarian cancer analyses.

Analysis
The data were analyzed with Poisson regression analysis using SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina). Incidence rate ratios (RRs) and 95% confidence intervals (CIs) were calculated for each model. Age was calculated from birth dates, which were extracted from personal identification numbers. Age was used as the timescale in the Poisson regression analyses, and data were divided into 5-year age bands (50-54, etc), assuming a constant risk of ovarian cancer within each band. Each model was checked for significance of interaction between age and exposure. All tests were 2 sided with a 5% significance level.

Furthermore, hysterectomy, period of use, and duration of HT were evaluated as possible effect modifiers; no effect modification was found, however. Potential confounders were number of births (0, 1, 2, >2) (ICD8/ICD10: 650-666/DO 60-84), hysterectomy (surgical code, 610/KLCD00-97), sterilization (608-640/KLGA), unilateral oophorectomy (60100/KLAE10-11), and unilateral salpingooophorectomy (60300/KLAE00/01), endometriosis (625-29-39/DN80), infertility (628/DN97), and educational status in 1995 (no education after elementary or high school; occupational basic education; short-term, middle-term, or long-term education; or educational status unknown). In addition, adjustments were made for period of use (1995-2002 or 2003-2005) to account for possible differences in ovarian cancer diagnosis in the Danish Cancer Register and Pathology Register. The following variables were time dependent: HT variables, hysterectomy, sterilization, unilateral oophorectomy or salpingooophorectomy, and number of births. Women who had been diagnosed with endometriosis or infertility were considered being in this condition during the study period.

The crude models included hormone exposure, age, and period of use. Analyses were performed for all ovarian cancers as well as for all epithelial cancers. The number of women exposed to progestin-only therapy, raloxifene, tibolone, hormone IUD combinations, and conjugated estrogens were too few to determine risk estimates.

The reference group were those who had never used any HT.

Differences between HT types were tested; ET vs EPT, long cyclic and cyclic vs continuous EPT, and transdermal or vaginal vs oral HT. We took consistency of findings into consideration when the interpretation was made.

The least detectable difference between never and current users with a power of 80% and significance level of 5% was an RR of 1.14. For comparisons between ET vs EPT and cyclic vs continuous EPT, the least detectable difference was an RR of 1.3.
Two sensitivity analyses were performed. In the first analysis, we carried forward the first recorded HT that each woman used to the remaining exposed time. Thus, events of ovarian cancer were linked to the first-used HT. In the second analysis, we censored women who had changed to another HT type during follow-up but were included in the analysis if they had started and stopped the same HT.

Incidence rates (cases/person-years) were calculated among never and current users per 1000 years using crude data. The absolute risk difference (incidence ratesexposed−incidence rateunexposed) and the number needed to harm (1/(incidence ratesexposed −incidence rateunexposed)) were also calculated.

**RESULTS**

From 1995 to 2005, 909,946 perimenopausal and postmenopausal women with no previous hormone-sensitive cancer or bilateral oophorectomy or salpingo-oophorectomy accumulated 7.3 million women-years corresponding to an average follow-up of 8.0 years. The number of incident malignant ovarian cancers during the study period was 3068. Of these, 2681 were epithelial tumors, including 1336 serous tumors, 377 endometroid, 293 mucinous, 159 clear cell, and 115 nonspecified epithelial tumors, and 401 adenocarcinoma not otherwise specified. Only 55 were nonepithelial tumors, and 324 were unspecified. Eight cases had no information on histology. The focus of this study was on the epithelial cancers.

At the end of follow-up, 63% of the women had not been taking HT, 22% were previous users of hormones, and 9% current users of hormones. Among the current users, 46% had used hormones for more than 7 years. Compared with never users, more hormone users had hysterectomy or unilateral salpingo-oophorectomy (Table 1). Among the never users, fewer women were sterilized and fewer were parous (Table 1). Compared with never users, more women taking ET and transdermal HT had surgical procedures (hysterectomy, unilateral salpingo-oophorectomy, or oophorectomy) and endometriosis. More women taking ET were sterilized.

### Table 1. Characteristics of the Study Population According to Hormone Use

<table>
<thead>
<tr>
<th>Characteristic at End of Follow-up</th>
<th>Hormone Status</th>
<th>Formulation</th>
<th>Type of Combined Regimen</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
<td>Previous</td>
<td>Current</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Women, No.</td>
<td>575,883</td>
<td>198,184</td>
<td>83,810</td>
<td>25,890</td>
</tr>
<tr>
<td>Women-years, No.</td>
<td>4,987,264</td>
<td>841,491</td>
<td>1,183,980</td>
<td>355,420</td>
</tr>
<tr>
<td>Incidence of ovarian cancer, No.</td>
<td>2011</td>
<td>320</td>
<td>620</td>
<td>195</td>
</tr>
<tr>
<td>Age, y, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>22.7</td>
<td>15.4</td>
<td>19.1</td>
<td>14.0</td>
</tr>
<tr>
<td>55-59</td>
<td>19.0</td>
<td>25.3</td>
<td>26.4</td>
<td>22.2</td>
</tr>
<tr>
<td>60-64</td>
<td>16.8</td>
<td>24.4</td>
<td>22.3</td>
<td>21.9</td>
</tr>
<tr>
<td>65-69</td>
<td>14.8</td>
<td>14.9</td>
<td>15.4</td>
<td>17.0</td>
</tr>
<tr>
<td>70-74</td>
<td>13.7</td>
<td>10.4</td>
<td>10.3</td>
<td>13.2</td>
</tr>
<tr>
<td>75-79</td>
<td>13.2</td>
<td>8.7</td>
<td>7.0</td>
<td>11.3</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>62.5 (8.8)</td>
<td>62.4 (7.5)</td>
<td>61.5 (7.5)</td>
<td>63.5 (7.9)</td>
</tr>
<tr>
<td>Duration of HT, y, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>18.6</td>
<td>5.1</td>
<td>4.7</td>
<td>5.4</td>
</tr>
<tr>
<td>1-4</td>
<td>31.4</td>
<td>15.2</td>
<td>12.8</td>
<td>16.1</td>
</tr>
<tr>
<td>&gt;4-7</td>
<td>20.7</td>
<td>18.7</td>
<td>15.0</td>
<td>19.6</td>
</tr>
<tr>
<td>&gt;7</td>
<td>29.2</td>
<td>45.8</td>
<td>56.2</td>
<td>44.0</td>
</tr>
<tr>
<td>Higher education, No. (%)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>17.8</td>
<td>20.4</td>
<td>16.3</td>
<td>23.3</td>
</tr>
<tr>
<td>Parous women, No. (%)</td>
<td>75.2</td>
<td>83.5</td>
<td>80.4</td>
<td>76.1</td>
</tr>
<tr>
<td>No. of children, mean (SD)</td>
<td>1.7 (1.3)</td>
<td>1.9 (1.2)</td>
<td>1.6 (1.2)</td>
<td>1.8 (1.1)</td>
</tr>
<tr>
<td>Medical history, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>6.2</td>
<td>12.2</td>
<td>18.0</td>
<td>50.9</td>
</tr>
<tr>
<td>Unilateral salpingo-oophorectomy</td>
<td>1.9</td>
<td>3.7</td>
<td>5.7</td>
<td>12.3</td>
</tr>
<tr>
<td>Unilateral oophorectomy</td>
<td>0.6</td>
<td>1.2</td>
<td>1.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Sterilized</td>
<td>5.4</td>
<td>7.9</td>
<td>8.4</td>
<td>8.4</td>
</tr>
<tr>
<td>Infertility</td>
<td>1.6</td>
<td>2.0</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>1.1</td>
<td>2.1</td>
<td>3.4</td>
<td>7.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Hormone interuterine device (IUD) not shown. Oral hormone therapy (HT) not shown, because current use mainly comprises oral administration.

<sup>b</sup>Exclusive vaginal estrogen therapy (ET), hormone IUD, and injections (2 cases).

<sup>c</sup>Exclusive oral HT.

<sup>d</sup>Exclusive vaginal ET.

<sup>e</sup>Exclusive long cycle estrogen plus progestin therapy.

<sup>f</sup>Exclusive vaginal ET and hormone IUD, thus percentages do not sum to 100%.

<sup>g</sup>To account for women redemining only 1 prescription (nonadherence).

<sup>h</sup>Educational status in 1995: higher education includes short term (1-2 y) (3.2%), middle term (3-4 y) (13.1%), and long (5-6 y) (2.1%) education.

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long-term users (>7 years) and fewer were parous than were women taking EPT (Table 1). Current users of HT had an overall increased risk of ovarian cancer (RR, 1.38; 95% CI, 1.26-1.51). When restricting the analyses to epithelial ovarian cancer, the RR among current users was 1.44 (95% CI, 1.30-1.58; Table 2). Previous users had an RR of 1.15 (95% CI, 1.01-1.30) compared with women who had never used HT. The RR values for ovarian cancer and epithelial ovarian cancer did not increase significantly with increasing durations of HT (Table 2). The duration categories of less than a year and between 1 to 4 years were combined because the risk values were similar.

We subcategorized previous users according to time since last use and found an increased risk for epithelial ovarian cancer for a period of up to 2 years after cessation of HT. Thereafter, the risk approached that observed in never users (Figure 2). The RRs for time since use in years were 1.22 (95% CI, 1.02-1.46) from 0 to 2 years, 0.98 (95% CI, 0.75-1.28) from more than 2 to 4 years, 0.72 (95% CI, 0.50-1.05) from more than 4 to 6 years, and 0.63 (95% CI, 0.41-0.96) for more than 6 years. The RR values for time since last use were similar after additional adjustment for previous hormone duration. Crude and adjusted RR values were nearly identical (data not shown).

**Continuous vs Cyclic Therapies**

Compared with women who had never taken HT, women taking cyclic EPT or EPT for long cycles were at higher risk of epithelial ovarian cancer (RR, 1.50; 95% CI, 1.34-1.68; Table 3). The difference between ET and EPT was not statistically significant (P = .16).

Compared with women who never took HT, increasing the daily dose of estrogen was not consistently associated with the risk of epithelial ovarian cancer, and adjustment for the duration of HT did not change the estimates (Table 3). Increasing the duration of ET was weakly associated with the risk of epithelial ovarian cancer, while no consistent associations between duration of EPT use and risks of epithelial ovarian cancer were found (Figure 3).

**Estrogen Therapy vs Combined Therapy**

Compared with women who had never taken HT, those who had were at increased risk of epithelial ovarian cancer (RR, 1.31; 95% CI, 1.11-1.54) (Table 3). Similarly, women currently taking EPT also had an increased risk of epithelial ovarian cancer compared with never users (RR, 1.50; 95% CI, 1.34-1.68; Table 3). The difference between ET and EPT was not statistically significant (P = .16).

Compared with women who never took HT, increasing the daily dose of estrogen was not consistently associated with the risk of epithelial ovarian cancer, and adjustment for the duration of HT did not change the estimates (Table 3). Increasing the duration of ET was weakly associated with the risk of epithelial ovarian cancer, while no consistent associations between duration of EPT use and risks of epithelial ovarian cancer were found (Figure 3).

---

**Figure 2. Risk of Epithelial Ovarian Cancer Among Former Hormone Users by Time Since Use**

Error bars indicate 95% confidence intervals.

---

**Table 2. Risk of Ovarian Cancer by Hormone Therapy Status and Duration of Use**

<table>
<thead>
<tr>
<th>HT Status</th>
<th>All Malignant Ovarian Cancers</th>
<th>Epithelial Ovarian Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Person-Years</td>
</tr>
<tr>
<td>Never</td>
<td>2011</td>
<td>4,987,264</td>
</tr>
<tr>
<td>Previous</td>
<td>320</td>
<td>841,491</td>
</tr>
<tr>
<td>Current</td>
<td>620</td>
<td>1,183,980</td>
</tr>
<tr>
<td>Other</td>
<td>117</td>
<td>258,209</td>
</tr>
<tr>
<td>Duration of HT, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>338</td>
<td>643,375</td>
</tr>
<tr>
<td>&gt;4-7</td>
<td>185</td>
<td>332,137</td>
</tr>
<tr>
<td>&gt;7</td>
<td>97</td>
<td>208,468</td>
</tr>
<tr>
<td>Other</td>
<td>117</td>
<td>258,209</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval; HT, hormone therapy, RR, relative risk.

a Due to missing information on histology, 8 cases were excluded.

b Adjusted for age, period of use, number of births, hysterectomy, sterilization, unilateral oophorectomy or salpingo-oophorectomy, endometriosis, infertility, and educational status.

c Comprises vaginal estrogen therapy, hormone interuterine device, and injections (2 cases).
norgestrel, or cyproterone acetate (Table 3).

**Route of Administration**

Compared with never users, the group treated with transdermal administration of ET had a risk of ovarian cancer of 1.13 (95% CI, 0.74-1.71) vs an increased risk for those taking oral ET (RR, 1.34; 95% CI, 1.12-1.60); however, the difference was not statistically significant (P = .44; Table 3). Also, vaginal administration of ET was associated with a slightly increased risk of epithelial ovarian cancer (RR, 1.23; 95% CI, 1.00-1.52), not different from oral estrogen (P = .53).

Women taking oral EPT had an increased risk of epithelial ovarian cancer (RR, 1.48; 95% CI, 1.32-1.65) compared with women who never took HT (Table 3). There was no significant difference in the risk of epithelial ovarian cancer between the use of oral and transdermal EPT (P = .54).

**Crude Absolute Risks**

Crude incidence rates for ovarian cancer per 1000 years was 0.40 in never users and 0.52 in current users, which translates to an absolute risk difference of 0.12 per 1000 years. If the difference in risk between never users and current users is due to HT, these results imply that use of HT resulted in about 1 extra case of ovarian cancer for roughly every 8300 women taking HT each year. Applying the absolute risk difference to the hormone use in Denmark from 1995 to 2005 (number of person years: 1 183 980), hormone use is estimated to have resulted in about 140 additional cases of ovarian cancer over the mean follow-up of 8 years.

**Sensitivity Analyses**

The results did not change when women were allocated to the HT type used first. Nor did the results change when women were censored during follow-up at time of change to another HT type.

**COMMENT**

This cohort study confirms that women who have taken HT are at higher risk

---

**Table 3. Risk of Epithelial Ovarian Cancer by Current Use of Different Types of Hormone Therapy**

<table>
<thead>
<tr>
<th>Hormone Use</th>
<th>No of Cases</th>
<th>Person-Years</th>
<th>RR (95% CI)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1725</td>
<td>4 987 230</td>
<td>1 [Referent]</td>
</tr>
<tr>
<td>Previous</td>
<td>280</td>
<td>841 491</td>
<td>1.15 (1.01-1.30)</td>
</tr>
<tr>
<td>Formulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen only$^c$</td>
<td>170</td>
<td>355 420</td>
<td>1.31 (1.11-1.54)</td>
</tr>
<tr>
<td>Estrogen + progestin</td>
<td>384</td>
<td>802 082</td>
<td>1.50 (1.34-1.68)</td>
</tr>
<tr>
<td>Other$^d$</td>
<td>122</td>
<td>282 841</td>
<td></td>
</tr>
<tr>
<td>Estrogen dose$^e$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>77</td>
<td>169 277</td>
<td>1.39 (1.10-1.74)</td>
</tr>
<tr>
<td>Middle</td>
<td>235</td>
<td>459 219</td>
<td>1.51 (1.32-1.74)</td>
</tr>
<tr>
<td>High</td>
<td>224</td>
<td>479 099</td>
<td>1.41 (1.22-1.62)</td>
</tr>
<tr>
<td>Other$^d$</td>
<td>140</td>
<td>335 573</td>
<td></td>
</tr>
<tr>
<td>Type of combined regimen$^f$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-cycle estrogen + progestin</td>
<td>31</td>
<td>46 891</td>
<td>2.05 (1.44-2.93)</td>
</tr>
<tr>
<td>Cyclic estrogen + progestin</td>
<td>238</td>
<td>512 562</td>
<td>1.50 (1.31-1.72)</td>
</tr>
<tr>
<td>Continuous estrogen + progestin</td>
<td>115</td>
<td>242 630</td>
<td>1.40 (1.16-1.69)</td>
</tr>
<tr>
<td>Other$^d$</td>
<td>292</td>
<td>355 542</td>
<td></td>
</tr>
<tr>
<td>Progestin type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norethisterone acetate</td>
<td>269</td>
<td>534 312</td>
<td>1.55 (1.36-1.76)</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>38</td>
<td>91 860</td>
<td>1.37 (0.99-1.89)</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>32</td>
<td>78 880</td>
<td>1.30 (0.92-1.85)</td>
</tr>
<tr>
<td>Levonorgestrel acetate</td>
<td>6</td>
<td>23 508</td>
<td>0.87 (0.39-1.93)</td>
</tr>
<tr>
<td>Other$^d$</td>
<td>331</td>
<td>713 607</td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral estrogen</td>
<td>145</td>
<td>286 926</td>
<td>1.34 (1.12-1.60)</td>
</tr>
<tr>
<td>Transdermal estrogen</td>
<td>23</td>
<td>64 155</td>
<td>1.13 (0.74-1.71)</td>
</tr>
<tr>
<td>Oral estrogen + progestin</td>
<td>376</td>
<td>789 960</td>
<td>1.48 (1.32-1.65)</td>
</tr>
<tr>
<td>Transdermal estrogen + progestin</td>
<td>28</td>
<td>57 717</td>
<td>1.67 (1.15-2.42)</td>
</tr>
<tr>
<td>Vaginal estrogen alone</td>
<td>94</td>
<td>218 379</td>
<td>1.23 (1.00-1.52)</td>
</tr>
<tr>
<td>Other$^d$</td>
<td>10</td>
<td>25 030</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval, RR, relative risk.

$^a$The table is based on 5 separate regression models for formulation, regimen, route, estrogen dose, and progestin type.

Adjusted for age, time period, number of births, hysterectomy, sterilization, unilateral oophorectomy and salpingo-oophorectomy, endometriosis, infertility, and educational status.

Exclusive vaginal estrogen. A total of 2 cases were receiving estrogen injections.

$^c$Comprises the other hormone therapy types not relevant for the specific hormone of interest.

$^d$Additionally adjusted for duration of use.

$^e$Long-cycle estrogen plus progestin therapy: 7-14 times more defined daily dose of estrogen than the defined daily dose of progestin; cyclic estrogen plus progestin therapy: up to 7 times more estrogen than progestin; continuous estrogen plus progestin therapy: daily estrogen and progestin administration.

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**Figure 3. Risk of Epithelial Ovarian Cancer According to Duration of Different Hormone Therapies**

Error bars indicate 95% confidence intervals.

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of epithelial ovarian cancer than women who have not (range, 30%-58%). In agreement with findings from the Million Women Study, the risk of ovarian cancer did not differ significantly by formulation, regimen, type of progestin, or route of administration.3

Duration and Dosage

Our data show increased risk of ovarian cancer even with short durations of hormone use (0-4 years). This finding contrasts some prior studies that were not able to detect increased risk with HT of less than 5 years.2-4

In regard to ET, we found an increasing risk of cancer with increasing length of use, which is in accordance with findings from the Nurses’ Health Study.2 One Danish study found that the cumulative ET dose was more important than the duration of use.8 In our study, however, no consistent association was found between increasing dose of ET and the risk of ovarian cancer.

In accordance with the Million Women Study and the Nurses’ Health Study, past HT users had only a slightly increased risk of ovarian cancer, and the excess risk was not apparent 2 years after cessation.2,3

Estrogen vs Combined Therapy

In agreement with 2 recent studies, we found that ET and EPT were associated with an approximately similar and increased risk of ovarian cancer.3,5 A review and meta-analysis of data published between 1966 and 2006 also supports our finding of an increased risk of ovarian cancer associated with both ET and EPT.1 Another recent study was only able to detect increased risks of ovarian cancer with use of combined therapies for 5 or more years.5

Cyclic vs Continuous Hormone Regimen

A higher risk of ovarian cancer has been suggested for women taking EPT cyclically than women taking EPT continuously.3,5 The Women’s Health Initiative (WHI) reported an increased risk of ovarian cancer associated with continuous EPT compared with placebo.9 We found that both cyclic and continuous EPT increased the risk of ovarian cancer, but the risks did not differ significantly in magnitude. Typically, women taking EPT continuously have taken cyclic EPT previously. However, the results were similar after restricting the analyses to women not changing HT type during follow-up.

Administration and Hormone Types

In accordance with the Million Women Study, we found no significant difference in risk according to route of administration.3 The slightly increased risk with vaginal administration of ET is not documented in other studies. Therefore, caution should be taken with conclusions assuming causality. In the present study, norethisterone demonstrated the same risk as the other types of progestins, which is in line with a previous study.3 Few women, however, were exposed to the other progestins; therefore, we were unable to detect minor differences in risk.

Implications

The absolute risk increase was 0.12 per 1000 years. If this association is causal, use of hormones has resulted in roughly 140 extra cases of ovarian cancer in Denmark over the mean follow-up of 8 years, ie, 5% of the ovarian cancers in this study. Even though this share seems low, ovarian cancer remains highly fatal, so accordingly this risk warrants consideration when deciding whether to use HT.

Strengths

Our nationwide study is a large-scale (historical) prospective cohort study with 909,946 Danish women followed up for 11 years. We had complete follow-up until diagnosis of cancer, bilateral oophorectomy, emigration, death, or end of study. Our large number of outcomes permitted us to perform detailed subanalyses of separate hormone formulations, regimens, routes of administration, progestin types, different estrogen dosages, as well as different durations of HT. We consider the validity of our outcome to be high, because the Cancer Register has both a high level of completeness and correctness of diagnosis.10-12 We used the Pathology Register for case finding from 2002 until 2005. The agreement of histological ovarian cancer diagnoses between the Pathology Register and the Cancer Register is high, and our estimates did not depend on the source of diagnoses.13

The validity of our exposure is presumed to be high because recall bias was eliminated. The information on the prescribed HT was transferred automatically from the pharmacies by bar codes. Our information on both exposures and confounders was updated daily. The exposure information comprised at what time the women were exposed during our follow-up, for how long, and to which type of HT. Information on HT and ovarian cancer was registered in the Danish registers without the aim of exploring the association between HT and clinical outcomes, making differential ascertainment of exposure and cancer incidence unlikely.

We excluded women with previous hormone-sensitive cancer because this might affect both HT and the subsequent risk of ovarian cancer. Our results were adjusted for age, period of use, educational status, number of births, hysterectomy, sterilization, unilateral oophorectomy and salpingo-oophorectomy, endometriosis, and infertility. There was no significant confounding by any of the included variables. We attempted to account for delay in the diagnosis of ovarian cancer by prolonging exposure data by 4 months. Finally, our sensitivity analyses showed that our results remained the same after addressing HT first used and women exposed only to 1 type of HT during follow-up.

Limitations

We were not able to adjust for age at menopause and use of oral contraceptives. Women with early natural menopause are more likely to use hormones compared with women with late natural menopause. Because natural early menopause tends to decrease the
risk of ovarian cancer, more women taking HT could have an a priori decreased risk of ovarian cancer. Similarly, more previous users of oral contraceptives become hormone users in later life. Because oral contraceptives decrease the risk of ovarian cancer, our results may be slightly underestimated. The Million Women Study adjusted for age at menopause, oral contraceptive use, body mass index, alcohol consumption, smoking, and physical activity, but these adjustments did not show substantial changes in their findings, indicating only minor confounding by these factors. In addition, the Nurses’ Health Study reported only minimal changes in the association between HT and ovarian cancer after adjustment for relevant potential confounders, including duration of oral contraceptive use, natural menopause, and age at menarche.

Women with a family history of cancer are less likely to use HT. The lack of this potential confounder might have underestimated our results. For high body mass index and smoking, a recent Danish study found no associations with ovarian cancer risk as a combined outcome. The effect of physical activity on ovarian cancer risk is controversial.

Information on women who underwent surgical procedures was not available in the registers among the oldest women. Hysterectomy and oophorectomy reduce the risk of ovarian cancer and often lead to HT, probably causing an underestimation of our results among the older women. However, despite our uneven adjustment for confounders, the risk of ovarian cancer was nearly identical across age groups and was similar for the different HT types across age.

The missing potential confounders in this study are therefore not a major concern and will most likely not overestimate the effect.

Another limitation is the lack of information on hormone exposure prior to study entry. Thus, older women who were not prescribed HT during follow-up might have been taking hormones before the study entry. However, the association between HT use, duration of use, and risk of ovarian cancer was similar among young women for whom complete information on HT exposure history was available, compared with older women. This finding reduces the probability of bias caused by exposure misclassification. Finally, it is worth stating that whether the prescribed medicine was actually taken is questionable. Repeated prescriptions, however, reduce this potential bias. It is possible that some women take fewer pills than the prescribed defined daily doses, thereby prolonging the HT. This would tend to underestimate our results.

**CONCLUSION**

In conclusion, our study suggests an increased risk of ovarian cancer with both estrogen therapy and combined HT, with little influence of different regimens, progestin types, routes of administration, length of use, and different doses. Thus, the risk of ovarian cancer is one of several factors to take into account when assessing the risks and benefits of hormone use.

**REFERENCES**


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Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes
A Randomized Controlled Trial

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Diabetes mellitus is a powerful risk factor for cardiovascular events. The Framingham Heart Study reported that diabetes was associated with odds ratios for coronary heart disease of 1.5 and 1.8 for men and women, respectively, and relative risks for stroke of 1.4 and 1.7 for men and women, respectively. Individuals with diabetes have a 2- to 4-fold increased risk of developing cardiovascular events than those without diabetes.

Several earlier investigations have shown that aspirin therapy is established as a secondary prevention strategy for cardiovascular events. Clinical guidelines have recommended that individuals with risk factors for coronary heart disease should take aspirin for primary prevention and for secondary prevention; in particular, those with diabetes were considered good candidates for aspirin except for those with contraindications.

Context Previous trials have investigated the effects of low-dose aspirin on primary prevention of cardiovascular events, but not in patients with type 2 diabetes.

Objective To examine the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

Design, Setting, and Participants Multicenter, prospective, randomized, open-label, blinded, end-point trial conducted from December 2002 through April 2008 at 163 institutions throughout Japan, which enrolled 2539 patients with type 2 diabetes without a history of atherosclerotic disease and had a median follow-up of 4.37 years.

Interventions Patients were assigned to the low-dose aspirin group (81 or 100 mg per day) or the nonaspirin group.

Main Outcome Measures Primary end points were atherosclerotic events, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease. Secondary end points included each primary end point and combinations of primary end points as well as death from any cause.

Results A total of 154 atherosclerotic events occurred: 68 in the aspirin group (13.6 per 1000 person-years) and 86 in the nonaspirin group (17.0 per 1000 person-years) (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.58-1.10; log-rank test, \( P = .16 \)). The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; \( P = .0037 \)). A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.44; log-rank test, \( P = .67 \)). The composite of hemorrhagic stroke and significant gastrointestinal bleeding was not significantly different between the aspirin and nonaspirin groups.

Conclusion In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.

Trial Registration clinicaltrials.gov Identifier: NCT00110448

Context

For editorial comment see p 2180.
tion are limited. Several large trials of aspirin for primary prevention have examined its effects in subgroups with diabetes; these subgroup analyses did not demonstrate a significant effect on reducing vascular events because they were underpowered.17-21 Thus, a primary prevention trial of aspirin for diabetic patients is needed.

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial was undertaken to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

**METHODS**

The JPAD trial was a prospective, randomized, open-label, controlled trial with blinded end-point assessment. Patient enrollment started in December 2002 and was completed in May 2005; patients were followed up until April 2008. Patients were enrolled and followed up at 163 institutions throughout Japan. The institutional review board at each participating hospital approved this trial, and written informed consent was obtained from each patient.

**Trial Population**

The inclusion criteria were diagnosis of type 2 diabetes mellitus, age between 30 and 85 years, and ability to provide informed consent. The exclusion criteria were electrocardiographic changes consisting of ischemic ST-segment depression, ST-segment elevation, or pathologic Q waves; a history of coronary heart disease confirmed by coronary angiography; a history of cerebrovascular disease consisting of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and transient ischemic attack; a history of arteriosclerotic disease necessitating medical treatment; atrial fibrillation; pregnancy; use of antiplatelet or antithrombotic therapy, defined as aspirin, ticlopidine, cilostazol, dipryridamole, trapidil, warfarin, and argatroban; a history of severe gastric or duodenal ulcer; severe liver dysfunction; severe renal dysfunction, and allergy to aspirin.

**Trial Protocol**

Enrolled patients were randomly assigned to the aspirin group or the nonaspirin group. The randomization was performed as nonstratified randomization from a random number table. The study center prepared the sealed envelopes with random assignments and distributed them by mail to the physicians in charge at the study sites. Patients in the aspirin group were assigned to take 81 mg or 100 mg of aspirin once daily. Patients were followed up at each hospital visit or by telephone if necessary. Follow-up visits were scheduled every 2 weeks for patients seen in a clinic setting and every 4 weeks for patients seen in a hospital setting. Data for patients who were lost to follow-up were included at the day of last follow-up. Patients were allowed to use any concurrent treatment. Patients in the nonaspirin group were also allowed to use antiplatelet/thrombotic therapy, including aspirin, if needed and vice versa.

**End Points**

The primary end point was any atherosclerotic event, which was a composite of sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis) during the follow-up period. Key secondary end points were each primary end point and combinations of primary end points and death from any cause. Adverse events analyzed included gastrointestinal (GI) events and any hemorrhagic events other than hemorrhagic stroke. All potential primary end points, secondary end points, and adverse events were adjudicated by an independent committee on validation of data and events that was unaware of the group assignments.

**Sample Size Calculation**

For sample size calculation, we first estimated the incidences of cardiovascular and cerebrovascular events among Japanese diabetic patients. The incidence of cardiovascular death, myocardial infarction, and cerebrovascular events were 7.5, 7.5, and 8.0 events per 1000 Japanese diabetic patients per year, respectively, according to the Hi-sayama-cho study22 and Funagata study.23 The total incidence of the atherosclerotic events, including peripheral arterial disease, was suggested to be 3 times the aforementioned number by the Hypertension Optimal Treatment (HOT) study.24 Because the recent incidence of atherosclerotic events among Japanese individuals seemed relatively lower than that previously reported in Japan, we discounted 25% of the estimated 69 events that were expected to occur and estimated that 52 events per 1000 Japanese diabetic patients would occur annually.

Based on a 2-sided α level of .05, a power of 0.95, an enrollment period of 2 years, and a follow-up period of 3 years after the last enrollment, we estimated that 2450 patients would need to be enrolled to detect a 30% relative risk reduction for an occurrence of atherosclerotic disease by aspirin.19

**Statistical Analyses**

Efficacy comparisons were performed on the basis of time to the first event, according to the intention-to-treat principle, including all patients in the group to which they were randomized with patients lost to follow-up censored at the day of the last visit. Safety analyses were performed on data from all enrolled patients. Following the descriptive statistics, cumulative incidences of primary and secondary end points were estimated by the Kaplan-Meier method and differences between groups were assessed with the log-rank test. We used the Cox proportional hazards model to estimate hazard ratios (HRs) of aspirin use along with 95% confidence intervals (CIs). We used the χ² test or Fisher exact test to evaluate adverse events.

We also conducted subgroup analyses for predetermined subgroups: sex (men, women); age (younger than 65 years, 65 years or older); hypertensive
status (hypertensive, normotensive); smoking status (current or past smoker, nonsmoker); and lipid status (hyperlipidemia, normolipidemia). Using the Cox proportional hazard model, proportional hazard assumptions were assessed on the plots of log (time) vs log [-log(survival)] stratified by index variables. Patients with missing values for any selected variable were excluded from the analyses that used the variable.

All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) and S-Plus version 7.0 (Insightful Corp, Seattle, Washington). P values of less than .05 were considered statistically significant. An independent safety monitoring board monitored the safety and efficacy of the study after 2 years of follow-up for an interim assessment and at the end of the study.

RESULTS
Study Population
The study screened 2567 patients with type 2 diabetes mellitus without a history of atherosclerotic disease, including cardiovascular disease, stroke, and peripheral vascular disease, from December 2002 to May 2005 in 163 institutions (FIGURE 1). Six patients who withdrew their informed consent were excluded. Twenty-two patients met exclusion criteria. We randomly assigned 2539 patients as follows: 1262 patients in the aspirin group and 1277 patients in the nonaspirin group. Patients were followed up until April 2008. The median follow-up period was 4.37 years (95% CI, 4.35-4.39). A total of 193 patients were lost to follow-up, and data for those patients were censored at the day of last follow-up.

Baseline Clinical Characteristics
Baseline clinical characteristics, including treatments for diabetes, hypertension, and dyslipidemia and diabetic microvascular complications, were similar between the 2 groups (TABLE 1). Overall mean (SD) age was 65 (10) years; 55% of patients were men. Median duration of diabetes was 7.3 years in the aspirin group and 6.7 years in the nonaspirin group. Diabetes was well controlled in both groups: mean (SD) levels of glycated hemoglobin were 7.1% (1.4%) in the aspirin group and 7.0% (1.2%) in the nonaspirin group. The prevalence of hypertension and dyslipidemia was 58% and 53%, respectively. Blood pressure was well controlled in both groups: mean (SD) systolic pressure, 136 (15) mm Hg; mean (SD) diastolic pressure, 77 (9) mm Hg in the aspirin group and mean (SD) systolic pressure, 134 (15) mm Hg; mean (SD) diastolic pressure, 76 (9) mm Hg in the nonaspirin group.

By the end of the study, 123 patients (10%) in the aspirin group had stopped taking the study medication. Since aspirin therapy was allowed in the nonaspirin group, 6 patients (0.5%) had taken aspirin and 3 patients (0.2%) had taken other antiplatelet medication.

Efficacy Analysis
A total of 154 atherosclerotic events occurred (TABLE 2). The incidence of the primary end point of any atherosclerotic event, a composite of sudden death, death from cardiovascular or aortic causes, nonfatal acute myocardial infarction, unstable angina, exertional angina, nonfatal ischemic and hemorrhagic stroke, transient ischemic attack, and nonfatal aortic and peripheral vascular disease (atherosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis), was not significantly different in the aspirin group (68 events, 5.4%) than in the nonaspirin group (86 events, 6.7%) (HR, 0.80; 95% CI, 0.58-1.10; log-rank test, P =.16) (TABLE 2 and FIGURE 2).

The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; P =.0037). Other secondary coronary, cerebrovascular, and peripheral vascular disease end points are shown in Table 2; there were no significant differences between the aspirin group and the nonaspirin group in these end points. There were 2 deaths due to aortic dissection, both in the low-dose aspirin group, and 1 nonfatal aortic dissection in the nonaspirin group. A total of 13 hemorrhagic strokes occurred; the incidences in each group were similar (6 in the aspirin group and 7 in the...
nonaspirin group). There was 1 fatal hemorrhagic stroke in the aspirin group and 4 in the nonaspirin group.

Death from causes other than cardiovascular events were as follows for the aspirin group and nonaspirin group, respectively: there were 15 and 19 deaths due to malignancy, 2 and 5 due to infection, 3 and 0 due to suicide, 2 and 0 due to traffic crashes, and 1 and 1 due to liver cirrhosis. Therefore, 23 patients in the aspirin group and 25 patients in the nonaspirin group died from causes other than cardiovascular events. Eight patients in the aspirin group and 3 patients in the nonaspirin group died from unknown causes. A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.14; log-rank test, \( P = .67 \)).

### Subgroup Analyses

In the 1363 patients aged 65 years or older (719 in the aspirin group and 644 in the nonaspirin group), the incidence of atherosclerotic events was significantly lower in the aspirin group (45 events, 6.3%) than in the nonaspirin group (59 events, 9.2%) (HR, 0.68; 95% CI, 0.46-0.99; \( P = .047 \)). In the 1176 patients younger than age 65 years, there were 23 events in the aspirin group (4.2%) and 27 events in the nonaspirin group (4.3%), a difference that was not significant (HR, 1.0; 95% CI, 0.57-1.70; \( P = .98 \)). A formal test of interaction with age did not show a significant result (\( P = .27 \)). There were no significant differences between the aspirin group and nonaspirin group in other subgroup analyses, including men, women, hypertensive, normotensive, current or past smokers, nonsmokers, dyslipidemia, and normolipidemia (FIGURE 3).

### Safety

The prespecified analysis of adverse events is shown in Table 3. The hemorrhagic events consisted of GI bleeding in 12 patients in the aspirin group and 4 in the nonaspirin group. There were 32 patients in the aspirin group and 36 patients in the nonaspirin group. In the aspirin group, 4 patients had serious adverse events that needed a transfusion; no patients in the non-

### Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin Group (n = 1282)</th>
<th>Nonaspirin Group (n = 1277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>65 (10)</td>
<td>64 (10)</td>
</tr>
<tr>
<td>Male</td>
<td>706 (56)</td>
<td>681 (53)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>289 (23)</td>
<td>248 (19)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>545 (43)</td>
<td>482 (38)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)(^a)</td>
<td>24 (4)</td>
<td>24 (4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>742 (59)</td>
<td>731 (57)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>680 (54)</td>
<td>665 (52)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>136 (15)</td>
<td>134 (15)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>77 (9)</td>
<td>76 (9)</td>
</tr>
<tr>
<td>Duration of diabetes, median (IQR), y</td>
<td>7.3 (2.8-12.3)</td>
<td>6.7 (3.0-12.5)</td>
</tr>
<tr>
<td>Diabetic microvascular complication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>187 (15)</td>
<td>178 (14)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>169 (13)</td>
<td>153 (12)</td>
</tr>
<tr>
<td>Proteinuria, (\geq 15) mg/dL</td>
<td>222 (18)</td>
<td>224 (18)</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>163 (13)</td>
<td>137 (11)</td>
</tr>
<tr>
<td>Dermal ulcer</td>
<td>6 (0.5)</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Treatment for diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>737 (58)</td>
<td>710 (56)</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>422 (33)</td>
<td>414 (32)</td>
</tr>
<tr>
<td>Biguanides</td>
<td>168 (13)</td>
<td>186 (13)</td>
</tr>
<tr>
<td>Insulin</td>
<td>166 (13)</td>
<td>160 (13)</td>
</tr>
<tr>
<td>Thiazolidines</td>
<td>63 (5)</td>
<td>65 (5)</td>
</tr>
<tr>
<td>Treatment for hypertension and dyslipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>436 (35)</td>
<td>440 (34)</td>
</tr>
<tr>
<td>Angiotensin-II receptor antagonists</td>
<td>260 (21)</td>
<td>266 (21)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>178 (14)</td>
<td>195 (15)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>75 (6)</td>
<td>87 (7)</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>53 (4)</td>
<td>38 (3)</td>
</tr>
<tr>
<td>Statins</td>
<td>322 (26)</td>
<td>328 (26)</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>526 (42)</td>
<td>513 (40)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>147 (12)</td>
<td>143 (11)</td>
</tr>
<tr>
<td>Stroke</td>
<td>275 (22)</td>
<td>251 (20)</td>
</tr>
<tr>
<td>Patient medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>83 (7)</td>
<td>96 (8)</td>
</tr>
<tr>
<td>Clinical laboratory measurements, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (A\textsubscript{1c}) level, %</td>
<td>7.1 (1.4)</td>
<td>7.0 (1.2)</td>
</tr>
<tr>
<td>Fasting plasma glucose level, mg/dL</td>
<td>148 (50)</td>
<td>146 (48)</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL</td>
<td>202 (34)</td>
<td>200 (34)</td>
</tr>
<tr>
<td>Fasting triglyceride level, mg/dL</td>
<td>135 (88)</td>
<td>134 (89)</td>
</tr>
<tr>
<td>HDL cholesterol level, mg/dL</td>
<td>55 (15)</td>
<td>55 (15)</td>
</tr>
<tr>
<td>Blood urea nitrogen level, mg/dL</td>
<td>16 (5)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Serum creatinine level, mg/dL</td>
<td>0.8 (0.3)</td>
<td>0.8 (0.2)</td>
</tr>
<tr>
<td>Red blood cells, (\times 10^{12})/mL</td>
<td>45.2 (4.7)</td>
<td>45.0 (4.8)</td>
</tr>
<tr>
<td>White blood cells, (\times 10^{12})/mL</td>
<td>6.2 (1.6)</td>
<td>6.1 (1.7)</td>
</tr>
<tr>
<td>Hemoglobin level, g/dL</td>
<td>14.0 (1.5)</td>
<td>14.0 (1.5)</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range.

*SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; to convert total and HDL cholesterol to mmol/L, multiply by 0.0259; to convert triglyceride to mmol/L, multiply by 0.0113; to convert urea nitrogen to mmol/L, multiply by 0.357; to convert creatinine to µmol/L, multiply by 88.4.*

\(^a\) Calculated as weight in kilograms divided by height in meters squared.
aspirin group required transfusion. Another 13 patients in the aspirin group had minor bleeding. There was no significant difference in the composite of hemorrhagic stroke and severe GI bleeding, which occurred in 10 patients in the aspirin group and in 7 patients in the nonaspirin group.

**COMMENT**

Myocardial infarction and ischemic stroke are leading causes of mortality and morbidity in patients with type 2 diabetes. Given the rapid increase in the number of patients with type 2 diabetes worldwide and especially in Asia, establishing effective means of primary prevention of coronary and cerebrovascular events is an important public health priority. In the JPAD primary prevention trial of 2339 type 2 diabetic patients without documented cardiovascular disease, the incidence of the primary end point of total atherosclerotic events, consisting of coronary, cerebrovascular, and peripheral vascular events, was not significantly different in the group that received prophylactic aspirin (81 or 100 mg once daily) than in the nonaspirin group. With the exception of fatal coronary and cerebrovascular events, none of the prespecified secondary end points were reduced significantly in the low-dose aspirin group. The incidence of fatal coronary and cerebrovascular events, a prespecified secondary end point, was significantly reduced in the low-dose aspirin group (P = .0037). A benefit of low-dose aspirin on the primary end point also was suggested in the subgroup of patients aged 65 years or older, which had a significant 32% relative reduction in total atherosclerotic events (P = .047).

The cardiovascular mortality benefit was achieved with a small increase in cases of serious GI bleeding (4 patients in the aspirin group had bleeding that required transfusion), but no excess of fatal GI or cerebral hemorrhages.

The JPAD trial enrolled 2339 diabetic patients without documented coronary or cerebrovascular complications; the sample size was the largest among the previous primary prevention studies in respect to the number of diabetic patients enrolled. However, no difference was found in the effect of aspirin on the primary end point or most secondary end points.

The interpretation of these results is challenging because the overall event rates were low: 17 in 1000 Japanese diabetic patients. This is one-third of the event rate anticipated in our sample-size calculations, which were based on the Hisayama-cho22 and Funagata23 epidemiologic studies conducted in Japan in the 1990s. Current treatment of cardiovascular risk factors in patients with type 2 diabetes has improved since the 1990s and may have ac-

### Table 2. Atherosclerotic Events

<table>
<thead>
<tr>
<th></th>
<th>Aspirin Group</th>
<th>Nonaspirin Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%)</strong></td>
<td>No. per 1000 Person-Years</td>
<td>No. per 1000 Person-Years</td>
</tr>
<tr>
<td>Primary end point: all atherosclerotic events</td>
<td>68 (5.4)</td>
<td>13.6</td>
</tr>
<tr>
<td>Coronary and cerebrovascular mortality</td>
<td>1 (0.08)</td>
<td>0.2</td>
</tr>
<tr>
<td>CHD events (fatal + nonfatal)</td>
<td>28 (2.2)</td>
<td>5.6</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>12 (1.0)</td>
<td>2.4</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>4 (0.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Stable angina</td>
<td>12 (1.0)</td>
<td>2.4</td>
</tr>
<tr>
<td>Cerebrovascular disease (fatal + nonfatal)</td>
<td>28 (2.2)</td>
<td>5.6</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>1 (0.08)</td>
<td>0.2</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>22 (1.7)</td>
<td>4.4</td>
</tr>
<tr>
<td>Ischemic</td>
<td>5 (0.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>5 (0.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>7 (0.6)</td>
<td>1.4</td>
</tr>
<tr>
<td>Peripheral artery diseasea</td>
<td>7 (0.6)</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.

aAtherosclerosis obliterans (5 in aspirin group and 8 in nonaspirin group); aortic dissection (2 fatal in the aspirin group and 1 nonfatal in the nonaspirin group); mesenteric artery thrombosis (1 in the nonaspirin group), and retinal artery thrombosis (1 in the nonaspirin group).
counted for the lower event rates: there is better control of glucose, blood pressure, and lipid levels in clinical practice. The baseline characteristics of patients in the JPAD trial were similar to those in previous studies except that body mass index was relatively lower in the JPAD trial than that in the previous studies, although similar to that in other studies of Japanese diabetics.4,6,10-12,17,28

A meta-analysis of primary prevention trials that included the British Doctors’ Trial, the Physicians’ Health Study, the Thrombosis Prevention Trial, the Hypertension Optimal Treatment (HOT) study, the Primary Prevention Project (PPP) trial, and the Women’s Health Study showed that aspirin therapy significantly reduced the risk of total coronary heart disease, nonfatal myocardial infarction, and total cardiovascular events with a nonsignificant trend for decreased risk of stroke, cardiovascular mortality, and all-cause mortality.29 However, the evidence for aspirin in prevention of cardiovascular events in diabetic patients has been surprisingly scant. Previous studies investigating the effects of low-dose aspirin on primary prevention of cardiovascular events did not enroll solely diabetic patients but enrolled patients with hypertension in the HOT study; patients with 1 or more cardiovascular risk factors in the Thrombosis Prevention Trial and the PPP trial; and a healthy population in the British Doctors' Trial, the Physicians’ Health Study, and the Women’s Health Study.

Several large primary prevention trials have included subgroup analyses of patients with diabetes. The Physicians’ Health Study of 22 071 healthy men randomized to receive 325 mg of aspirin every other day or placebo showed a significant reduction in myocardial infarction for the entire population, but there was no significant difference for the small number of individuals with diabetes in the 2 treatment groups (11/275 in the aspirin group and 26/258 in the placebo group).18 The Antithrombotic Trialists’ Collaboration meta-analysis of 287 randomized trials reported effects of antiplatelet therapy (mainly aspirin) vs control in 135 000 patients and showed a nonsignificant 7% reduction in the odds for serious vascular events for the subgroup of 5126 patients with diabetes.19

Sacco et al20 described the effects of aspirin on atherosclerotic disease in patients with diabetes as a subgroup of the PPP trial, which investigated the effects of aspirin and vitamin E in a 2-by-2 factorial trial of 4495 patients with at least 1 known major cardiovascular risk factor.21 The original study was stopped on ethical grounds after a mean follow-up of 3.6 years because aspirin was associated with a lower risk of atherosclerotic disease in the overall group. The results of a subgroup analysis of 1031 diabetic patients did not

<table>
<thead>
<tr>
<th>Table 3. Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Bleeding, gastrointestinala</td>
</tr>
<tr>
<td>Hemorrhagic gastric ulcer</td>
</tr>
<tr>
<td>Bleeding from esophageal varices</td>
</tr>
<tr>
<td>Bleeding from colon diverticula</td>
</tr>
<tr>
<td>Gastrointestinal bleeding due to cancer</td>
</tr>
<tr>
<td>Hemorrhoid bleeding</td>
</tr>
<tr>
<td>Gastrointestinal bleeding (cause unknown)</td>
</tr>
<tr>
<td>Bleeding, other</td>
</tr>
<tr>
<td>Retinal bleeding</td>
</tr>
<tr>
<td>Bleeding after tooth extraction</td>
</tr>
<tr>
<td>Subcutaneous hemorrhage</td>
</tr>
<tr>
<td>Hematuria</td>
</tr>
<tr>
<td>Nose bleeding</td>
</tr>
<tr>
<td>Chronic subdural hematoma</td>
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<tr>
<td>Nonbleeding gastrointestinal event</td>
</tr>
<tr>
<td>Nonhemorrhagic gastritis</td>
</tr>
<tr>
<td>Nonhemorrhagic gastric ulcer</td>
</tr>
<tr>
<td>Nonhemorrhagic duodenal ulcer</td>
</tr>
<tr>
<td>Only gastrointestinal symptom</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
</tbody>
</table>

aIn the aspirin group, 4 cases of severe gastrointestinal bleeding required transfusion.
reach statistical significance, possibly because of the early stopping of the trial and the subgroup size. In addition, medication adherence was poor in the PPP trial: 28.2% of subjects assigned to aspirin had stopped this therapy by the conclusion of the trial. In the JPAD study, only 10% of patients in the aspirin group stopped this therapy by the end of the mean 4.37 years of follow-up.

Because of the low event rate in JPAD, our study was underpowered for demonstrating that aspirin had a significant effect on reducing total atherosclerotic events. However, the observation in the JPAD trial of an effect of aspirin on the secondary outcome of fatal cardiovascular events was also seen in the PAP trial. Aspirin did not reduce cardiovascular mortality in the HOT study, and it did not reduce fatal stroke in the Women’s Health Study. The reason for the discrepancy in the preventive effect of aspirin on fatal cardiovascular events is not clear at present. The total number of fatal events was small (ranging from 13 to 49) in the JPAD trial as well as the PAP trial and in the subgroup population with diabetes in the HOT study. A larger trial is needed to determine the efficacy of low-dose aspirin on mortality. The JPAD trial composite primary end point also included hemorrhagic stroke. The finding that aspirin did not increase the risk of hemorrhagic stroke was consistent with findings from prior reports, although the population studied was patients with diabetes. The finding of no increase in hemorrhagic stroke in the JPAD trial is of particular clinical importance because hemorrhagic stroke is more common in Japanese populations than in the West. Moreover, there was no fatality due to hemorrhagic events except for hemorrhagic stroke; however, the hemorrhagic events that required surgical interventions or transfusion were observed in 4 patients in aspirin group.

The study design may be considered a limitation of the JPAD trial (prospective, randomized, open-label, controlled trial with blinded end-point assessment), as it did not have the advantages of a double-blind, randomized trial. The Japanese Pharmaceutical Affairs Law limits the use of placebo in physician-initiated studies because it is an unapproved medicine. However, the end-point classification was conducted by a blinded, independent committee on validation of data and events that was unaware of the group assignments.

Previous clinical studies indicate that a cardiovascular risk reduction is difficult to achieve by aggressively controlling plasma glucose levels in diabetic patients. These studies suggested that the contribution of lowering glucose levels to the reduction of macrovascular events appears to be minimal, at least in the first few years of treatment. Although improved glucose control can protect against the development of microvascular complications, the absence of a reduction in macrovascular events implicates an additive effect of nonglycemic risk factors that often accompany diabetes, such as hypertension, hyperlipidemia, and hypercoagulability. Additional medications such as angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, statins, and antiplatelet agents may be needed in patients with type 2 diabetes mellitus. The JPAD trial indicates that among these medications, aspirin is well tolerated for primary prevention and may provide an additional low-cost option.

In summary, in the JPAD trial, the first prospectively designed trial to evaluate low-dose aspirin in patients with type 2 diabetes without previous cardiovascular disease, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events. Despite a large sample size, the event rate in the study was lower than anticipated. Aspirin was well tolerated in these patients, as there was no increase in hemorrhagic strokes and a small increase in serious GI hemorrhagic events (4 patients required transfusion). These findings should be interpreted in context with the low incidence of atherosclerotic disease in Japan and the current management practice for cardiovascular risk factors and suggest the need to conduct additional studies of aspirin for primary prevention of cardiovascular disease in diabetic patients.
Role of the Sponsor: The funding source had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Japanese Primary Prevention of Atherosclerotic With Aspirin for Diabetes (JPAD) Trial Investigators: Hisagawa (principal investigator). Steering Committee: Yoshikiko Shishido, Satoru Umekawa, and Katsunori Kasaoka. Research Management: Masafumi Nakayama, Kazuo Kako, and Ken-ichi Iyoda. Data Management: Katsunori Nakayama. Statistical Analysis: Takashi Nakahara, Masayuki Ogihara, and Kenji Nakai. The JPAD Trial Steering Committee. Role of the Sponsor: Gerke, ELS, of Innovex (a division of Quintiles Transnational) had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Aspirin for Diabetes (JPAD) Trial Investigators: Izumi Yasue, Yuji Mizuno, Sueo Momosaki, Koji Tokube, Kiyotaka Kudou, Tetsuo Kukashima, Atsushi Hagihara, Hiroshi Bando, Tateo Ogura, Kenichi Doi, Masayuki Ikeda, Chieko Imamoto, and Hisakazu Suefuji. The JPAD Trial Steering Committee.

REFERENCES

these neuronal circuits are long lasting and some of these persist months after drug discontinuation.\textsuperscript{6}

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Financial Disclosures: None reported.


CORRECTIONS

Incorrect Data in Text and Table: In the Original Contribution titled “Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes: A Randomized Controlled Trial,” published in the November 12, 2008, issue of JAMA (2008;300[18]:2134-2141), incorrect numbers of adverse events appeared in the text and in 1 table. On page 2137 in the last paragraph, the second sentence should have read, “The hemorrhagic events consisted of GI bleeding in 12 patients in the aspirin group and 4 in the nonaspirin group and retinal hemorrhage in 8 patients in the aspirin group and 5 in the nonaspirin group.” In Table 3 on page 2139, the data for the Nonaspirin Group in the row Retinal bleeding should have been 5 and in the row Subcutaneous hemorrhage should have been 1.

Omission of Disclaimer: In the Original Contribution titled “Access to Kidney Transplantation Among Remote and Rural-Dwelling Patients With Kidney Failure in the United States” published in the April 22/29, 2009, issue of JAMA (2009;301[16]:1681-1690), a disclaimer was omitted. The disclaimer should read, “The data reported herein have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.” This article was corrected online for errors in data on April 21, 2009, prior to publication of the correction in print.
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. Bioequivalence can be established on the basis of the maximum serum concentration 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.6-10

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, 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, hematology), 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 (LD₅₀) and median effective dose (ED₅₀) 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 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

### 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 bioequivalence 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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**Figure 1. Study Selection**

8556 Articles found

3932 EMBASE
2848 MEDLINE
1776 International Pharmaceutical Abstracts

8485 Excluded
7401 Did not meet inclusion criteria for title and abstract
1084 Citations overlapped

71 Articles considered for inclusion

2 Articles added after evaluation of citations from articles that were considered

26 Excluded
6 Did not compare brand-name with generic drugs
5 Did not report clinical outcomes
6 Used surveys or other qualitative outcomes
8 Were not in English-language journals
1 Was a brief report of a trial included in the final analysis

47 Studies included in meta-analysis
38 Randomized controlled trials
9 Retrospective studies
34 Trials used WTI drugs
13 Trials used NTI drugs

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

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**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>
<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>Jadad or Newcastle-Ottawa Score</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 insurers (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 of 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>Mirfazaelian et al,27 2003</td>
<td>Tenormin vs atenolol</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>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 = .05)</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 of 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>
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<tr>
<td>Sarkar et al,30 1996</td>
<td>Tenormin vs atenolol</td>
<td>31 (NA)/1 dose of 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 1989</td>
<td>Inderal vs Inderal LA (long-acting) vs propranolol</td>
<td>15 (46)/4 wk of 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 of 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; no difference in self-reported adverse effects among group taking generic at initiation of study (P = .13); median HR slightly less for brand-name (P = .05)</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 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 = .01) (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 Studied[4]</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Population (Setting)</th>
<th>Jadad or Newcastle-Ottawa Score[5]</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al, 1984[6]</td>
<td>Lasix vs 3</td>
<td>17 (60)/1 wk of each product</td>
<td>Bioequivalence 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 intra-individual variability</td>
<td>Brand-name manufacturer</td>
</tr>
<tr>
<td>Awad et al, 1986[7]</td>
<td>Lasix vs furosemide</td>
<td>20 (21-32)/1 dose of each with washout</td>
<td>Bioequivalence 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, 1989[8]</td>
<td>Lasix vs furosemide</td>
<td>8 (25-39)/1 dose of each with washout</td>
<td>Bioequivalence 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, 1993[9]</td>
<td>Lasix vs 3</td>
<td>30 (55)/3 wk of brand and 3 wk of generic</td>
<td>Bioequivalence 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[10]</td>
<td>Intravenous Lasix vs intravenous furosemide</td>
<td>5 (20-51)/1 dose of each with washout</td>
<td>Bioequivalence 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, 1988[11]</td>
<td>Lasix vs 3</td>
<td>12 (NA)/1 dose of each with washout</td>
<td>Bioequivalence 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[12]</td>
<td>Lasix vs furosemide</td>
<td>8 (26)/2 doses of each with washout</td>
<td>Bioequivalence 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[13]</td>
<td>Lasix vs furosemide</td>
<td>16 (NA)/1 dose of each with washout</td>
<td>Bioequivalence 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[14]</td>
<td>Lasix vs furosemide</td>
<td>5 (NA)/2 d of each</td>
<td>Bioequivalence 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>Maiti et al, 1984[15]</td>
<td>Lasix vs 6</td>
<td>6 (NA)/1 dose of each with washout</td>
<td>Bioequivalence study; RCT with crossover</td>
<td>Healthy subjects (non-US)</td>
<td>0</td>
<td>&quot;Acceptable level of diuresis&quot; in self-reported urine output (no statistical tests done)</td>
<td>Government</td>
</tr>
<tr>
<td>Martin et al, 1984[16]</td>
<td>Lasix vs furosemide</td>
<td>12 (18-42)/1 dose of each with washout</td>
<td>Bioequivalence 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.


[5]The 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 β-blockers. 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 (Imperial; 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. 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

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studied</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Population (Setting)</th>
<th>Jadad or Newcastle-Ottawa Score</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al,2007</td>
<td>Norvasc vs amiodipine camysylate</td>
<td>189 (53)/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 (non-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,2007</td>
<td>Norvasc vs amiodipine 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,2004</td>
<td>Norvasc vs atenolol</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,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>Generics 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,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,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 with crossover</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,1993</td>
<td>Isoptin vs 1 of 2 versions of verapamil</td>
<td>Youth cohort: 8 (27)/1 wk of each with washout; elderly cohort: 8 (73)/3 wk of each 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.

1Norvasc 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.

2The 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 bioequiva-
lency studies in healthy volunteers, Tenormin was not found to be supe-
rior to the generic version in lowering heart rate and blood pressure.\textsuperscript{27,29,30} In

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studied\textsuperscript{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\textsuperscript{b}</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashraf et al,\textsuperscript{32} 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 60.7%, (P = .72))</td>
<td>Generic manufacturer, government</td>
</tr>
<tr>
<td>Rao et al,\textsuperscript{33} 2003</td>
<td>Plavix vs clopidogrel</td>
<td>20 (27)/10 d</td>
<td>Bioequivalency 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,\textsuperscript{34} 1996</td>
<td>Enteric-coated aspirin vs 3 versions of enteric-coated acetylsalicylic acid</td>
<td>12 (18-45)/1 dose of each with washout</td>
<td>Bioequivalency 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,\textsuperscript{35} 2004</td>
<td>Vasotec vs enalapril</td>
<td>24 (23)/1 dose of each with washout</td>
<td>Bioequivalency 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,\textsuperscript{36} 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, creatinine, creatine kinase levels (unpaired (t) test, (\alpha = .05))</td>
<td>Generic manufacturer</td>
</tr>
<tr>
<td>Wiwanitkit et al,\textsuperscript{37} 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,\textsuperscript{38} 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 hypertension (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.

\textsuperscript{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.

\textsuperscript{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,60</td>
<td>Rythmex vs propafenone</td>
<td>119 (65)/18 mo</td>
<td>Retrospective cohort study (pre/post design without concurrent controls)</td>
<td>Patients with atrial fibrillation stable while receiving brand for ≥18 mo switched to generic (non-US)</td>
<td>4</td>
<td>Generic use associated with slight reduction in total ED discharges and ED visits for chest pain (P &lt; .01); no significant differences in clinic visits, admissions, cardioversions, and rate of use of other cardiovascular medications (P &gt; .05)</td>
<td>Generic manufacturer</td>
</tr>
<tr>
<td>Kasner et al,61</td>
<td>Pronestyl vs procamidine</td>
<td>10 (62)/6 doses of each separated by 1 wk of prior therapy</td>
<td>Bioequivalence study; single-blind RCT with crossover</td>
<td>Patients with ventricular dysrhythmias (US)</td>
<td>1</td>
<td>No significant change in type or frequency of VPBs on telemetry (P &gt; .05)</td>
<td>Generic manufacturer, National Institutes of Health</td>
</tr>
<tr>
<td>Handler et al,61</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>Double-blind RCT with crossover</td>
<td>Outpatients with arrhythmia (US)</td>
<td>5</td>
<td>No significant differences in INR (P = .40), dose adjustments, adverse events (P &gt; .05)</td>
<td>Generic manufacturer</td>
</tr>
<tr>
<td>Pereira et al,62</td>
<td>Coumadin vs warfarin</td>
<td>7 (63)/Five 3-wk periods of each</td>
<td>Double-blind RCT with crossover</td>
<td>Outpatients with indications for anticoagulation</td>
<td>4</td>
<td>No significant differences in INR measurements or variation (P = .98)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Paterson et al,63</td>
<td>Coumadin vs 1 of 2 versions of warfarin</td>
<td>36 724 (≥69)/40 mo before, 1 mo of transition, and 9 mo following switch</td>
<td>Population-based, cross-sectional time-series analysis</td>
<td>Elderly outpatients with numerous indications for anticoagulation taking Coumadin (non-US)</td>
<td>5</td>
<td>No significant differences in INR testing (P = .93) or hospitalization for hemorrhage (P = .89) or thromboembolism (P = .97)</td>
<td>Government</td>
</tr>
<tr>
<td>Lee et al,64</td>
<td>Coumadin vs warfarin</td>
<td>35 (52)/4 wk of Coumadin and when 6 wk of warfarin vs 4 wk of warfarin and then 8 wk of Coumadin</td>
<td>Single-blind RCT with crossover</td>
<td>Patients with mechanical heart valves who received Coumadin for ≥2 mo (non-US)</td>
<td>3</td>
<td>Dose changes were rare; no significant differences in pooled INRs or frequency of adverse effects (P &gt; .05)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Halkin et al,65</td>
<td>Coumadin vs warfarin</td>
<td>975 (70)/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 (non-US)</td>
<td>5</td>
<td>After the switch, INR values were lower and warfarin doses prescribed were higher, especially in those who were subtherapeutic when receiving Coumadin (P &lt; .01)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Witt et al,66</td>
<td>Coumadin vs warfarin</td>
<td>2299 659/3 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>

(continued)

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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.34,38,42 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 intradividual 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

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Drugs Studied&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Results</th>
<th>Source of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milligan et al,37 2002</td>
<td>Coumadin vs warfarin</td>
<td>182 (75)/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 = .3), dose adjustments (P = .41), adverse events</td>
<td>Insurance company</td>
<td></td>
</tr>
<tr>
<td>Welb et al,38 2000</td>
<td>Coumadin vs warfarin</td>
<td>113 (70)/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>Generic manufacturer</td>
<td></td>
</tr>
<tr>
<td>Swenson and Fundak,39 2000</td>
<td>Coumadin vs warfarin</td>
<td>210 (78)/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)/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&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Coumadin vs warfarin</td>
<td>55 (57)/wk 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.<sup>a</sup>Rythmix is manufactured by Knoll Pharmaceuticals, Detlifshaus, Germany; Pronestyl, E. R. Squibb & Sons, New Brunswick, New Jersey; and Coumadin, DuPont Pharmaceuticals, Wilmington, Delaware.<sup>b</sup>The Jadad score range is 1-5 for RCTs; the Newcastle-Ottawa score range, 1-9 stars for observational studies.<sup>c</sup>Although conducted in the United States, this study did not involve a bioequivalent generic.

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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 associ-
ed changes in heart rate or other clinical outcomes in either of those studies.50,51

The remaining 7 studies evaluated an-
tiplatelet agents (clopidogrel; [Plavix; 
Bristol-Myers Squibb, New York, New York] and enteric-coated aspirin [ace-
tylsalsicylic 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 Labo-
ratories, 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 sta-
tistically significant differences in lower-
ing 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 outcomes related to platelet aggregation and 
bleeding time, not incidence of cardio-
vacular disease such as myocardial in-
farction.52,53 The study involving enala-
pril 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 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 (proprafenone [Rythmex; Knoll Pharmaceuticals, 
Dekelheim, 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-
ration 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 
clinical visits, coprescription with other 
medications, or rates of cardioversion in 
the 18 months after switching to a ge-
nic drug and a slight reduction in emerg-
ency department visits with the ge-
nic 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 adjustments.61,62,64,68-70 Five retrospective 
observational studies evaluated patient 
INRs and clinical outcomes in pa-
patients 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 
studies 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-
ty.68 A fourth retrospective cohort study 
found increased health care system uti-
лизization 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-

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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Studies</th>
<th>Subjects</th>
<th>Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>6</td>
<td>135</td>
<td>0.00 (−0.24 to 0.25)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>10</td>
<td>135</td>
<td>−0.03 (−0.28 to 0.22)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4</td>
<td>242</td>
<td>0.00 (−0.53 to 0.53)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>2</td>
<td>50</td>
<td>0.21 (−0.19 to 0.61)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>1</td>
<td>23</td>
<td>−0.09 (−0.68 to 0.50)</td>
</tr>
<tr>
<td>Statins</td>
<td>2</td>
<td>71</td>
<td>−0.25 (−0.62 to 0.12)</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>1</td>
<td>43</td>
<td>0.06 (−0.37 to 0.50)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4</td>
<td>138</td>
<td>−0.09 (−0.33 to 0.15)</td>
</tr>
<tr>
<td>Overall</td>
<td>30</td>
<td>837</td>
<td>−0.03 (−0.15 to 0.08)</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; CI, confidence interval.
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 morbidities; 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 commentators 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 insensitivity 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-
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: Kesselheim, Stedman, Brookhart, Choudhry. Obtained funding: Kesselheim, Shrank. Administrative, technical, or material support: Kesselheim, Misono, Lee, Shrank. Study supervision: Kesselheim, Shrank.

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