Background: Laboratory investigations suggest that the simultaneous use of aspirin and ibuprofen may attenuate the antiplatelet effect of aspirin, making it less useful for cardioprotection. To determine if there is clinical evidence of this potentially harmful interaction, we conducted a retrospective matched case-control study.

Methods: All patients issued outpatient prescriptions for aspirin or ibuprofen from January 1, 1990, to December 31, 2000, at the Durham Veterans Affairs Medical Center pharmacy were included in the study. Patients who used aspirin and ibuprofen concurrently were matched against those who used aspirin only by race, sex, age within 10 years, and cholesterol levels (either low-density lipoprotein or total cholesterol) to within 30 mg/dL (0.78 mmol/L). The rate ratio of experiencing a myocardial infarction per patient-month of drug exposure was then determined.

Results: Some 3859 patients received both aspirin and ibuprofen, for a total of 52,139 patient-months of medication use. This group experienced 138 infarctions. The 10,239 patients receiving aspirin only, for a total of 156,417 patient-months of use, experienced 684 infarctions. The rate ratio of having an infarction was 0.61 (95% confidence interval, 0.50-0.73) (P<.001), favoring the group that took aspirin and ibuprofen simultaneously. An analysis of diabetic patients found a rate ratio of 0.48 (95% confidence interval, 0.34-0.66) (P<.001). An examination of patients who spent time in both groups at different times resulted in a rate ratio of infarction during combined use of 0.70 (95% confidence interval, 0.59-0.83) (P<.001).

Conclusion: There does not seem to be an increased risk of myocardial infarction among patients simultaneously consuming aspirin and ibuprofen compared with aspirin alone.

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The therapeutic use of aspirin has consistently increased during the past decade following the publication of several large prospective trials and reviews that proved the substantial benefits of aspirin for the primary and secondary prevention of myocardial infarction (MI). These studies used a wide range of dosing schemes, from 75 to 1500 mg/d of aspirin, with equivalent clinical efficacy. The use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, is also quite prevalent. These agents are used to treat common problems, such as headaches, osteoarthritis, and rheumatoid arthritis. With the increasing use of aspirin and nonaspirin NSAIDs, the number of patients consuming both drugs will continue to grow.

The importance of aspirin and the prevalence of NSAID use have led to investigations of what effects their concurrent use may have. Aspirin and NSAIDs bind the cyclooxygenase 1 and 2 enzymes and inhibit thromboxane A2-dependent platelet aggregation. This inhibition is considered irreversible for aspirin but not for other NSAIDs. Previous in vitro studies have suggested that NSAIDs, in particular ibuprofen, prevent irreversible inhibition of cyclooxygenase by aspirin. A recent trial by Catella-Lawson et al evaluated the effects of ibuprofen and other NSAIDs on aspirin-induced platelet aggregation inhibition and thromboxane B2 levels. Their experiments demonstrated significant blunting of the antiplatelet effects of aspirin when ibuprofen was administered in a single daily dose before aspirin or in a multidose daily regimen. While the results of these studies are interesting and provocative, they do not include clinical outcomes. Further studies that can help establish or refute a link between aspirin, ibuprofen, and clinical cardiovascular risk are needed.
We performed a retrospective analysis of one hospital's clinical experience to determine if a pattern of aspirin and ibuprofen use leads to an increase in MIs when compared with the use of aspirin alone.

**METHODS**

**PATIENT POPULATION AND DATA SOURCE**

The clinical database of the Durham Veterans Affairs (VA) Medical Center served as the data source of this study and contains demographic information, including date of birth, sex, race, laboratory information (including cardiac markers and cholesterol values), and a record of every outpatient prescription issued from the hospital pharmacy. From this database, we extracted the records of all patients who filled prescriptions for aspirin or ibuprofen at the hospital pharmacy between January 1, 1990, and December 31, 2000. All patients who filled 2 consecutive prescriptions for a medication without evidence of prescription lapse were considered to be consuming it regularly during the prescribing interval that preceded the last issuance and were eligible for inclusion in our analysis.

The hospital's institutional review board approved our use of the clinical databases for this study.

**DETERMINATION OF DIABETES MELLITUS PREVALENCE**

The presence of diabetes mellitus, a major risk factor for cardiovascular disease and one that potentially influences the prescribing of NSAIDs, was determined by extracting data on prescriptions filled for diabetic medications. This method has been validated, and effectively captures 85% to 90% of all diabetic persons in outpatient veteran populations. The subset of patients treated for diabetes mellitus at or before the time they received aspirin or ibuprofen was analyzed separately.

**DETERMINATION OF MI**

Biochemical evidence of MI was determined from examination of troponin I values and creatine kinase-MB. Following the Joint European Society of Cardiology/American College of Cardiology consensus statement, levels of creatine kinase-MB or troponin above the 99th percentile of the assay used by our laboratory when they were measured were defined as pathologic. The sensitivity and specificity for MI of the troponin assay used at the Durham VA Medical Center are 97% and 95% overall, respectively. However, troponin I did not become available at the Durham VA Medical Center until 1998. Therefore, creatine kinase-MB was used to define MIs before then.

We did not exclude multiple MIs experienced by the same patient from analysis. However, we dated each MI at the first elevated cardiac marker and did not consider subsequent elevations in cardiac enzymes to represent a subsequent unique MI in the same patient unless the elevation occurred more than 30 days later than the initial abnormal value.

**MATCHING**

Most prescriptions for long-term medicines are dispensed in units of months, and we used that unit of time for our analyses. From the population of eligible patients, we identified each unique patient-month for which a patient was simultaneously consuming aspirin and ibuprofen. For each patient-month of combined use, we identified from the population of aspirin-only users 3 patient-months matched by patient sex, race, age during the patient-month of interest within 10 years, and low-density lipoprotein cholesterol level within 30 mg/dL (0.78 mmol/L). For combined-use patients with no low-density lipoprotein cholesterol value on record, we matched instead on total cholesterol level within 30 mg/dL. For patients with more than a single low-density lipoprotein or total cholesterol level on record, we matched on the earliest recorded value, because this is most likely to be their baseline cholesterol value, which has been shown to be the best marker of future cardiac risk. Patient-months drawn from the population of aspirin and ibuprofen users who could not be adequately matched were not included in the analysis. By using this method, a single patient's data could be counted more than once in the analysis, as long as the points in time of data inclusion were separated by at least 1 month. We then repeated this same matching procedure using only prescription records from the subset of patients who were known to have diabetes mellitus when their prescriptions were issued.

We performed a separate analysis to determine how individual patients' risk of MI changed depending on whether or not they were consuming ibuprofen in addition to aspirin. No matching was performed for this third comparison. Instead, for all patients who consumed aspirin and ibuprofen at one time and aspirin alone at another, we simply aggregated the patient-months spent in each category.

**STATISTICAL ANALYSIS**

When analyzing demographic information, the binomial distribution was used to determine the standard error of race and sex variables. The t test was used to assess for differences between groups for continuous variables, and a χ² analysis was used to assess for differences between groups for categorical variables.

After summarizing the patient-months of medication use for each group, we determined the number of MIs that occurred during each exposure period and calculated the incidence rate of experiencing an MI per patient-month of medication use. We compared this value between the 2 groups and derived a rate ratio for experiencing an MI when using aspirin and ibuprofen concomitantly vs aspirin alone. All statistics were performed with statistical software (Stata). Baseline demographic characteristics are shown in Table 1. We were able to identify 52,139 patient-months during which 3899 unique patients consumed both aspirin and ibuprofen regularly. This was matched against 156,417 patient-months of aspirin-only use accumulated by 10,239 unique patients. Because the unit of matching was the patient-month, and not the patient, we tested for differences between the patients who comprised each group. Although statistical differences were found for race and total cholesterol values, there were no clinically significant differences between any of the demographic or matching variables.

Overall, 92% of daily aspirin prescriptions were for 325 mg, 7% were for 81 mg, and less than 1% were for other doses. Enteric-coated formulations of aspirin were used for 96% of the 325-mg doses and 89% of the 81-mg doses. The average daily dose of ibuprofen was 1947 mg. This distribution of dosing and formulation was similar among all subgroups analyzed.

Concurrent users of aspirin and ibuprofen experienced 138 MIs over 52,139 patient-months of medica-
tion use, for a rate of 0.0026 MIs per patient-month of use. Aspirin-only users experienced 684 MIs over 156417 patient-months of medication use, for a rate of 0.0044 MIs per patient-month. This yields a rate ratio for experiencing an MI of 0.61 (P<.001), favoring the group that took aspirin and ibuprofen simultaneously (Table 2).

This analysis was repeated for diabetic patients. Among diabetic patients, we calculated a rate ratio of 0.48 (P<.001), favoring patients who were prescribed both medications (Table 2). We also identified 4378 patients who received both aspirin and ibuprofen during some part of the study period and aspirin alone during other parts. The rate ratio for this group experiencing an MI was 0.70 (P<.001), favoring times when patients were prescribed both medications (Table 2).

The findings of this retrospective study suggest a protective effect of combination aspirin and ibuprofen therapy for the prevention of acute MI. We demonstrated a 40% reduction in the rate of developing an MI when taking both aspirin and ibuprofen compared with the MI rate when taking aspirin alone. The rate reduction seems even greater among patients with diabetes mellitus. A smaller, but still significant, effect was seen among all patients who consumed aspirin alone or aspirin and ibuprofen at different times. These consistent results contradict previous in vitro studies that suggest a reversal of the protective effects of aspirin when ibuprofen is administered concurrently. Concerns raised by laboratory studies about increased cardiovascular risk during concurrent aspirin and ibuprofen use may be premature.

Studies of the effect of ibuprofen on cardiovascular disease, particularly acute MI, have led to disparate results in animal models. In early models, ibuprofen therapy demonstrated a protective effect. However, in later studies, including a human study of postinfarction pericarditis, immediate therapy or pretreatment with ibuprofen was shown to increase infarct size and lead to infarct scar thinning. Drugs in the same class as ibuprofen have been studied in humans in prevention trials with more consistent results. In the Flurbiprofen French Trial, flurbiprofen was more effective than placebo at reducing the risk of reinfarction or reclosure of the infarct-related artery after a first MI treated with reperfusion therapy. In addition, Fornaro et al demonstrated a reduction in the risk of embolic cardiovascular events, including MI, when comparing indobufen with placebo in patients at risk for cardiogenic emboli.

Data on the combination use of aspirin and nonaspirin NSAIDs for prophylaxis are sparse. In a recent report, MacDonald and Wei studied mortality among patients with a recent hospital admission for cardiovascular disease who were prescribed aspirin alone compared with those prescribed aspirin with ibuprofen, diclofenac sodium, or other NSAIDs on discharge. They found that all-cause and cardiovascular-related mortality was significantly increased among patients prescribed aspirin and ibuprofen compared with the other groups. While our study did not address mortality, there certainly seems to be an important disparity between the 2 results. Our study differs from theirs in several ways that might underlie the different findings. Although they assign patients to groups based on the medications they were prescribed on discharge from the hospital, the researchers do not use a measurement of compliance to assess how many of the patients actually consumed aspirin and ibuprofen as directed. Because of this, they cannot temporally link their measured outcome with known medication use at the time of death. In addition, the number of patients in their study who concurrently used aspirin and ibuprofen was small compared with the aspirin-only cohort. Finally, their patients were considered for analysis only after being diagnosed as having vascular disease that required hospitalization, and it is possible that the use of these agents for secondary prevention has different effects than when applied to a more heterogeneous cohort.

In another recent trial by Ko et al, NSAID use after MI was studied using the Cooperative Cardiovascular Project database. Patients discharged from the hospital while taking aspirin, a nonaspirin NSAID, or both medications had a reduced 1-year mortality compared with patients discharged from the hospital while not taking either medication. In addition, there was no significant mortality difference between the groups who used one or both of the NSAIDs. No distinction was made between the types of nonaspirin NSAID used, and no measure of compliance with or duration of NSAID therapy was possible. Because recent data suggest that different NSAIDs have disparate cardiovascular effects, especially the cyclooxygenase 2 inhibitors, it is possible that analysis of particular NSAIDs would show drug-specific effects when used in combination with aspirin.

Compliance with medical therapy is often impossible to assess in a retrospective trial. Despite this, we believe that particular strengths of this study over others are our use of a stringent criterion of 2 consecutive prescription fills, adjacent in time, as a marker for regular consumption and our ability to link MIs in time to these periods of presumed medication use. Most retrospective analyses, including the study by Ko et al, are lim-

### Table 1. Baseline Characteristics of the 2 Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Those Who Received Aspirin Plus Ibuprofen</th>
<th>Those Who Received Aspirin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of unique patients</td>
<td>3859</td>
<td>10,239</td>
</tr>
<tr>
<td>No. of patient-months of exposure</td>
<td>52,139</td>
<td>156,417</td>
</tr>
<tr>
<td>No. of myocardial infarctions</td>
<td>138</td>
<td>684</td>
</tr>
<tr>
<td>Average date of birth</td>
<td>1/11/34</td>
<td>8/14/03</td>
</tr>
<tr>
<td>Male sex†</td>
<td>97.5 ± 0.25</td>
<td>97.6 ± 0.15</td>
</tr>
<tr>
<td>Race†</td>
<td>6.66 ± 0.76</td>
<td>68.7 ± 0.46</td>
</tr>
<tr>
<td>Cholesterol level, mg/dL</td>
<td>30.8 ± 0.74</td>
<td>27.8 ± 0.44</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>196 ± 0.70</td>
<td>194 ± 0.43</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>125 ± 0.81</td>
<td>124 ± 0.49</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert low-density lipoprotein and total cholesterol to millimoles per liter, multiply by 0.0259.

*Data are given as mean ± SE unless otherwise indicated.
†Data are given as percentage of each group.
‡P = .02.
§P = .0005.
||P = .01.
likely that a tendency to be hospitalized for an MI at an-
other hospital would vary based on whether a patient re-
ceived just aspirin or aspirin in addition to ibuprofen from
our hospital pharmacy.

This study has important implications that should be
interpreted with caution. Its results are consistent with
those of other trials showing a beneficial effect of ibu-
profen for cardiovascular prophylaxis. To our knowl-
edge, it is the first to show a benefit above that obtained
with aspirin alone. This finding cannot be accounted for
by differences in the prevalence of the cardiovascular risk
factors of age, sex, cholesterol level, or diabetes mellitus
between the 2 groups, and suggests an independent and
additive protective effect of ibuprofen when added to
aspirin. However, the significant renal and gastrointes-
tinal toxic effects of NSAIDs must be respected.31-34 We
cannot advocate use of combination therapy for cardio-
vascular prophylaxis, especially in the face of conflict-
ing data from other studies, unless these results are con-
firmed in a major randomized trial that includes a
mortality end point. Further studies that investigate the
use of aspirin in addition to ibuprofen for cardiac pro-
phylaxis and that include the measurement of mortality
will be needed before any clinical recommendations can
be made. We also advocate further study to determine if
ibuprofen could act as a reasonable substitute for aspir-
in in patients intolerant to aspirin or who are already
using ibuprofen for other ailments. Meanwhile, we found
no clinical evidence of increased MI risk posed by com-
bination therapy with aspirin and ibuprofen.

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vember 20, 2002; Chicago, Ill.

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of antiplatelet therapy-1: prevention of death, myocardial infarction, and stroke

Table 2. Rate and Rate Ratios of MI

<table>
<thead>
<tr>
<th>Patients</th>
<th>Aspirin Plus Ibuprofen Group</th>
<th>Aspirin Alone Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient-months</td>
<td>MIs</td>
</tr>
<tr>
<td>All</td>
<td>52,139</td>
<td>138</td>
</tr>
<tr>
<td>Those with diabetes mellitus</td>
<td>15,365</td>
<td>39</td>
</tr>
<tr>
<td>Combined†</td>
<td>55,711</td>
<td>133</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MI, myocardial infarction.
*Measured as MIs per patient-month of drug use.
†Patients who received aspirin and ibuprofen during some part of the study and aspirin alone during other parts.
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