Effect of Selective Cyclooxygenase 2 Inhibitors and Naproxen on Short-term Risk of Acute Myocardial Infarction in the Elderly

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Background: Recent debate has emerged regarding the cardiovascular safety of selective cyclooxygenase 2 inhibitors and the possible cardioprotective effect of naproxen sodium. We compared the rates of acute myocardial infarction (AMI) among elderly patients dispensed selective cyclooxygenase 2 inhibitors, naproxen, and nonselective nonnaproxen nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods: We conducted a population-based retrospective cohort study using administrative health care data from Ontario, Canada, from April 1, 1998, to March 31, 2001. We identified NSAID-naive cohorts of subjects aged 66 years and older in whom treatment was initiated with celecoxib (n=15271), rofecoxib (n=12156), naproxen (n=5669), and nonnaproxen nonselective NSAIDs (n=33868), along with a randomly selected control cohort not exposed to NSAIDs (n=100000). Multivariate Cox proportional hazards models were used to compare AMI rates between study drug groups while controlling for potential confounders.

Results: Relative to control subjects, the multivariate model showed no significant differences in AMI risk for new users of celecoxib (adjusted rate ratio [aRR], 0.9; 95% confidence interval [CI], 0.7-1.2), rofecoxib (aRR, 1.0; 95% CI, 0.8-1.4), naproxen (aRR, 1.0; 95% CI, 0.6-1.7), or nonnaproxen nonselective NSAIDs (aRR, 1.2; 95% CI, 0.9-1.4).

Conclusions: The findings of this observational study suggest no increase in the short-term risk of AMI among users of selective cyclooxygenase 2 inhibitors as commonly used in clinical practice. Furthermore, the findings do not support a short-term reduced risk of AMI with naproxen.

Arch Intern Med. 2003;163:481-486
hibitors with naproxen failed to find any association between these drugs and AMI in the more commonly used doses. The findings of this study, however, have not been verified.

We examined the incidence of AMI in more than 70,000 elderly new users of selective COX-2 inhibitors, naproxen, and nonnaproxen nonselective NSAIDs relative to NSAID-naive control subjects.

### METHODS

#### STUDY OBJECTIVE, HYPOTHESIS, AND DESIGN

The primary objective of this study was to compare the incidence of hospitalization for AMI among NSAID-naive elderly subjects dispensed celecoxib, rofecoxib, naproxen, or non-naproxen nonselective NSAIDs as commonly used in clinical practice with a NSAID-naive community control group.

We conducted a population-based retrospective cohort study by linking the health care records of more than 1.44 million residents aged 66 years and older in Ontario, Canada, from April 1, 1998, through March 31, 2001. Ontario's elderly residents have universal access to prescription drug coverage, hospital care, and physician services. This research study was approved by the Ethics Review Board of Sunnybrook and Women's College Health Sciences Centre, Toronto.

#### DATA SOURCES

The administrative health care databases in Ontario allowed for cohort identification, comorbidity assessment, and end point ascertainment. The linked databases included computerized pharmacy records of the Ontario Drug Benefit Program, which records prescription drugs dispensed to all Ontario residents 65 years and older. Both celecoxib and rofecoxib were first listed on the Ontario Drug Benefit Program formulary on April 17, 2000, on a limited-use basis for patients in whom traditional NSAIDs failed or who were intolerant of them, or for patients with a history of upper gastrointestinal tract hemorrhage or ulcer. The approved indications for celecoxib included osteoarthritis and rheumatoid arthritis, whereas rofecoxib was approved only for use in osteoarthritis. No such restrictions governed the prescribing of nonselective NSAIDs. We were unable to examine meloxicam because it was not available on the Ontario Drug Benefit Program formulary during the study period.

We obtained hospitalization records from the Canadian Institute for Heath Information Discharge Abstract Database, which contains a detailed record of all hospital admissions, including diagnostic and procedural information. The Ontario Health Insurance Plan provided physician billing information for inpatient and outpatient services, and the Ontario Registered Persons Database contained basic demographic and vital statistics information, including death date, for every registered Ontario resident. These databases were linked anonymously at the individual patient level by means of encrypted unique health card numbers.

#### COHORT DEFINITION

We compared users of celecoxib, rofecoxib, naproxen, and non-naproxen nonselective NSAIDs with a random sample of 100,000 controls dispensed none of these medications. Although we acknowledge potential differences in morbidity between users and nonusers of NSAIDs, we chose an NSAID-naive control group as a base reference for 2 reasons. First, the overall population provides a useful baseline risk estimate of non–NSAID-related AMI. Second, previously published studies examining the association between NSAID use and AMI are largely limited to those with non–NSAID-using controls; a non–NSAID-using control group in this study would allow comparison of our incidence and relative risk estimates with such studies. Patrice comparisons of the different NSAID study groups in relation to one another instead of the non-NSAID control group were also conducted.

For the 4 drug cohorts, the initial prescription during the study period following a patient's 66th birthday served as the index date. To create a cohort of NSAID-naive subjects within these 4 drug groups, we excluded individuals who were dispensed a medication from any of the 4 study groups in the year preceding the index date. Subjects dispensed prescriptions for drugs from more than 1 study drug group on the same day were excluded. To exclude sporadic users of NSAID therapy, we included only individuals who were dispensed at least 2 successive prescriptions and who received enough drug for at least 30 days of observation. Events occurring during this initial 30-day period were included in the analysis.

To create the control cohort, all Ontario residents not included in any of the previously described cohorts were randomly assigned index dates within the observation period. Individuals 66 years and older who were alive on the assigned index date were screened for NSAID use 1 year before the index date. From those without a prescription for any NSAID in the year before the index date or during the observation period, we randomly selected 100,000 individuals to form the control cohort. This group was not age and sex matched to any one particular group, but rather represented the general non–NSAID-dispensed elderly population of Ontario.

#### DURATION OF EXPOSURE

For each of the 4 study drug groups, we defined the duration of exposure as the period of continuous, exclusive enrollment in any of the study medication groups starting from the index date. A maximum follow-up of 1 year was allowed for subjects in each study drug group to correspond to the maximum follow-up data available for users of celecoxib and rofecoxib. In the nonselective NSAID group, subjects were allowed to switch between different nonselective NSAIDs during the observation period. The “days supply” variable of the pharmacy claims database allowed us to estimate the intended duration of each prescription. If subjects were dispensed a drug before the end of this period, the excess drug supply was carried over to the next prescription’s days supply estimation. Subjects were allowed a 20% grace period on the previous days supply to refill the next prescription. If subjects failed to refill their prescription for the study drug within these successive time windows, they were deemed to have discontinued the study drug.

Observation ended when patients were admitted to the hospital for AMI. Occurrence of AMI was defined as a hospital admission with a primary International Classification of Diseases, Ninth Revision diagnosis code of 410, which has a positive predictive value and sensitivity of approximately 89% and a specificity of approximately 93%. Subjects were censored if they were exposed to a medication from another study group, discontinued their study medication, died, reached the end of the 1-year follow-up limit, or reached the end of the observation period (March 31, 2001).

For the non-NSAID random control cohort, each individual was allowed at least 30 days of follow-up from the index date, and the end of the observation period was randomly assigned up to a maximum of 1 year after the index date to correspond to the follow-up period for the other study groups, unless the control subject experienced the outcome of interest or died beforehand.
As an overall measure of comorbidity, we examined the number of distinct drugs dispensed in the 1 year before the index date, a measure comparable to the Charlson Comorbidity Index.15 All pairwise combinations of hazard ratios for different exposure groups were compared. The proportional hazards assumption for each exposure variable was assessed in each analysis for any violations.

Several sensitivity analyses were conducted to examine the impact of the study design features on our findings. First, the analyses were repeated with the use of controls matched by age (within 1 year of the birth date) and sex to all patients in the 4 study drug groups as a sensitivity analysis. Second, because women are more likely than men to receive NSAIDs and may have a relatively lower risk of AMI,17 we repeated analyses separately for men and women. Third, we repeated the AMI analysis excluding those with a previous history of AMI. Fourth, a sensitivity analysis was conducted to address differences between study groups in periods for subject accrual. More time was allowed for patient accrual in the naproxen and nonnaproxen nonselective NSAID groups relative to the celecoxib and rofecoxib groups to maximize sample size in all study groups (ie, naproxen and nonnaproxen nonselective NSAIDs were available throughout the study period, whereas celecoxib and rofecoxib were available only after April 17, 2000). We limited this analysis to the naproxen, nonnaproxen nonselective NSAID, and control groups throughout the study period and repeated the analyses with the addition of an interaction term indicating whether the naproxen and nonnaproxen nonselective NSAID users entered the cohort before or after the introduction of celecoxib and rofecoxib. The interaction terms were then examined for significant differences in AMI rates between these periods among the 2 study drug groups.

All analyses were performed with SAS for UNIX, Version 8.2 (SAS Institute Inc, Cary, NC).

STATISTICAL ANALYSIS

Time-to-event analyses were conducted for AMI by means of Cox proportional hazards models with the control group as the reference. Covariates in the model are outlined in Table 1. As an overall measure of comorbidity, we examined the number of distinct drugs dispensed in the 1 year before the index date, a measure comparable to the Charlson Comorbidity Index. All pairwise combinations of hazard ratios for different exposure groups were compared. The proportional hazards assumption for each exposure variable was assessed in each analysis for any violations.

Several sensitivity analyses were conducted to examine the impact of the study design features on our findings. First, the analyses were repeated with the use of controls matched by age (within 1 year of the birth date) and sex to all patients in the 4 study drug groups as a sensitivity analysis. Second, because women are more likely than men to receive NSAIDs and may have a relatively lower risk of AMI,17 we repeated analyses separately for men and women. Third, we repeated the AMI analysis excluding those with a previous history of AMI. Fourth, a sensitivity analysis was conducted to address differences between study groups in periods for subject accrual. More time was allowed for patient accrual in the naproxen and nonnaproxen nonselective NSAID groups relative to the celecoxib and rofecoxib groups to maximize sample size in all study groups (ie, naproxen and nonnaproxen nonselective NSAIDs were available throughout the study period, whereas celecoxib and rofecoxib were available only after April 17, 2000). We limited this analysis to the naproxen, nonnaproxen nonselective NSAID, and control groups throughout the study period and repeated the analyses with the addition of an interaction term indicating whether the naproxen and nonnaproxen nonselective NSAID users entered the cohort before or after the introduction of celecoxib and rofecoxib. The interaction terms were then examined for significant differences in AMI rates between these periods among the 2 study drug groups.

All analyses were performed with SAS for UNIX, Version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Of approximately 1.44 million potential subjects 65 years and older, 593808 (41%) were dispensed a prescription NSAID during the study period. From these individuals, we identified 15271 users of celecoxib, 12156 users of rofecoxib, 5669 users of naproxen, 33868 users of nonnaproxen nonselective NSAIDs, and 100000 controls (Table 2) who met our inclusion criteria. Among nonselective NSAID users, most subjects initiated treatment with the combination of diclofenac and misoprostol (58%), ibuprofen (14%), or diclofenac (13%). A greater proportion of rofecoxib and celecoxib users were women compared with the other groups. The control group generally used fewer health care resources than the other study groups. More rofecoxib and celecoxib users had cardiovascular-related hospitalizations before cohort entry and were dispensed cardiovascular medications compared with the other groups (Table 2).

During more than 75000 person-years of follow-up, we observed 701 hospitalizations for AMI (Table 3). Relative to the control group, model-based estimates adjusted for the covariates in Table 1 did not disclose any statistically significant association with AMI for users of celecoxib (adjusted rate ratio [aRR], 0.9; 95% confidence interval [CI], 0.7-1.2), rofecoxib (aRR, 1.0; 95% CI, 0.8-1.4), naproxen (aRR, 1.0; 95% CI, 0.6-1.7), or nonnaproxen nonselective NSAIDs (aRR, 1.2; 95% CI, 0.9-1.4). When the drug groups were compared with each other through pairwise comparisons, no significant differences in AMI rates were observed between the drug groups after controlling for possible confounders.

Analyses using age- and sex-matched controls, separate analyses for men and women, and analyses exclud-
ing subjects with a previous history of AMI yielded similar findings. No significant differences in AMI rates between the 2 subject accrual periods were observed for the naproxen and nonnaproxen nonselective NSAID groups.

### Table 2. Characteristics of Cohort Groups

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Community Control Group</th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
<th>Naproxen Sodium</th>
<th>Nonnaproxen Nonselective NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (% female)</td>
<td>100 000 (56)</td>
<td>15 271 (70)</td>
<td>12 156 (71)</td>
<td>5669 (59)</td>
<td>33 868 (62)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>75.2 ± 7.2</td>
<td>76.5 ± 6.9</td>
<td>76.6 ± 7.0</td>
<td>75.0 ± 6.5</td>
<td>76.4 ± 7.0</td>
</tr>
<tr>
<td>Residence in long-term care facility, No. (%)</td>
<td>4197 (4)</td>
<td>665 (4)</td>
<td>548 (5)</td>
<td>291 (5)</td>
<td>2550 (8)</td>
</tr>
<tr>
<td>Low-income status, No. (%)</td>
<td>21 666 (22)</td>
<td>4517 (30)</td>
<td>3625 (30)</td>
<td>1742 (31)</td>
<td>11 602 (34)</td>
</tr>
<tr>
<td>Hospitalization in past year, No. (%)</td>
<td>11 878 (12)</td>
<td>2934 (19)</td>
<td>2363 (19)</td>
<td>1100 (19)</td>
<td>6292 (19)</td>
</tr>
<tr>
<td>No. of prescription drugs in past year, mean ± SD</td>
<td>5.3 ± 5.5</td>
<td>9.3 ± 6.4</td>
<td>9.7 ± 6.5</td>
<td>7.8 ± 6.2</td>
<td>8.3 ± 6.3</td>
</tr>
<tr>
<td>Hospitalizations/procedures in past 5 y, No. (%)</td>
<td>3.314 (3)</td>
<td>752 (5)</td>
<td>608 (5)</td>
<td>208 (4)</td>
<td>1209 (4)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4758 (5)</td>
<td>836 (5)</td>
<td>634 (5)</td>
<td>492 (9)</td>
<td>1968 (6)</td>
</tr>
</tbody>
</table>

**Drug use in 120 d before index date to end of follow-up, No. (%):**

- ACEIs: 21 915 (22) | 5308 (35) | 4404 (36) | 1429 (25) | 9333 (28)
- Aspirin: 12 236 (12) | 2670 (17) | 2148 (18) | 1028 (18) | 6550 (19)
- Antiarrhythmics: 2317 (2) | 473 (3) | 378 (3) | 248 (4) | 122 (2)
- Anticoagulants: 5645 (6) | 1339 (9) | 1028 (8) | 217 (4) | 1426 (4)
- Antihyperglycemics: 9155 (9) | 1872 (12) | 1512 (12) | 762 (13) | 4589 (14)
- Antiplatelet drugs: 976 (1) | 288 (2) | 248 (2) | 43 (1) | 368 (1)
- Antituberculosis: 0 | 639 (4) | 313 (3) | 77 (1) | 619 (2)
- β-Blockers: 14 869 (15) | 3335 (22) | 2644 (22) | 943 (17) | 5772 (17)
- Calcium channel antagonists: 17 002 (17) | 4121 (27) | 3488 (29) | 1167 (21) | 7822 (23)
- Digoxin: 6424 (6) | 1210 (8) | 908 (7) | 351 (6) | 2355 (7)
- Diuretics: 9097 (9) | 2527 (17) | 1988 (16) | 727 (13) | 4970 (15)
- Other diuretics: 14 790 (15) | 4041 (26) | 3166 (26) | 1147 (20) | 6975 (21)
- Estrogen: 5506 (6) | 1871 (12) | 1456 (12) | 484 (9) | 2698 (8)
- Lipid-lowering drugs: 15 540 (16) | 3668 (24) | 3020 (25) | 1055 (19) | 6360 (19)
- Nitrates: 9746 (10) | 2478 (16) | 1927 (16) | 670 (12) | 4389 (13)
- Other antihypertensives: 3710 (4) | 772 (5) | 655 (5) | 308 (5) | 1796 (5)

**Abbreviations:** ACEIs, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; CHF, congestive heart failure; IHD, ischemic heart disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Defined as previous coronary angiography or revascularization procedure.

### Table 3. Primary Analysis: AMI Outcomes

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Community Control Group (n = 100 000)</th>
<th>Celecoxib (n = 15 271)</th>
<th>Rofecoxib (n = 12 156)</th>
<th>Naproxen Sodium (n = 5569)</th>
<th>Nonnaproxen Nonselective NSAIDs (n = 33 868)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of admissions</td>
<td>419</td>
<td>75</td>
<td>58</td>
<td>15</td>
<td>134</td>
</tr>
<tr>
<td>Days of follow-up, mean ± SD</td>
<td>187 ± 101</td>
<td>168 ± 97</td>
<td>144 ± 89</td>
<td>100 ± 88</td>
<td>120 ± 101</td>
</tr>
<tr>
<td>Total follow-up, person-years</td>
<td>51 194</td>
<td>7004</td>
<td>4806</td>
<td>1559</td>
<td>11 085</td>
</tr>
<tr>
<td>Crude AMI rate/1000 person-years</td>
<td>8.2</td>
<td>10.7</td>
<td>12.1</td>
<td>9.6</td>
<td>12.1</td>
</tr>
<tr>
<td>Model-based risk ratios</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted rate ratio (95% CI)</td>
<td>1.0 (Reference)</td>
<td>1.3 (1.0-1.7)</td>
<td>1.5 (1.1-1.9)</td>
<td>1.2 (0.7-2.0)</td>
<td>1.5 (1.2-1.8)</td>
</tr>
<tr>
<td>Adjusted rate ratio (95% CI)</td>
<td>1.0 (Reference)</td>
<td>0.9 (0.7-1.2)</td>
<td>1.0 (0.8-1.4)</td>
<td>1.0 (0.6-1.7)</td>
<td>1.2 (0.9-1.4)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AMI, acute myocardial infarction; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs.

This study has 2 primary findings of importance to clinicians and patients. First, there does not appear to be an increased short-term risk of AMI among users of ce-
lecixib or rofecoxib as commonly used relative to the general non–NSAID-using population. Second, naproxen does not appear to significantly decrease the short-term risk of AMI. These results suggest that the findings from the subanalysis of the VIGOR trial examining AMI rates were either spurious or not applicable to the lower doses of rofecoxib that are more commonly used in clinical practice.

Although selective COX-2 inhibitors interfere with the synthesis of vascular prostacyclin and do not block the synthesis of thromboxane A₂, in contrast to nonselective NSAIDs,¹⁸ the clinical implications of such activity are largely unknown. Our neutral findings for celecoxib and rofecoxib are consistent with previously published reviews of randomized controlled trials that have failed to demonstrate an increased risk of AMI with these drugs.⁴⁻⁵ Naproxen has been reported to inhibit the production of thromboxane and reduce platelet aggregation to a much greater extent than other nonselective NSAIDs.¹⁹ However, the clinical implications of these effects are also uncertain. Three case-control studies have recently demonstrated cardioprotective benefits for naproxen⁶⁻⁸,¹⁰ in contrast to another case-control study that failed to find such an association.⁹ These studies have not demonstrated dose-response, duration-response, or temporal relationships, making it difficult to assess the validity of their findings. Such relationships have been examined in a large cohort study by Ray et al⁸ that followed up NSAID-naïve subjects from the time of nonselective NSAID initiation onward. This study failed to demonstrate cardioprotective benefits for naproxen relative to nonuse, even when stratifying by dose.

Several limitations of this study deserve mention. First, although we controlled for many important confounders, we were unable to account for some potentially important factors such as smoking, obesity, and alcohol consumption. However, we believe this is an unlikely explanation for our findings. Despite a potentially heavier disease burden among the rofecoxib and celecoxib groups relative to the other study groups, which may have resulted from the limited-use policy for selective COX-2 inhibitors in Ontario, neutral risk ratios were still observed for these drug groups relative to the other study groups after adjustment for available confounders. Our population-based incidence estimates for AMI (Table 3) among the control group are also consistent with those of previous studies.²⁰

Second, we used administrative databases to identify and define exposure to study drugs and clinical outcomes. We have no direct measure of indication, adherence, or appropriateness of use and were unable to identify use of nonprescription NSAIDs. However, ibuprofen is the only nonprescription, nonaspirin nonselective NSAID available in Canada, and subjects in our study have a strong financial incentive to obtain these drugs by prescription. Nearly half of elderly residents of Ontario were dispensed aspirin during the study period. Although these figures suggest minimal over-the-counter use of these drugs, the actual magnitude of such activity is unknown. We identified outcomes by means of diagnostic codes that have been validated previously, but we were unable to capture AMI that resulted in death before reaching the hospital. Third, the low absolute number of events in the study groups precluded reliable subgroup analyses examining the outcomes of those using specific NSAIDs and aspirin concurrently or the dose-related effects of these drugs. These issues would be important to examine, since recent evidence suggests that concomitant administration of ibuprofen but not rofecoxib, acetaminophen, or diclofenac antagonizes the irreversible platelet inhibition induced by aspirin²¹ and therefore may alter its cardioprotective effects. Furthermore, Ray et al¹¹ have recently demonstrated increased risk of AMI among users of high-dose rofecoxib, which is consistent with the findings of the rofecoxib trial,² but not the more commonly used lower doses of rofecoxib.¹¹ Fourth, the generalizability of our findings to younger patients or settings with less restrictive access to these drugs over longer durations of follow-up is uncertain.

In summary, we observed no significant increased risk of AMI among users of celecoxib or rofecoxib, nor did we observe a significant protective effect for naproxen as these drugs are commonly used in clinical practice. While our findings relieve concerns about increased risks of AMI associated with celecoxib and rofecoxib, they call into question the cardioprotective benefits of naproxen observed in previous studies.

Accepted for publication September 30, 2002.

From the Institute for Clinical Evaluative Sciences (Drs Mamdani, Rochon, Juurlink, Anderson, Naglie, Austin, and Laupacis and Mr Kopp); Faculty of Pharmacy (Dr Mamdani) and the Departments of Medicine (Drs Rochon, Juurlink, Naglie, and Laupacis), Health Policy, Management, and Evaluation (Dr Anderson), and Public Health Sciences (Dr Austin), Faculty of Medicine, University of Toronto; Division of General Internal Medicine, Sunnybrook and Women’s College Health Sciences Centre (Drs Juurlink and Laupacis); Department of Geriatric Medicine, University Health Network and Toronto Rehabilitation Institute (Dr Naglie); and Department of Geriatric Medicine, Baycrest Centre for Geriatric Care (Dr Rochon), Toronto, Ontario. In the past 2 years, Dr Mamdani has conducted research in an unrelated content area at the request of an academic institution whose funding was supported by Pharmacia Corporation (Peapack, NJ), but none of the funding for this study was provided by any pharmaceutical company.

Dr Mamdani is supported by a New Investigator award from the New Emerging Teams of the Canadian Institutes of Health Research (CIHR), Ottawa, Ontario. Dr Rochon is supported by a Career Scientist award from the CIHR. Dr Juurlink is supported by a fellowship award from the CIHR and from the Clinician-Scientist Program of the Department of Medicine at the University of Toronto, Toronto. Dr Laupacis is a Senior Scientist of the CIHR. This study was supported by a CIHR operating grant (MOP-49527) and a CIHR Chronic Disease New Emerging Team program grant.
(NET-54010). The New Emerging Teams program receives joint sponsorship from the Canadian Diabetes Association, the Kidney Foundation of Canada, the Heart and Stroke Foundation of Canada, and the CIHR Institutes of Nutrition, Metabolism & Diabetes and Circulatory & Respiratory Health, Ottawa.

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