ORIGINAL INVESTIGATION

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors and the Risk of Cancer

A Nested Case-Control Study

Lucie Blais, PhD; Alain Desgagné, MSc; Jacques LeLorier, MD, PhD

Background: During the past 15 years there has been an exponential increase in the number of prescriptions for lipid-lowering drugs. Uncertainties remain about the long-term impact of these medications on cancer, which is particularly bothersome given that the duration of these treatments may extend for several decades.

Objective: To explore the association between 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and cancer incidence.

Methods: Using the administrative health databases of the Régie de l'Assurance-Maladie du Québec we performed a nested case-control study. We selected a cohort of 6721 beneficiaries of the health care plan of Quebec who were free of cancer for at least 1 year at cohort entry, 65 years and older, and treated with lipid-modifying agents. Cohort members were selected between 1988 and 1994 and were followed up for a median period of 2.7 years. From the cohort, 542 cases of first malignant neoplasm were identified, and 5420 controls were randomly selected. Users of HMG-CoA reductase inhibitors were compared with users of bile acid–binding resins as to their risk of cancer. Specific cancer sites were also considered.

Results: Users of HMG-CoA reductase inhibitors were found to be 28% less likely than users of bile acid–binding resins to be diagnosed as having any cancer (rate ratio, 0.72; 95% confidence interval, 0.57-0.92). All specific cancer sites under study were found to be not or inversely associated with the use of HMG-CoA reductase inhibitors.

Conclusion: The results of our study provide some degree of reassurance about the safety of HMG-CoA reductase inhibitors.

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NEWMAN and Hulley[1] reviewed the findings on rodent carcinogenicity of lipid-lowering drugs and concluded that fibrates and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors initiate or promote cancer in rodents. In some cases, the levels of exposure were similar to those prescribed to humans. In humans, the relation between low cholesterol levels and cancer is the object of intense debate and justifiable preoccupation. Although cohort studies[2,3] have demonstrated that low cholesterol levels are associated with more cancer deaths, the evidence for causality is weak, since preexisting cancer and other confounding variables might be responsible for the association. Evidence from clinical trials of lipid-modifying therapies is reassuring but not conclusive. Law et al[4,5] published a meta-analysis of randomized controlled trials. They reported an odds ratio for cancer death of 1.07 (95% confidence interval [CI], 0.90-1.26). In an overview of randomized trials testing HMG-CoA reductase inhibitors, Hebert et al[6] found no significant increase in the incidence of cancer (risk ratio, 1.03; 95% CI, 0.90-1.17).

Given the level of uncertainty about their potential carcinogenic effects, their expanding indication in primary prevention, and the fact that they will be used for extended periods, it is clear that more data are needed on the potential carcinogenicity of lipid-lowering drugs. To explore the association of HMG-CoA reductase inhibitors and cancer in a large number of patients, we conducted a nested case-control study in a Canadian administrative database.

From the Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Unité de Pharmaco-Économie et de Pharmaco-Épidémiologie, Montreal, Quebec.

RESULTS

During the follow-up of the study cohort (6721 subjects followed up for a maximum of 7 years and a median of 2.7 years)

METHODS

This study is based on data selected from the computerized health databases of the Régie de l'Assurance-Maladie du Québec (RAMQ), the government body that administers health programs available to residents of Quebec, a Canadian province of 7 million inhabitants. The RAMQ administers a drug insurance plan, which covers approximately 97% of individuals 65 years or older living in Quebec.[7] The RAMQ is also responsible for the payment of physician and hospitalization services for all residents of the province.

The RAMQ owns several computerized databases, namely the Prescription Drugs Database and the Medical Services Database. The Prescription Drugs Database records information related to all prescription drugs dispensed to beneficiaries of the provincial drug plan, including the dispensation date, name, strength, dosage form, quantity and duration of the medication, and information on the physician who prescribed the medication. The Medical Services Database records information on all medical services provided in the province, including the date the service is provided, the primary diagnosis coded with *International Classification of Diseases, Ninth Revision (ICD-9)*[8] codes, the specialty of the treating physician, and where the service was provided (hospital, emergency department, or physician's office). The RAMQ databases also contain sociodemographic variables such as age and sex, and the date of death. In addition, all RAMQ databases contain a unique subject identifier, which allows the linkage of the databases. These databases have previously been used for epidemiological research, and prescription drug data have been shown to be accurate and valid.[9-12]

STUDY COHORT

From a 10% random sample of the beneficiaries of the RAMQ drug plan who were 65 years or older, we selected a cohort of 6721 users of lipid-reducing agents from January 1, 1988, to December 31, 1994. We included in the cohort all subjects who had at least 1 prescription of HMG-CoA reductase inhibitors (lovastatin, pravastatin sodium, and simvastatin) or bile acid–binding resins (cholestyramine resin and colestipol hydrochloride) dispensed from January 1, 1988, to December 31, 1994, and no diagnosis of neoplasm (benign or malignant) for at least 1 year before the first prescription of these medications. Cohort entry was therefore defined as the date of the first prescription of HMG-CoA reductase inhibitors or bile acid–binding resins dispensed on or after January 1, 1988. Cohort members were followed up until death or December 31, 1994.

NESTED CASE-CONTROL DESIGN

To assess the association between HMG-CoA reductase inhibitors and the risk of cancer, we performed a case-control analysis within the cohort. Users of HMG-CoA reductase inhibitors were compared with users of bile acid–binding resins. Bile acid–binding resins were chosen as the reference category because they are prescribed for the same indication as the HMG-CoA reductase inhibitors but are not absorbed from the gastrointestinal tract[13] and have not been found to be associated with an increased risk of cancer in rodents or humans.[15]

The main study end point was the first diagnosis of any malignant neoplasm (all sites). As secondary end points, we studied specific cancer sites, namely, skin, prostate, lung, breast, colon, bladder and kidney, uterus, and lymphoma. These cancer sites were selected because they represent the cancers with the highest incidence in our cohort and in Canada during the mid-1990s.[14]

To identify cancer cases, the cohort was linked to the Medical Services Database. For the primary end point, cases were defined as any cohort member who received a medical diagnosis of malignant neoplasm after cohort entry; only the first diagnosis of malignant neoplasm was retained. Cancer diagnoses were defined with the *ICD-9* codes ranging from 140.0 to 208.9.

For each first case of malignant neoplasm, we randomly selected 10 controls among the cohort members. To avoid selection bias, we used density sampling (ie, selection

we identified 542 subjects who received at least 1 diagnosis of malignant neoplasm, for an incidence rate of first cancer of 2.9% per year. Among these 542 cancer cases, 381 received exactly 1 diagnosis of cancer, 129 received 2 diagnoses of cancer, and 32 received 3 or more diagnoses of cancer.

For the case-control analysis with the primary end point we used the 542 cases of first malignant neoplasm and 5420 selected controls. **Table 1** shows the sociodemographic characteristics of the subjects and their exposure to medications. Cases were slightly older than controls and more often men. Cases were more than 3 times more likely than controls to have had a diagnosis of benign neoplasm before the index date and more likely to enter the cohort before 1990. Approximately 77% of cases and 82% of controls were dispensed at least 1 prescription of HMG-CoA reductase inhibitors from entry to index date. Only 11% of cases and 10% of controls used both study medications during the study period, and similar proportions of cases and controls used fibric acid and other lipid-modifying agents.

In **Table 2**, we present the distribution of potential confounders for users of HMG-CoA reductase inhibitor and users of bile acid–binding resins. This table shows that users of bile acid–binding resins entered the cohort earlier and used more fibric acid and more other lipid-modifying agents than users of HMG-CoA reductase inhibitor.

Using a logistic regression model adjusting for age on the index date, sex, use of fibric acid, use of other lipid-reducing agents, previous benign neoplasm, year of cohort entry, and the score of comorbidity, we estimated that users of HMG-CoA reductase inhibitors were 28% less likely to have a diagnosis of malignant neoplasm than users of bile acid–binding resins (RR, 0.72; 95% CI, 0.57-0.92; **Table 3**). As expected, this model showed that older subjects and men had an increased risk of cancer and that the overall incidence of cancer tended to decrease over

of an individual on a specific day), where a case may be selected as a control before he or she becomes a case and a subject may be selected as a control several times for different cases.[15]

For the secondary end points, which represent specific cancer sites, we used the same selection procedure with the following *ICD-9* codes: skin (172.0-173.9), prostate (185.0-185.9), lung (162.9), breast (174.0, 174.8, 174.9), colon (153.0-154.9), bladder and kidney (188.0-189.0), uterus (179.9-183.0), and lymphoma (201.9, 203.9). Each cancer site was analyzed separately, and for every case in a specific site, we selected 10 controls. It is worth noting that for these secondary end points we did not limit the analysis to the first diagnosis of malignant neoplasm; individuals who received 2 different diagnoses of cancer during the study period were used as cases in 2 different analyses. For example, if a subject was first diagnosed as having skin cancer and later as having lung cancer, he or she contributed as a case to both the skin cancer analysis and the lung cancer analysis.

For each case and control, we assessed the exposure to the study medications from cohort entry to index date (date of cancer diagnosis for cases and date of selection for controls). We first identified whether the study subjects were users of HMG-CoA reductase inhibitors or bile acid–binding resins only or users of both medications. For users of HMG-CoA reductase inhibitors, we also evaluated the cumulative dose measured as the total number of milligrams received from cohort entry to index date.

Age at index date, sex, whether the subjects had a diagnosis of neoplasm (benign or malignant) before the index date, calendar year of entry in the cohort, use of fibric acids (clofibrate, fenofibrate, and gemfibrozil), use of other lipid-modifying agents (dextrothyroxine sodium, nicotinic acid, and probucol), and a score of comorbidity were treated as confounders. For the primary end point (first diagnosis of malignant neoplasm), the variable prior neoplasm can only represent benign neoplasms. On the other hand, for the secondary end points (specific cancer sites), this variable may represent either a malignant or a benign (*ICD-9* codes 210.0-229.9) neoplasm that was diagnosed before the index date. Year of entry in the cohort was used to adjust for changing secular trends in the prescription of the 2 study medications. The score of comorbidity is a score ranging from 0 to 16 based on concomitant medications dispensed in the year before the index date. This score was explicitly developed to be used in studies based on computerized drug databases and was found to be valid as a measure of general health.[16]

STATISTICAL ANALYSIS

The effect of HMG-CoA reductase inhibitors on cancer incidence was estimated with logistic regression models adjusting for all confounders described in the previous section. We used 9 different models: one model for the primary end point and one model for each of the 8 secondary end points.

For each of the 9 study end points, we estimated the rate ratio (RR) of cancer incidence comparing users of HMG-CoA reductase inhibitors (whether or not they took bile acid–binding resins between entry and index date) with subjects who used only bile acid–binding resins from entry to index date.

For the primary end point, we also performed 3 supplementary analyses. First we performed a dose-response analysis in which we used cumulative dose of HMG-CoA reductase inhibitors from entry to index date as the main exposure. The cumulative dose was divided in 6 categories, 0 through 600, 601 through 1200, 1201 through 1800, 1801 through 3600, 3601 through 7200, and 7201 mg or more, which corresponds to 0 through 30, 31 through 60, 61 through 90, 91 through 180, and 181 days or more of treatment with an HMG-CoA reductase inhibitor at a dose of 20 mg/d, respectively. Second, we performed a similar analysis in which the duration of follow-up (time between cohort entry and index date) was stratified in 6 categories. Finally, we did a third analysis where users of HMG-CoA reductase inhibitor were simultaneously classified according to the cumulative dose of medication dispensed (<1200, 1200-3600, and >3600 mg) and the duration of follow-up (<3 years and ≥3 years).

time.[13] This model also showed that subjects with previous benign neoplasm were 4 times more likely to develop cancer than subjects without such diagnoses (RR, 3.89; 95% CI, 3.00-5.04) and that use of fibric acid and other lipid-reducing agents was not associated with the risk of cancer.

In **Table 4**, we present the results of the analysis stratified by dose and duration of follow-up. The dose-response model shows that subjects with a cumulative exposure of 1800 mg or less were not significantly likely to have a reduction in the risk of the first cancer, whereas subjects who accumulated more than 1800 mg were significantly less likely than users of bile acid–binding resins to have cancer. However, the RRs from this model were not found to be statistically different (test of homogeneity, $P=.98$). For the analysis stratified by the duration of follow-up, we also found no increase in the risk of cancer associated with HMG-CoA reductase inhibitor, and the RRs for the 6 categories of duration of follow-up were not statistically different (test of homo neity, $P=.95$). When both cumulative dose and durat of follow-up were considered together, we found no creased risk of cancer for users of HMG-CoA reduct inhibitors. For subjects who were dispensed more t 3600 mg of HMG-CoA reductase inhibitors and lowed up for 3 years or more, we found a RR of 0.81 (9 CI, 0.59-1.11).

In **Table 5**, we present the results of the 8 logi regression models used to estimate the RR for each cer site and the results of another model for "other cers," regrouping all cancer sites that were not stu individually. These analyses show a trend toward a tective effect of HMG-CoA reductase inhibitors fo ery cancer site that we investigated except for l phoma (RR, 2.17; 95% CI, 0.38-12.36), although the RRs associated with cancer of the uterus (RR, (95% CI, 0.11-0.81) and "other cancers" (RR, 0.61; CI, 0.43-0.85) reached statistical significance.

Table 1. Characteristics of Study Subjects (All First Malignant Neoplasms Combined)*

Characteristic	Cases (n = 542)	Controls (n = 5420)
Age at index date, y		
65-74	51.7	55.0
75-84	35.1	35.1
≥85	13.3	9.9
Male	44.6	31.2
Previous nonmalignant neoplasm(s)	17.5	5.1
Year of cohort entry		
1988-1989	31.5	27.6
1990-1991	36.3	39.2
1992-1994	32.1	33.2
Use of study medications from cohort entry to index date		
HMG-CoA reductase inhibitors only	66.8	72.4
Bile acid–binding resins only	22.5	17.6
Both medications	10.7	9.9
Cumulative dose of HMG-CoA reductase inhibitors from cohort entry to index date, mg		
0 (Bile acid–binding resins only)	22.5	17.6
1-600	10.5	10.4
601-1200	6.3	6.4
1201-1800	4.6	5.6
1801-3600	10.1	13.4
3601-7200	13.1	15.9
≥7201	32.8	30.7
Use of fibric acid	11.3	11.4
Use of other lipid-modifying agents†	2.6	2.3
Comorbidity score, mean ± SD	4.5 ± 3.1	4.1 ± 3.0

*Data are given as percentage of subjects, except where otherwise noted. HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A.
†Dextrothyroxine sodium, nicotinic acid, and probucol.

Table 2. Distribution of Covariates Comparing Statin Users to Resin Users (All First Malignant Neoplasms Combined)*

Covariates	Statins (n = 4884)	Resins (n = 1078)
Age at index date, y		
65-74	56.8	45.1
75-84	33.9	40.6
≥85	9.3	14.3
Male	33.5	27.3
Previous nonmalignant neoplasm(s)	6.1	6.5
Year of cohort entry		
1988-1989	22.7	51.7
1990-1991	40.7	31.1
1992-1994	36.5	17.3
Use of fibric acid	10.0	17.5
Use of other lipid-modifying agents†	2.0	4.0
Comorbidity score, mean ± SD	4.2 ± 3.0	3.9 ± 3.1

*Data are given as percentage of subjects, except where otherwise noted.
†Dextrothyroxine sodium, nicotinic acid, and probucol.

COMMENT

We did not find a significant positive association between use of HMG-CoA reductase inhibitors and the incidence of malignant neoplasm. On the contrary, for all malignant neoplasms combined, we found that users of HMG-CoA reductase inhibitors were 28% less likely than users of bile acid–binding resins to develop cancer. No increase in cancer risk was also found for users of HMG-CoA reductase inhibitors when the analysis was stratified by cumulative dose and duration of follow-up. Except for lymphomas (RR, 2.17; 95% CI, 0.38-12.36), none of the specific cancer sites that we studied were found to be positively associated with the use of HMG-CoA reductase inhibitors.

Table 3. Effect of HMG-CoA Reductase Inhibitors on Cancer Incidence (All First Malignant Neoplasms Combined)*

Determinants	Crude Rate Ratio	Adjusted Rate Ratio† (95% CI)
HMG-CoA reductase inhibitors	0.74	0.72 (0.57-0.92)
Bile acid–binding resins	Referent	Referent
Age at index date, y		
65-74	Referent	Referent
75-84	1.06	1.06 (0.86-1.30)
≥85	1.43	1.45 (1.08-1.93)
Sex (M/F)	1.78	1.83 (1.52-2.19)
Previous nonmalignant neoplasms (yes/no)	3.99	3.89 (3.00-5.04)
Year of cohort entry		
1988	Referent	Referent
1989	0.86	0.99 (0.69-1.42)
1990	0.72	0.80 (0.55-1.16)
1991	0.75	0.90 (0.62-1.31)
1992	0.81	1.01 (0.69-1.47)
1993	0.74	0.95 (0.62-1.45)
1994	0.48	0.62 (0.27-1.42)
Use of fibric acid (yes/no)	0.99	0.93 (0.70-1.25)
Use of other lipid-reducing agents (yes/no)‡	1.12	0.93 (0.52-1.67)
Comorbidity score (5-point difference)	1.26	1.22 (1.05-1.40)

*HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A; CI, confidence interval.
†Adjusted rate ratios were estimated from 1 logistic regression model, including all variables presented in this table.
‡Dextrothyroxine sodium, nicotinic acid, and probucol.

Our results diverge from those of the literature review that led Newman and Hulley[1] to the conclusion that all the studied fibrates and statins produce cancer in rodents but are concordant with those of meta-analyses of randomized clinical trials on HMG-CoA reductase inhibitors.

Although our study is nonexperimental, it is unlikely that its results would be explained by confounding by indication (or contraindication), since we investigated an unintended effect of HMG-CoA reductase inhibitors.[17] We believe that the choice between HMG-CoA reductase inhibitors and bile acid–binding resins made by treating physicians and their patients was not based on cancer risks.

To minimize detection bias, users of HMG-CoA reductase inhibitors were compared with patients treated for the same indications who were therefore likely to have similar contacts with health services and consequently a similar likelihood of having their cancer diagnosed. Bile acid–binding resins are a good choice for the reference category as long as they are not associated with cancer risks. In the Lipid Research Clinics Coronary Primary Pre-

Table 4. Effect of Cumulative Dose of HMG-CoA Reductase Inhibitors on the Incidence of Cancer (All First Malignant Neoplasms Combined)*

Determinants	Cases, No.	Controls, No.	Crude Rate Ratio	Adjusted Rate Ratio† (95% CI)
Cumulative dose of HMG-CoA reductase inhibitors, mg‡				
1-600	57	564	0.79	0.85 (0.59-1.21)
601-1200	34	345	0.77	0.82 (0.54-1.25)
1201-1800	25	303	0.65	0.65 (0.41-1.04)
1801-3600	55	724	0.60	0.60 (0.42-0.85)
3601-7200	71	863	0.64	0.63 (0.45-0.88)
≥7201	178	1665	0.84	0.77 (0.59-1.01)
Duration of follow-up, y§				
<1	126	1455	0.68	0.72 (0.53-0.98)
1-2	115	1257	0.72	0.69 (0.51-0.93)
2-3	72	890	0.63	0.58 (0.42-0.82)
3-4	55	468	0.92	0.84 (0.58-1.20)
4-5	37	268	1.08	0.96 (0.63-1.50)
≥5	15	126	0.93	0.72 (0.40-1.32)
Bile acid–binding resins only	122	956	Referent	Referent

*HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A; CI, confidence interval.
†The rate ratios are adjusted for age at index date, sex, previous neoplasm, year of entry in the cohort, use of fibric acid, use of other lipid-reducing agents, an the comorbidity score.
‡Dose of HMG-CoA reductase inhibitors cumulated from cohort entry to index date. Test of homogeneity for the 6 dose-specific rate ratios, P = .98.
§Follow-up time is the time between cohort entry and the index date. Test of homogeneity for the 6 duration-specific rate ratios, P = .95.

Table 5. Effect of HMG-CoA Reductase Inhibitors on Incidence of Specific Cancer Sites*

	HMG-CoA Reductase Inhibitors vs Bile Acid–Binding Resins			
Cancer Sites	Cases, No.	Controls, No.	Crude Rate Ratio	Adjusted Rate Ratio (95% CI)
Skin†	113	1130	0.75	0.81 (0.47-1.39)
Prostate‡	78	780	1.06	0.74 (0.36-1.51)
Lung†	70	700	0.79	0.94 (0.43-2.05)
Female breast‡	65	650	0.67	0.67 (0.33-1.38)
Colon†	56	560	0.56	0.83 (0.37-1.89)
Bladder and kidney§	31	310	0.62	0.43 (0.16-1.13)
Uterus‖	26	260	0.34	0.30 (0.11-0.81)
Lymphoma§	24	240	2.61	2.17 (0.38-12.36)
All other cancers†	276	2760	0.60	0.61 (0.43-0.85)

*HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A; CI, confidence interval.
†The rate ratios were adjusted for age at index date, sex, previous neoplasm, year of cohort entry, use of fibric acids, use of other lipid–reducing agents, and comorbidity score.
‡The rate ratios were adjusted for all variables listed above except sex.
§The rate ratios were adjusted for all variables listed above except other lipid-reducing agents.
‖The rate ratios were adjusted for all variables listed above except sex and other lipid-reducing agents.

vention Trial,[18] which investigated the efficacy of cholestyramine, no significant excess in cancer risk was found during a follow-up period of 13 years. Although users of HMG-CoA reductase inhibitors are likely to be more similar to users of bile acid–binding resins than to the general population, bias due to unmeasured confounders cannot be completely ruled out.

By using computerized databases, it was possible to follow up a large number of subjects for a maximum of 7 years (median follow-up, 2.7 years) and attain sufficient power as well as eliminate recall bias for drug exposure. However, the exposure to study medications was entirely based on dispensed prescriptions and may overrepresent the medications actually taken. If present, this type of misclassification would underestimate the effect of HMG-CoA reductase inhibitors. In addition, cases of cancer were identified using medical diagnoses recorded in the Medical Services Database but were n confirmed through medical chart review. This may ha caused nondifferential misclassification of the outcor that would possibly dilute the effect of HMG-C reductase inhibitors.[19] Another limitation of this stu is the fact that a proportion of the study subje (<13%) were already treated with the study medi tions when they entered the cohort. This is because t Prescription Drugs Database starts to record dispens medications only at the age of 65 years. This le censored exposure information might have resulted some degree of exposure misclassification in the do response and duration analyses, but there is no reas to believe that it might be differential between cases a controls.

Given the nonexperimental nature of our stu and the ever-present possibility of residual confound

by unmeasured variables, we do not believe that our results should be interpreted as strong evidence of a protective effect of HMG-CoA reductase inhibitors on the incidence of cancer. It would, however, be extremely unlikely to see residual confounding move the RR from statistically significant values less than 1, indicating a protective effect (RR, 0.72; 95% CI, 0.57-0.92), to statistically significant values above 1, which would indicate an initiating or promoting effect of HMG-CoA reductase inhibitors on cancer. However, to further investigate the possibility that HMG-CoA reductase inhibitors have an initiating effect on cancer, we redid the analysis presented in Table 3, excluding all cancers that occurred during the first 3 years of follow-up. In this analysis, we found an adjusted RR of 0.92 (95% CI, 0.56-1.52) for users of HMG-CoA reductase inhibitors compared with users of bile acid–binding resins, indicating no excess risk associated with HMG-CoA reductase inhibitors.

The results of our study provide some evidence against the theory according to which HMG-CoA reductase inhibitors might have initiating or promoting effects on the incidence of cancer. These results provide reassurance about the safety of a group of drugs that are being used by numerous patients for long periods.

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Reprints: Jacques LeLorier, MD, PhD, Centre de Recherche, Hôtel-Dieu du CHUM, Pavillon Masson, 3850 Saint-Urbain, Montreal, Quebec, Canada H2W 1T8.

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