

Null Results in Brief

Reported Use of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors Was Not Associated with Reduced Recurrence of Colorectal Adenomas

Jeffrey T. Wei,¹ Leila A. Mott,² John A. Baron,² Robert S. Sandler,¹
and for the Polyp Prevention Study Group

¹University of North Carolina, Chapel Hill, North Carolina and ²Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Abstract

We did a secondary analysis of data from three large colorectal adenoma chemoprevention trials to assess the association between 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor use and reduced risk of recurrent colorectal adenomas. Reported use of HMG-CoA reductase inhibitors was not associated with

a reduced recurrence of colorectal adenomas, multiple adenomas, or advanced adenomas. Lack of statistical power from limited exposure to HMG-CoA reductase inhibitors might be responsible for the lack of association. (Cancer Epidemiol Biomarkers Prev 2005; 14(4):1026-7)

Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been suggested as chemopreventive agents against the development of colon cancer. These drugs have been shown to reduce carcinogen-induced colon cancers in rodent models (1) and to decrease proliferation and induce apoptosis in colon cancer cell lines (2). Moreover, a synergistic effect on decreasing proliferation of colon cancer cells was seen when sulindac, a nonsteroidal anti-inflammatory drug (NSAID), was added to the HMG-CoA reductase inhibitor lovastatin (3). The proposed mechanism of action is through an interruption of isoprenylation of intracellular proteins, a crucial process for membrane attachment and function (4).

Although two large randomized controlled trials showed a nonsignificant decrease in colorectal cancer risk in patients on HMG-CoA reductase inhibitors (5, 6), other clinical trials of cholesterol reduction published contrary findings (7).

To further investigate the role of HMG-CoA reductase inhibitors in chemoprevention, we analyzed existing data from three colorectal adenoma prevention studies. We hypothesized that subjects on HMG-CoA reductase inhibitors would have a reduced risk for recurrence of colorectal adenomas, possibly with a greater decrease in risk for subjects who used aspirin or NSAIDs concurrently with HMG-CoA reductase inhibitors.

Materials and Methods

Subjects were participants in three large randomized trials of potential chemopreventive agents for the recurrence of colorectal adenomas in patients with a history of adenomas. In the antioxidant polyp prevention study (8), 864 patients

were randomly assigned in a 2 × 2 factorial design to placebo, β-carotene (25 mg daily), vitamin C (1 g daily), and vitamin E (400 mg daily); or β-carotene and vitamins C and E. In the calcium polyp prevention study (9), 930 subjects were randomly assigned to treatment with calcium carbonate (3 g daily) or placebo. In the aspirin/folate polyp prevention study (10), 1,121 subjects were randomized using a 3 × 2 factorial design to aspirin (placebo, 81 mg/d, or 325 mg/d) and folate (placebo or 1 mg/d). The folate intervention of this trial is still ongoing and no data regarding it will be presented here. Details on eligibility criteria and study protocol have been described previously (8-10).

Medication use was recorded on self-completed questionnaires at baseline. Follow-up questionnaires were administered every 4 months in the antioxidant and aspirin/folate studies and every 6 months in the calcium study. Approximately 95% of expected questionnaires were returned for all of the studies. HMG-CoA reductase inhibitor use, the main exposure in our analysis, was defined as reported use on one or more questionnaires. "Consistent" use was defined as reported use on >20% of returned questionnaires.

The primary outcome measure was the proportion of subjects in whom at least one adenoma was detected at follow-up endoscopy. The secondary outcome measure was detection of multiple adenomas or detection of an advanced adenoma (defined as a neoplastic polyp ≥1 cm), at least 25% villous elements, or evidence of high-grade dysplasia. Risk ratios were calculated from log-linear models controlling for possible confounders. Analysis was done on data from each individual study as well as on pooled data from all three studies.

Covariates included age, sex, center, length of follow-up, lifetime number of adenomas, treatment assignment, and body mass index. Stratified analyses were used to evaluate aspirin or NSAID use as an effect modifier. Aspirin or NSAID use was defined as reported use on one or more questionnaires, except in the aspirin/folate chemoprevention trial; for that study, aspirin or NSAID use was defined as treatment assignment to one of the aspirin groups. Additional analyses were restricted to subjects on placebo only, to subjects not reporting HMG-CoA reductase inhibitor use at baseline, and to subjects who

Received 5/16/03; revised 7/23/03; accepted 12/13/04.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Jeffrey T. Wei, Division of Gastroenterology and Hepatology, University of North Carolina, Campus Box 7080, Chapel Hill, NC 27599.
E-mail: jwei@med.unc.edu

Copyright © 2005 American Association for Cancer Research.

Table 1. Prevalence of HMG-CoA reductase inhibitor use, crude risks of recurrent adenomas, and adjusted relative risks for recurrent adenomas

Study/ subgroup (n)	n with Any/advanced/ multiple adenomas	Adjusted RR, any adenoma	Adjusted RR, any advanced adenoma	Adjusted RR, multiple adenomas (>1)
Antioxidant PPS				
No use (726)	269/55/108			
Any use (12)	3/2/1	0.70 (0.28, 1.75)	2.15 (0.55, 8.40)	0.64 (0.10, 3.96)
Calcium PPS				
No use (768)	263/64/119			
Any use (56)	20/4/9	1.07 (0.74, 1.55)	0.98 (0.38, 2.54)	1.25 (0.66, 2.37)
Aspirin PPS				
No use (931)	399/69/173			
Any use (145)	68/12/38	1.04 (0.86, 1.27)	1.15 (0.63, 2.10)	1.31 (0.95, 1.81)
Pooled data				
No use (2,425)	931/188/391			
Any use (213)	91/18/48	1.04 (0.87, 1.23)	1.13 (0.70, 1.81)	1.25 (0.95, 1.65)
Aspirin PPS				
No use (931)	399/69/173	1.00 (0.80, 1.25)	1.22 (0.64, 2.33)	1.27 (0.89, 1.82)
Consistent use (112)	51/10/29			
Pooled data, placebo groups				
No use (716)	277/60/117	0.85 (0.56, 1.29)	0.87 (0.30, 2.50)	1.03 (0.51, 2.09)
Any use (46)	15/3/7			
Pooled data, baseline nonusers				
No use (2,414)	928/186/390	1.06 (0.86, 1.30)	1.18 (0.68, 2.02)	1.26 (0.91, 1.75)
Any use (146)	63/13/33			

NOTE: Consistent users were compared with nonusers in the aspirin polyp prevention study only. Relative risks were adjusted for age, sex, center, time to follow-up exam, lifetime number of adenomas, treatment assignment, and body mass index. Abbreviations: RR, relative risks; PPS, polyp prevention study.

reported consistent use. The subanalysis on consistent users compared with never-users of the drugs was restricted to the aspirin/folate study due to small numbers of consistent users in the antioxidant and calcium studies.

Results

Of the 2,915 subjects randomized in the three trials, 2,638 underwent follow-up colonoscopy and were eligible for analysis. Users and nonusers of HMG-CoA reductase inhibitors were similar with regard to age, sex, race, smoking status, body mass index, and lifetime number of adenomas. Overall, 8.1% of patients reported use of the drugs on at least one questionnaire. The prevalence of use by study and the crude risks of adenoma recurrence are displayed in Table 1.

Compared to never-users, the pooled multivariate risk ratios among users were as follows: for any adenoma, 1.03 (95% confidence interval, 0.87-1.23); for any advanced adenoma, 1.13 (95% confidence interval, 0.70-1.81); and for multiple adenomas, 1.25 (95% confidence interval, 0.95-1.65; Table 1).

The results were similar when we restricted the analysis to consistent users, subjects assigned to placebo only, or to baseline nonusers of HMG-CoA reductase inhibitors (Table 1). There were no significant differences in the risk ratios between strata of aspirin or NSAID use. Exclusion of seven subjects who participated in more than one of the studies did not alter the pooled results.

Discussion

In this secondary analysis of three chemoprevention trials of colorectal adenomas, we did not find reported use of HMG-CoA reductase inhibitors to be associated with a reduced risk for recurrence of colorectal adenomas, advanced adenomas, or multiple adenomas.

There are several important limitations to this study. Only a small proportion of subjects reported use of HMG-CoA reductase inhibitors. Inadequate exposure in terms of prevalence of use, frequency, dose, or duration of use could be responsible for the lack of association. Furthermore, we did not

independently validate medication data obtained on self-administered questionnaires. Therefore, patients who reported taking the medications may not have been taking the medications consistently. Alternatively, subjects may have been taking medications that they did not report. Such measurement error would generally tend to introduce a conservative bias.

Conclusions

Contrary to prior expectation, reported use of HMG-CoA reductase inhibitors was not associated with a reduced risk for recurrence of colorectal adenomas, advanced adenomas, or multiple adenomas. Lack of statistical power from limited exposure to the drugs might be responsible for the lack of association.

References

- Narisawa T, Fukaura Y, Terada K, et al. Prevention of 1,2-dimethylhydrazine-induced colon tumorigenesis by HMG-CoA reductase inhibitors, pravastatin and simvastatin, in ICR mice. *Carcinogenesis* 1994;15:2045-8.
- Agarwal B, Bhendwal S, Halmos B, Moss SF, Ramey WG, Holt PR. Lovastatin augments apoptosis induced by chemotherapeutic agents in colon cancer cells. *Clin Cancer Res* 1999;5:2223-9.
- Agarwal B, Rao CV, Bhendwal S, et al. Lovastatin augments sulindac-induced apoptosis in colon cancer cells and potentiates chemopreventive effects of sulindac. *Gastroenterology* 1999;117:838-47.
- Agarwal B, Halmos B, Feoktistov AS, et al. Mechanism of lovastatin-induced apoptosis in intestinal epithelial cells. *Carcinogenesis* 2002;23:521-8.
- Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.
- Pederson TR, Berge K, Cook TJ, et al. Safety and tolerability of cholesterol lowering agents with simvastatin during 5 years in Scandinavian simvastatin survival study. *Arch Intern Med* 1996;156:3085-92.
- Bjerre LM, LeLorier J. Do statins cause cancer? A meta-analysis of large randomized clinical trials. *Am J Med* 2003;110:738-40.
- Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group. *N Engl J Med* 1994;331:141-7.
- Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 1999;340:101-7.
- Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003;348:891-9.