There Is No Evidence for an Increase in Acute Coronary Syndromes After Short-Term Abrupt Discontinuation of Statins in Stable Cardiac Patients

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Background—For a variety of reasons, many patients abruptly discontinue statin therapy. The present analysis was conducted to determine whether the risk of cardiovascular outcomes increases after withdrawal of statin therapy in a stable cardiac population.

Methods and Results—In the Treating to New Target (TNT) study, 2 doses of atorvastatin (10 and 80 mg once daily) are being used in a double-blind parallel-group design. Of the 18,468 patients screened for study participation, 16,619 entered a dietary lead-in/drug-washout period, and of these, 15,432 eligible participants began treatment with atorvastatin 10 mg/d on an open-label basis. Of the subjects who entered the dietary lead-in/drug-washout period, 57% were receiving prior statin therapy. During the 6-week drug-washout period, there were 24 primary events (defined as coronary heart disease death, nonfatal myocardial infarction, resuscitated cardiac arrest, and fatal or nonfatal stroke); throughout the subsequent 8-week open-label period, there were 31 primary events. This equated to monthly Kaplan-Meier event rates of 0.20% during washout and 0.26% in the open-label phase. Event rates were therefore similar during the 2 phases.

Conclusions—The present analysis demonstrates that short-term discontinuation of statin therapy in stable cardiac patients apparently does not lead to a clinically important increased risk of acute coronary syndromes. (Circulation. 2004;110:2333-2335.)

Key Words: coronary disease ▪ statins ▪ drugs ▪ hyperlipoproteinemia

In persons with coronary artery disease (CAD), hyperlipidemia is a major risk factor for recurrent cardiac events. There is now strong evidence that lowering LDL cholesterol (LDL-C) significantly decreases the incidence of adverse clinical outcomes (worsening angina, hospitalizations for angina, myocardial infarction [MI], percutaneous coronary interventions, CAGB, stroke, and death).1-8 On the basis of these studies, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults recommends the use of HMG-CoA reductase inhibitors or statins in persons with cardiovascular disease who fail to achieve target LDL-C levels with therapeutic lifestyle changes alone.9

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Statin postulated to provide cardiovascular protection by a number of different mechanisms. Although LDL reduction via inhibition of the HMG-CoA reductase enzyme is likely the most important mechanism, it may not account for all benefits associated with statin therapy. A number of pleiotropic effects of statins have been proposed. Statins have been shown to upregulate endothelial nitric oxide synthase, resulting in improved vasodilatation.10,11 Gertz and colleagues12 have recently shown that within 48 hours of statin withdrawal, normocholesterolemic mice reduced their nitric oxide production by 90% with no significant alteration in lipid levels. Endothelial dysfunction is also characterized by elevated levels of the vasoconstrictive substance endothelin-1,13 and statins have also been shown to inhibit the expression of endothelin-1 in vascular endothelial cells.14 In addition, statins have demonstrated the ability to inhibit platelet aggregation15,16 and monocyte adhesion to the endothelial surface17,18 and to possess antioxidant19 and antiinflammatory activity, particularly the reduction in C-reactive protein levels.20,21 Although some of these nonlipid effects may be operative even before substantial lipid benefits accrue, others may not be truly independent of lipid reduction.22

Despite the known benefit of statin therapy, many stable cardiac patients abruptly discontinue therapy.23 Additionally, nearly all clinical trials involving statins require a dietary lead-in period of 4 to 6 weeks. During this lead-in period, study participants taking a daily statin at the time of recruitment are required to discontinue such therapy.

Heeschen and colleagues24 reported an ∼3-fold increase in the risk of death and nonfatal MI when statins therapy was...
withdrawn after an admission for an acute coronary syndrome. The same group subsequently reassessed their analysis and found only a trend toward greater cardiac risk with abrupt statin discontinuation. Data have recently been published from the Global Registry of Acute Coronary Events (GRACE), which includes 19,537 men and women admitted with an acute coronary syndrome. Of the 4056 events (GRACE), which includes 19,537 men and women published from the Global Registry of Acute Coronary Syndrome, therapy in this patient population.

cardiovascular outcomes increases after abrupt discontinuation. Although the vascular milieus of stable and unstable cardiac patients are clearly vastly different, the sheer number of individuals with stable cardiac disease in the United States alone makes it imperative to determine whether the risk of cardiovascular outcomes increases after abrupt discontinuation of statin therapy in this patient population.

Methods
To analyze the risk associated with withdrawal of statin therapy in stable cardiac patients, we evaluated the overall monthly primary cardiac event rates in the washout and open-label treatment periods for those subjects who were taking a statin on enrollment in the TNT study. The design of the TNT study has been described elsewhere. Briefly, this randomized, double-blind, placebo-controlled, lipiddowning trial was recently concluded in 14 countries across 4 continents. The primary hypothesis of the TNT study is that incremental reduction in CAD risk can be achieved by lowering LDL-C levels beyond currently recommended minimum targets in persons with a history of CAD. To test this hypothesis, 2 doses of atorvastatin (10 and 80 mg once daily) are being used in a double-blind parallel-group design. Of the 18,468 patients screened for study participation, 16,619 entered the dietary lead-in/drug-washout period, and of these, 15,432 eligible participants began treatment with atorvastatin 10 mg/d on an open-label basis. Participants with an LDL-C between 130 and 250 mg/dL (3.4 to 6.5 mmol/L) and triglycerides ≤600 mg/dL (6.8 mmol/L) were eligible for treatment during the open-label period.

Of the subjects who entered the dietary lead-in/drug-washout period, 57% (9395 of 16,619) were receiving prior statin therapy. We report here the overall monthly primary cardiac event rates in the washout and open-label treatment periods.

Statistical Analysis
Event rates were estimated for each study period separately by the Kaplan-Meier method using the time to first event. Subjects who did not experience an event in a given study period were censored at the time of withdrawal or at the end of the respective study period.

Results
The mean ± SD LDL-C level at the start of the washout period was 106 ± 30.4 mg/dL (2.7 ± 0.8 mmol/L). Patients entering the open-label run-in period had a mean ± SD LDL-C level of 153 ± 37.8 mg/dL (4.0 ± 1.0 mmol/L).

Primary events were defined as coronary heart disease death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke. During the 6-week drug-washout period, there were 24 primary events, and throughout the subsequent 8-week open-label period, there were 31 primary events (Table). This equated to 30-day Kaplan-Meier event rates of 0.20% during washout and 0.26% in the open-label phase. The event rates were therefore similar during the 2 phases.

Discussion
The present evaluation of the monthly primary event rates in the washout and open-label treatment periods for subjects taking statin therapy before the washout period of the TNT study suggests that there is no increase in risk associated with a discontinuation of statin therapy for up to 6 weeks. This finding is of great importance for a number of reasons. Many patients discontinue medications because of financial constraints, forgetfulness, or side effects. Additionally, nearly all clinical trials involving statin therapy require a drug washout period of ≥6 weeks. If abrupt withdrawal of statins resulted in an increase in cardiovascular events, this hazard would need to be weighed against proven long-term benefits. Although statins have consistently been found to have important effects on vascular function independent of their lipid-lowering benefits, this study demonstrates that short-term discontinuation of statin therapy in stable cardiac patients apparently does not lead to a clinically important increased risk of acute coronary syndromes.

Study Limitations
Data on the length of time that study participants had been on a statin before enrollment in the TNT study were not collected. It is probable, however, that most participants had been treated with a statin for months to years before discontinuation for the diet/drug-washout period. It is likely that as a result of long-term statin therapy, their lipid plaques were depleted of nondistensible lipid-laden macrophage foam cells. One could speculate that even an abrupt reduction in nitric oxide in such a setting would not lead to an acute increase in cardiovascular risk. Participants in the TNT study were required to meet all inclusion and exclusion criteria. Major exclusion criteria included any of the following: active liver disease or hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase > 1.5 times the upper limit of normal; nephrotic syndrome; uncontrolled diabetes mellitus; uncontrolled hypertension; previous MI; coronary revascularization procedure or severe/unstable angina within 1 month of screening; any planned procedure for...
the treatment of atherosclerosis; ejection fraction <30%; hemodynamically important vascular disease; gastrointestinal disease limiting drug absorption or partial ileal bypass; any nonskin malignancy, malignant melanoma, or other survival-limiting diseases; unexplained creatine phosphokinase levels >6 times the upper limit of normal; concurrent therapy with lipid-regulating drugs not specified as study treatment in the protocol; or history of alcohol abuse for participation. In short, study participants tended to be relatively healthy and stable cardiac patients. Such a population appears to demonstrate dramatic clinical differences from those individuals who suffer an acute coronary event. For this latter group, the degree of risk associated with abrupt statin discontinuation is still to be resolved.

References
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_Circulation_. 2004;110:2333-2335; originally published online October 11, 2004;
doi: 10.1161/01.CIR.0000145118.55201.15

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/16/2333

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