Intestinal Cholesterol Absorption, Treatment With Atorvastatin, and Cardiovascular Risk in Hemodialysis Patients

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ABSTRACT

BACKGROUND Hemodialysis patients are high absorbers of intestinal cholesterol; they benefit less than other patient groups from statin therapy, which inhibits cholesterol synthesis.

OBJECTIVES This study sought to investigate whether the individual cholesterol absorption rate affects atorvastatin’s effectiveness to reduce cardiovascular risk in hemodialysis patients.

METHODS This post-hoc analysis included 1,030 participants in the German Diabetes and Dialysis Study (4D) who were randomized to either 20 mg of atorvastatin (n = 519) or placebo (n = 511). The primary endpoint was a composite of major cardiovascular events. Secondary endpoints included all-cause mortality and all cardiac events. Tertiles of the cholestanol-to-cholesterol ratio, which is an established biomarker of cholesterol absorption, were used to identify high and low cholesterol absorbers.

RESULTS A total of 454 primary endpoints occurred. On multivariate time-to-event analyses, the interaction term between tertiles and treatment with atorvastatin was significantly associated with the risk of reaching the primary endpoint. Stratified analysis by cholestanol-to-cholesterol ratio tertiles confirmed this effect modification: atorvastatin reduced the risk of reaching the primary endpoint in the first tertile (hazard ratio [HR]: 0.72; p = 0.049), but not the second (HR: 0.79; p = 0.225) or third tertiles (HR: 1.21; p = 0.287). Atorvastatin consistently significantly reduced all-cause mortality and the risk of all cardiac events in only the first tertile.

CONCLUSIONS Intestinal cholesterol absorption, as reflected by cholestanol-to-cholesterol ratios, predicts the effectiveness of atorvastatin to reduce cardiovascular risk in hemodialysis patients. Those with low cholesterol absorption appear to benefit from treatment with atorvastatin, whereas those with high absorption do not benefit.

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Statin treatment is effective in primary and secondary prevention of cardiovascular (CV) events in patients without chronic kidney disease (CKD) (1) and in patients with moderately impaired renal function (2–5). However, statin therapy appears to be less effective in reducing CV risk in patients with severely impaired renal function and patients on maintenance hemodialysis treatment...
Specifically, 20 mg of atorvastatin versus placebo did not significantly reduce the composite risk of CV death, nonfatal myocardial infarction (MI), and stroke in the 4D (German Diabetes Dialysis Study) study (7). Likewise, 10 mg of rosuvastatin did not significantly reduce the composite risk of death from CV causes, nonfatal MI, and nonfatal stroke in the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) study (8). The reasons for these results remain incompletely understood (9).

Body cholesterol, which comes from 2 sources, is either endogenously synthesized or taken up from the diet in the intestine (10). Statins inhibit cholesterol synthesis, but they do not interfere with cholesterol absorption (10). Notably, patients on maintenance hemodialysis treatment are high absorbers of intestinal cholesterol, which may account for the low effectiveness of atorvastatin to reduce CV risk in these patients (11). The present research was therefore stimulated by the question as to whether the individual cholesterol absorption rate may modify the effectiveness of atorvastatin treatment to reduce CV risk in hemodialysis patients.

To answer this question, we performed a post-hoc analysis of data from the 4D study (7). Cholesterol absorption efficiency was estimated using an established biomarker, namely, the circulating cholestanol-to-total cholesterol ratio (12,13).

METHODS

STUDY DESIGN AND PARTICIPANTS. The design of 4D has been previously reported (7,14). Briefly, 4D is a prospective, randomized, double-blind, multicenter trial that included 1,255 patients with type 2 diabetes, who were 18 to 80 years of age, and who were on maintenance hemodialysis treatment for <2 years. Cholestanol was measured in 1,030 of the 1,255 participants of the 4D study. Among the 1,030 participants with available data on cholestanol, 519 patients received 20 mg of atorvastatin and 511 patients received placebo once daily. They were re-examined at 4 weeks and then every 6 months after randomization to obtain information about study endpoints or serious adverse events. The study was approved by the local medical ethics committee, and written informed consent was obtained from all participants before inclusion. The data were monitored and collected by a contract research organization (7).

ENDPOINTS. The study endpoints and serious adverse events were reported to the contract research organization. Every endpoint was adjudicated by 3 members of the endpoint committee on the basis of pre-defined criteria that were part of the study protocol. The classification by the endpoint committee was on the basis of consensus or majority vote. All committee members were blinded to the treatment assignments until August 13, 2004 (7). The primary endpoint of the 4D study was a composite of death resulting from cardiac causes, fatal or nonfatal stroke, and nonfatal MI. Death resulting from cardiac causes included sudden death, fatal MI, death caused by congestive heart failure, death resulting from coronary heart disease (CHD) during or within 28 days after an intervention, and all other deaths ascribed to CHD. Sudden cardiac death was considered death as verified by terminal rhythm disorders as seen on an electrocardiogram (ECG), witness-observed death within 1 hour after the onset of cardiac symptoms, death confirmed by autopsy, and unexpected death of presumably or possibly of cardiac origin and in the absence of an increased potassium level before the start of the 3 most recent hemodialysis treatment sessions. MI was diagnosed when 2 of the following 3 criteria were met: typical symptoms; elevated levels of cardiac enzymes (creatine kinase-MB, lactic dehydrogenase, and troponin T); or diagnostic changes on the ECG. An ECG at rest was recorded every 6 months.
and evaluated by independent cardiologists from the ECG monitoring board, according to the Minnesota classification system for ECGs (codes 1-1-1 through 9-2 for QRS complex, ST-segment, or T-wave changes). An ECG that documented silent MI was considered evidence of a primary endpoint. When death occurred within 28 days post-MI, as previously described, it was classified as death caused by MI. Fatal MI was classified only as death from MI, not sudden cardiac death. “All cardiac events” were defined as a composite of cardiac death, nonfatal MI, and cardiac revascularizations. Stroke was defined as a neurological deficit that lasted >24 h. Computed tomographic or magnetic resonance imaging of the brain was recommended and available in all but 16 cases (7,14). “All cerebrovascular events,” in addition to stroke, included transient ischemic attack and prolonged ischemic neurological deficit.

LABORATORY PROCEDURES. Blood samples were taken before the start of dialysis and administration of heparin or further drugs and before randomization. Cholesterol was measured with enzymatic reagents (Wako Chemicals GmbH, Neuss, Germany) on a 30R analyzer (Wako Diagnostics, Richmond, Virginia) or AU640 analyzer (Olympus Corporation, Tokyo, Japan). Cholestanol was measured with gas chromatography and mass spectrometry using the significant ion m/z 445.4. The details of the method have previously been described (15).

STATISTICAL ANALYSES. The baseline characteristics are reported as counts (percentages) for categorical data and as means ± SD for continuous data according to the atorvastatin and the placebo groups, within tertiles of the cholestanol-to-cholesterol ratio. Differences in the distributions of baseline characteristics between the atorvastatin and the placebo groups within these tertiles were tested for with the chi-square test for categorical data and Student t test and analysis of variance for continuous data. The effect of atorvastatin treatment on the risk of reaching the endpoints in the entire cohort was tested using time-to-events analyses (Cox regression for endpoints with exclusively fatal events and Andersen-Gill models for endpoints that included nonfatal events) (16). The model included the previously mentioned covariates, the ratio tertiles, atorvastatin treatment (main effect), and the interaction term between the cholestanol-to-cholesterol ratio tertiles and atorvastatin treatment. Goodness of fit was tested according to Grønnesby and Borgan (17). Next, stratified analyses were performed to test the effect of atorvastatin treatment on the risk of reaching endpoints within the tertiles using the previously mentioned adjustment, and omitting the tertiles and the interaction term between the cholestanol-to-cholesterol ratio tertiles and the atorvastatin treatment. All interaction tests and subgroup analyses within the tertiles were performed using both the intention-to-treat and the per-protocol approach. In addition, Kaplan-Meier curves were plotted and log-rank tests were performed to test the effect of the atorvastatin treatment within the tertiles of the cholestanol-to-cholesterol ratio for the primary endpoint. All statistical tests were 2-sided, and p values <0.05 were considered significant. Statistical analysis was conducted using the STATA statistical software package (release 13; StataCorp LP, College Station, Texas).

RESULTS

Summary statistics stratified by treatment group within cholestanol-to-cholesterol ratio tertiles are shown in Table 1. There were no significant differences of any baseline characteristics across or within the tertiles nor between treatment groups, except for the prevalence of CAD in the second tertile and albumin and arrhythmia in the third tertile. Potential confounding caused by these nonbalanced variables was controlled for by including them as covariates in the time-to-event models.

The mean duration of follow-up was 4.1 years. Only 1 patient was lost to follow-up, and this patient was included in the analysis until loss to follow-up (7). The patient was allocated to the placebo group in the first tertile. A total of 454 primary endpoints occurred. The absolute numbers for all endpoints by treatment groups within cholestanol-to-cholesterol ratio tertiles are shown in Table 2. By performing multivariate
analyses, the effect of atorvastatin treatment on the risk of reaching the endpoints (Table 3) was consistent with the results reported for all 1,255 participants (14).

By performing intention-to-treat analyses, the interaction term between the tertiles and the treatment group was significantly associated with the risk of reaching the primary endpoint (Table 4). The probability value of the Grønnesby and Borgan (17) test confirmed satisfactory goodness of fit (Table 4). Subgroup analyses within the cholestanol-to-cholesterol ratio tertiles showed that atorvastatin reduced the risk of reaching the primary endpoint in the first tertile, but did not do so in the second and third tertiles (Table 4, Central Illustration). These results were confirmed by per-protocol analyses (Online Table 1).

Consistent with the primary endpoint results, atorvastatin treatment reduced the risk of death from any cause, the risk of all cardiac events, and the risk of cardiac death in the first tertile, but not in the second or third tertiles of the cholestanol-to-cholesterol ratio on the basis of the intention-to-treat analyses (Table 4). For sudden cardiac death, nonfatal MI, and cerebrovascular endpoints, the number of events was relatively small (Table 2). Nevertheless, the effect of atorvastatin treatment appeared to be least beneficial in the third tertile of the cholestanol-to-cholesterol ratio for each of these endpoints (Table 4). These results were confirmed by per-protocol analyses (Online Table 1).

DISCUSSION

This post-hoc analysis of the 4D trial shows that patients on maintenance hemodialysis treatment with
low cholesterol absorption rates may benefit from treatment with atorvastatin (Central Illustration). The finding is of relevance, because hemodialysis patients have an extremely high CV risk (18,19). Moreover, therapeutic strategies to reduce this risk are scarce or virtually absent (9). In particular, treatment with statins has generally not been recommended in patients on maintenance hemodialysis treatment (20).

These data agree with findings from the 4S (Scandinavian Simvastatin Survival Study) trial (21), beyond the obvious exception that statins appeared to be more effective in reducing CV risk in the 4S than in the 4D study (21). In the 4S study, simvastatin treatment versus placebo significantly reduced the risk of major coronary events by 38% in the lowest quartile of the cholestanol-to-cholesterol ratio, but such treatment increased the risk of major coronary events by 17% in the highest quartile (21). Both the 4S and 4D studies fit well into our current understanding of cholesterol homeostasis (10): there is some reason to think that treatment with statins, which interfere with cholesterol synthesis, is less effective in patients with advanced CKD who absorb most of their cholesterol (11). In line with this idea, the mean cholestanol-to-cholesterol ratio was higher in the 4D study (1.8 mg/mg) than in the LURIC (Ludwigshafen Risk and Cardiovascular Health) study (1.5 mg/mg) (15), the Framingham Offspring Study (1.4 μg/mg) (22), and especially the 4S study (1.3 μg/mg) (21).

In contrast, inhibition of cholesterol absorption may be instrumental to reduce CV risk in patients with high cholesterol absorption (10). This pathophysiological background could be 1 of the reasons for the results of the SHARP (Study of Heart And Renal Protection) (23). All participants in the SHARP study had

<table>
<thead>
<tr>
<th>Event Type</th>
<th>First Tertile Atorvastatin (n = 165)</th>
<th>Placebo (n = 178)</th>
<th>Second Tertile Atorvastatin (n = 177)</th>
<th>Placebo (n = 166)</th>
<th>Third Tertile Atorvastatin (n = 177)</th>
<th>Placebo (n = 167)</th>
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<td>63 (35.6)</td>
<td>61 (36.7)</td>
<td>75 (42.4)</td>
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<td>Death from all causes</td>
<td>73 (44.2)</td>
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<td>78 (47.0)</td>
<td>90 (50.8)</td>
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<td>All cardiac events</td>
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<td>80 (44.9)</td>
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<td>60 (36.1)</td>
<td>63 (35.6)</td>
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<tr>
<td>Cardiac death</td>
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<td>48 (27.0)</td>
<td>39 (22.0)</td>
<td>32 (19.3)</td>
<td>39 (22.0)</td>
<td>42 (25.1)</td>
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<tr>
<td>Sudden cardiac death</td>
<td>17 (10.3)</td>
<td>25 (14.0)</td>
<td>29 (16.4)</td>
<td>18</td>
<td>22 (12.4)</td>
<td>21 (12.6)</td>
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<tr>
<td>Nonfatal MI</td>
<td>18 (10.9)</td>
<td>24 (13.5)</td>
<td>15 (8.5)</td>
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<td>20 (11.3)</td>
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<td>All cerebrovascular events</td>
<td>16 (9.7)</td>
<td>23 (12.9)</td>
<td>8 (4.5)</td>
<td>24 (14.5)</td>
<td>18 (10.2)</td>
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<td>Stroke</td>
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<td>11 (6.2)</td>
<td>14 (7.9)</td>
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Values are n (%). MI = myocardial infarction.

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Cholesterol Absorption and Outcomes in 4D Study

et al

Silbernagel

Cholesterol absorption on the effectiveness of statin treatment. The cohort is large and well characterized, in patients who received maintenance hemodialysis treatment. A total of 9,270 participants were randomized to either simvastatin plus ezetimibe, a cholesterol absorption inhibitor, or placebo. The combination therapy of simvastatin and ezetimibe reduces triglycerides. Sevelamer, a phosphate-binding acid sequestrant, was not used by any patient, because in Germany this medicine is regarded as contra-indicated for hemodialysis patients because of its interference with cholesterol metabolism.

This work has major strengths. First, we report on data from the 4D study that represents 1 of only 2 randomized controlled trials that investigated the effectiveness of statin treatment to reduce CV risk only in patients who received maintenance hemodialysis treatment. The cohort is large and well characterized, and there was a comprehensive follow-up with a considerable amount of fatal and nonfatal events yielding high statistical power. Second, the present study is the first to investigate the impact of cholesterol absorption on the effectiveness of statin treatment to prevent CV complications in patients on maintenance hemodialysis treatment. Third, we used the cholestanol-to-cholesterol ratio as a measure of cholesterol absorption. This estimate is less prone to confounding by diet than other biomarkers for cholesterol absorption efficiency. Fourth, the laboratory personnel responsible for measuring cholestanol were blinded to all of the clinical and biochemical data of the participants. Fifth, confounding due to the use of drugs that interfere with cholesterol metabolism is unlikely. Cholestyramine, a bile acid sequestrant, was not used by any patient, because in Germany this medicine is regarded as contra-indicated for hemodialysis patients because of its interference with cholesterol metabolism.

STUDY LIMITATIONS. The observational character of the present study might be a limitation because the study was a post-hoc analysis. However, we had a clear hypothesis that was confirmed following a pre-defined statistical analysis plan. In addition, dietary intake of cholesterol or saturated fat was not recorded by survey or questionnaire. Finally, single nucleotide polymorphisms in the ABCG8 (e.g., rs4245791, rs4299376, rs41260247, rs6576629, and rs4953023) and ABO (e.g., rs657152) genes, which
have been implicated in cholesterol absorption and low-density lipoprotein cholesterol concentrations \(^{(13)}\), were not analyzed in the 4D study. These single nucleotide polymorphisms might help to predict the effectiveness of statin treatment to reduce CV risk. A large meta-analysis that includes several statin intervention trials testing for such a relationship is therefore encouraged.

Cholesterol absorption is regulated in a complex fashion \(^{(10)}\). In hemodialysis, specific metabolic alterations probably play a more dominant role in the regulation of cholesterol absorption than genetic variations. However, the prevalence of common low-density lipoprotein cholesterol-raising variants in the ABCG8 and ABO genes may be slightly higher in hemodialysis patients with a high cholesstanol-to-cholesterol ratio. Moreover, it will be of interest to test whether the expression of these genes is influenced by the uremic state.

In a post-hoc analysis of hemodialysis patients participating in the German Diabetes and Dialysis Study randomized to atorvastatin or placebo group, and stratified by tertiles of the cholesstanol-to-cholesterol ratio, statin effectiveness was dependent on intestinal cholesterol absorption. Those in the first tertile (A) experienced a reduction in the risk of reaching the primary endpoint, a composite of major cardiovascular events; patients in the second (B) and third (C) tertiles had no similar risk reduction.
CONCLUSIONS

We found that measurement of cholesterol absorption may help to identify hemodialysis patients who will benefit from treatment with statins. Beyond that, the data might argue in favor of a combination therapy that addresses both cholesterol synthesis and absorption to reduce CV risk in hemodialysis patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Guenther Silbernagel, Department of Angiology, Swiss Cardiovascular Center, Inselspital, University of Bern, Freiburgstrasse, 3010 Bern, Switzerland. E-mail: guenther.silbernagel@insel.ch.

REFERENCES


COMPETENCY IN MEDICAL KNOWLEDGE: The efficacy of atorvastatin to reduce cardiovascular risk in patients who are receiving hemodialysis is inversely related to cholesterol absorption.

TRANSLATIONAL OUTLOOK: Future studies should investigate the safety and efficacy of interventions that inhibit cholesterol absorption in patients on hemodialysis with high rates of cholesterol absorption.

APPENDIX For a supplemental table, please see the online version of this article.