Effects of *Niacin*, *Statin*, and *Fenofibrate* on Circulating Proprotein Convertase Subtilisin/Kexin Type 9 Levels in Patients With Dyslipidemia

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Recent trials demonstrated substantial improvement in lipid parameters with inhibition of proprotein convertase subtilisin-like/kexin type 9 (PCSK9). Although statins and fibrates have been reported to increase plasma PCSK9 levels, the effect of niacin on PCSK9 is unknown. We investigated the impact of niacin, atorvastatin, and fenofibrate on PCSK9 levels in 3 distinct studies. A statin-only study randomized 74 hypercholesterolemic patients to placebo, atorvastatin 10 mg/day, or atorvastatin 80 mg/day for 16 weeks. A dose-related increase in PCSK9 was noted such that atorvastatin 80 mg increased PCSK9 by a mean +27% (95% confidence interval [CI] +12 to +42), confirming the effect of statin therapy on raising PCSK9. A second study randomized 70 patients with carotid atherosclerosis to simvastatin 20 mg/day, simvastatin 80 mg/day, or simvastatin 20 mg/extended-release (ER) niacin 2 g/day. PCSK9 levels were increased with statin therapy, but decreased with the simvastatin 20 mg/ER niacin combination (mean −13%, CI −3 to −23). A final study involved 19 dyslipidemic participants on atorvastatin 10 mg with serial addition of fenofibric acid 135 mg followed by ER niacin 2 g/day. Fenofibric acid led to a +23% (CI +10 to +36, p = 0.001) increase in PCSK9; the addition of niacin resulted in a subsequent −17% decrease (CI −19 to −5, p = 0.004). A positive association was noted between change in PCSK9 and low-density lipoprotein cholesterol levels (r = 0.62, p = 0.006) with the addition of niacin. In conclusion, niacin therapy offsets the increase in PCSK9 levels noted with statin and fibrate therapy. A portion of the low-density lipoprotein cholesterol reduction seen with niacin therapy may be due to reduction in PCSK9. **(Am J Cardiol 2015;115:178−182)**

Proprotein convertase subtilisin-like/kexin type 9 (PCSK9) is a secreted protease that binds to the low-density lipoprotein (LDL) receptor in the liver, thereby accelerating lysosomal degradation of the receptors and increasing circulating LDL-cholesterol (LDL-C) levels.[1] Inhibition of PCSK9 has emerged as a novel therapeutic target with several clinical trials confirming robust LDL-C reduction.[2−5] Statin therapy has been reported to increase circulating PCSK9 levels,[6−8] a mechanism that may limit the additional LDL-C reduction noted with dose intensification. Reports regarding fibrate therapy have yielded mixed results, although preliminary data have suggested that fibrates also raise PCSK9 levels.[9−11] Nicotinic acid (niacin) has been used clinically as an LDL-lowering drug for >50 years, but to date the mechanism of LDL-lowering remains unclear. There have been no reports to our knowledge on the effect of niacin on plasma PCSK9 levels, either as monotherapy or in combination with statins or fibrates. We used 3 separate clinical studies involving statins, fenofibric acid, and niacin to address the dose-dependence effects of statins on PCSK9 levels, assess the effect of a fibrate on PCSK9 when added to a statin, and determine the impact of niacin on PCSK9 levels on the background of statin and statin and/or fibrate therapy.

Methods

The impact of pharmacotherapies for dyslipidemia on circulating PCSK9 levels was assessed in 3 distinct populations, each enrolled at the University of Pennsylvania using institutional review board-approved protocols. Study 1 included 74 subjects with available samples from a previously reported randomized controlled trial involving 120 patients with hyperlipidemia randomly assigned to treatment with 10 mg of atorvastatin daily (QD), 80 mg of atorvastatin QD, or placebo.[12] PCSK9 concentrations were assessed at both baseline and after 16 weeks of therapy.

A second study was derived from a previously described randomized controlled trial (*ClinicalTrials.gov*

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The study involving treatment with simvastatin versus extended-release niacin (study 2) was supported by investigator-initiated grants from Merck Pharmaceuticals (Whitehouse Station, New Jersey) and KOS Pharmaceuticals, now Abbott Pharmaceuticals (Abbott Park, Illinois). The study involving sequential therapy with fenofibric acid, atorvastatin, and niacin (study 3) was supported by Abbot Pharmaceuticals (Abbott Park, Illinois) and the National Center for Research Resources, grant UL1RR024134. Companies had no influence on study design, analysis, or manuscript preparation. All authors have approved the final manuscript draft submitted for publication.

See page 181 for disclosure information.

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http://dx.doi.org/10.1016/j.amjcard.2014.10.018

Table 1
Relationship between baseline biomarkers and PCSK9 concentrations across 3 studies.

Variable	Cohort One Atorvastatin (n = 74)	Cohort Two Simvastatin/Niacin (n = 70)	Cohort Three: Atorvastatin/ Fenofibric acid/Niacin (n = 19)
Total Cholesterol	+ 0.23	+ 0.14	+ 0.03
HDL-Cholesterol	−0.08	+ 0.10	+ 0.32
LDL-Cholesterol	−0.13	+ 0.16	−0.20
Log Triglyceride	+ 0.31*	−0.07	+ 0.04
Log hsCRP	+ 0.24*	−0.07	Unavail
Apolipoprotein B	+ 0.15	+ 0.20	−0.02

Values represent unadjusted correlation coefficients.
HDL = high-density lipoprotein; hsCRP = high sensitivity C-Reactive Protein; LDL = low-density lipoprotein.
* denotes P < 0.05.

NCT00307307) involving participants with carotid atherosclerosis randomized to simvastatin 20 mg QD plus placebo, simvastatin 80 mg QD plus placebo, or simvastatin 20 mg plus extended-release (ER) niacin, titrated up to 2 g QD.[13] PCSK9 levels were measured in 70 of 75 total participants at baseline and after 12 months of therapy.

Study 3 was an open-label lipid kinetics study involving 19 dyslipidemic patients treated with 4 weeks of atorvastatin 10 mg QD followed by sequential addition of fenofibric acid (ABT335) of 135 mg QD for 8 weeks and finally ER niacin titrated to a dose of 2 g QD for 10 weeks (*ClinicalTrials.gov* NCT00728910). Inclusion criteria included low high-density lipoprotein cholesterol (HDL-C; defined as ≤40 mg/dl in men or ≤50 mg/dl in women and ≤42 mg/dl in men or ≤52 mg/dl in women on statin therapy) and elevated triglycerides (TG/HDL ratio ≥3.5). Participants with LDL-C >190 mg/dl were excluded. PCSK9 concentrations were assessed at each of the 3 study visits.

Fasting plasma samples were obtained as part of the study protocol at the previously referenced time points and stored at −80°C. Lipid subfraction, apolipoproteins levels, and high-sensitivity C-reactive protein (hsCRP) were assayed using enzymatic techniques as previously described.[12,13] The plasma PCSK9 concentrations in all 3 studies were measured using a validated sandwich enzyme-linked immunosorbent assay designed to recognize free and LDL-bound PCSK9 (ELISA; R&D Systems Inc, Minneapolis, Minnesota).[14] All plasma specimens were assayed in singlicate and controls in duplicates. Intra-assay and inter-assay coefficients of variation for the control samples were 5.7% and 9.7%, respectively.

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and SDs or medians and interquartile ranges (IQR) for variables with skewed distributions. The association of PCSK9 with circulating biomarkers was assessed with the use of Pearson's correlation coefficients. Paired *t* tests were used to assess the effect of pharmacologic interventions on PCSK9 concentrations. These changes were compared across treatment arms with the use of analysis of covariance, which included the patient's baseline value and the treatment group as covariates. All reported p values are 2-tailed, with a p value of 0.05 indicating statistical significance.

Results

In study 1, PCSK9 measurements were available in 74 hypercholesterolemic patients treated for 16 weeks with atorvastatin 10 mg QD (n = 26), atorvastatin 80 mg QD (n = 25), or placebo (n = 23). Baseline laboratory values, expressed as mean ± SD were total cholesterol (TC) 242 ± 32 mg/dl, HDL-C 47 ± 11 mg/dl, LDL-C 164 ± 33 mg/dl, apolipoprotein B 110 ± 13 mg/dl, and PCSK9 290 ± 80 ng/ml. Median (IQR) values included TGs 128 (88 to 161) mg/dl and hsCRP 1.4 (0.7 to 3.5) mg/L. No significant differences in baseline characteristics were noted across treatment groups (Supplementary Table 1).

Baseline PCSK9 values were somewhat greater in female patients compared with male patients (303 vs 280 ng/ml), a finding that did not reach statistical significance. No significant relation was noted between baseline PCSK9 levels and TC, LDL-C, or apolipoprotein B (Table 1). A nominally significant positive association was present between levels of PCSK9 and log-transformed levels of both TGs (r = +0.31, p = 0.007) and hsCRP (r = +0.25, p = 0.03).

As expected, statin therapy led to significant reductions in LDL-C levels with mean ± SD percent change of −32 ± 16 with atorvastatin 10 mg and −43 ± 24 with atorvastatin 80 mg compared with −8 ± 31 in the placebo arm. In contrast, PCSK9 levels were increased in a dose-dependent fashion with statin therapy compared with placebo (Table 2). A modest inverse association was noted between percent change in PCSK9 level and corresponding change in LDL-C level (r = −0.24, p = 0.048; Figure 1). In contrast, change in PCSK9 did not predict change in either apolipoprotein B (r = −0.19, p = 0.11) or hsCRP (r = −0.09, p = 0.43).

Similar analyses were conducted in study 2 participants randomized to 12 months of simvastatin 20 mg/placebo (n = 24), simvastatin 80 mg/placebo (n = 22), or simvastatin 20 mg/niacin titrated up to 2 g QD (n = 24). The study population had a mean age of 70 years and included 49 (70%) men. A total of 64% of subjects were receiving statin therapy and study drug therapy was initiated without a washout period. Baseline lipid parameters were TC mean 191 ± SD 39, HDL-C 46 ± 15 mg/dl, LDL-C 117 ± 32 mg/dl, TG median 139 (IQR 92 to 170), and PCSK9 383 ± 117 ng/ml. Average PCSK9 values were 341 ng/ml for statin-naïve patients and 407 ng/ml for those maintained on chronic statin therapy (p = 0.02). Baseline characteristics were similar across treatment arms (Supplementary Table 2). Baseline lipid subfraction and hsCRP levels did not predict PCSK9 levels at baseline (Table 1).

As previously reported,[13] mean changes in lipids from baseline included the following: simvastatin 20 mg (LDL-C −6%, HDL-C +3%, and TG +23%), simvastatin 80 mg (LDL-C −25%, HDL-C +7%, and TG −7%), simvastatin 20 mg/niacin (LDL-C −41%, HDL-C +24%, and TG −24%). No significant increase in PCSK9 level was noted in the simvastatin 20 mg group, consistent with the minimal reduction in LDL-C that likely reflected prevalence of baseline statin usage. Simvastatin 80 mg led to a substantial increase in mean PCSK9 level from 379 to