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Endothelin Receptor Antagonism Improves Lipid Profiles and Lowers PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) in Patients With Chronic Kidney Disease

Tariq E. Farrah,* Atul Anand,* Peter J. Gallacher, Robert Kimmitt, Edwin Carter, James W. Dear, Nicholas L. Mills, David J. Webb, Neeraj Dhaun

Abstract—Dyslipidemia is common in chronic kidney disease (CKD). Despite statins, many patients fail to adequately lower lipids and remain at increased risk of cardiovascular disease. Selective ET₄ receptor antagonists reduce cardiovascular disease risk factors. Preclinical data suggest that ET₄ antagonism has beneficial effects on circulating lipids. We assessed the effects of selective ET₄ antagonism on circulating lipids and PCSK9 (proprotein convertase subtilisin/kexin type 9) in CKD. This was a secondary analysis of a fully randomized, double-blind, 3-phase crossover study. Twenty-seven subjects with predialysis CKD on optimal cardio- and renoprotective treatment were randomly assigned to receive 6 weeks dosing with placebo, the selective ET₄ receptor antagonist, sitaxentan, or long-acting nifedipine. We measured circulating lipids and PCSK9 at baseline and then after 3 and 6 weeks. Baseline lipids and PCSK9 did not differ before each study phase. Whereas placebo and nifedipine had no effect on lipids, 6 weeks of ET₄ antagonism significantly reduced total (−11±1%) and low-density lipoprotein–associated cholesterol (−20±3%); lipoprotein (a) (−16±2%) and triglycerides (−20±4%; high-density lipoprotein–associated cholesterol increased (+14±2%); P<0.05 versus baseline for all. Additionally, ET₄ receptor antagonism, but neither placebo nor nifedipine, reduced circulating PCSK9 (−19±2%; P<0.001 versus baseline; P<0.05 versus nifedipine and placebo). These effects were independent of statin use and changes in blood pressure or proteinuria. Selective ET₄ antagonism improves lipid profiles in optimally-managed patients with CKD, effects that may occur through a reduction in circulating PCSK9. ET₄ receptor antagonism offers a potentially novel strategy to reduce cardiovascular disease risk in CKD.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00810732. (Hypertension. 2019;74:323-330. DOI: 10.1161/HYPERTENSIONAHA.119.12919.) • Online Data Supplement

Key Words: atherosclerosis ▪ cardiovascular disease ▪ cholesterol ▪ endothelins ▪ triglycerides

Chronic kidney disease (CKD) is common and an important independent risk factor for cardiovascular disease (CVD).1 This increased risk is partly explained by a high prevalence of traditional CVD risk factors, such as diabetes mellitus and hypertension.2 Dyslipidemia is also common in CKD and contributes to the development of accelerated atherosclerosis and CVD.3 HMG-CoA (hydroxymethylglutarate co-enzyme A) reductase inhibitors (statins) lower cholesterol, particularly low-density lipoprotein–associated cholesterol (LDL-C) and have proven efficacy in the reduction of CVD risk in those with and without CKD.4,5 However, despite the use of statins, many patients with CKD continue to have elevated lipids.6 Furthermore, the side effects associated with these drugs can limit their use.7 Thus, novel therapies that might lower cholesterol both in patients established on-statin treatment and in those intolerant of statins would be of major clinical value.

PCSK9 (proprotein convertase subtilisin/kexin type 9) is a serine protease produced mainly in the liver and is an important regulator of tissue LDL-R (LDL receptor) expression and cholesterol homeostasis.8 In the circulation, PCSK9 binds to cell surface LDL-R promoting their lysosomal degradation, leading to a rise in circulating LDL-C. Inhibition of circulating PCSK9 using novel humanized monoclonal antibodies leads to important reductions in LDL-C in patients on and off statins.9,10 Recent preclinical studies have shown that PCSK9 expression increases during systemic inflammation11 and with podocyte injury.12 Both are central features of CKD and contributed to by ET-1 (endothelin-1).13 ET-1 is the most potent endogenous vasoconstrictor and plays an important role in the development and progression of CKD.13 The major pathological effects of ET-1 are mediated via ET₄ (endothelin-A) receptors.13 Preclinical data using
ET receptor antagonists have suggested beneficial effects on circulating lipids and atherosclerosis, but subsequent clinical studies have produced conflicting results, and none have explored potential mechanisms. Thus, we hypothesized that in a cohort of optimally-managed proteinuric patients with CKD, selective ETA receptor antagonism would lead to a reduction in circulating lipids and PCSK9.

**Table 1. Baseline Study Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Nifedipine</th>
<th>ET&lt;sub&gt;α&lt;/sub&gt; Antagonist</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48±12</td>
<td>49±16</td>
<td>46±10</td>
<td>0.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>23 (85)</td>
<td>24 (86)</td>
<td>25 (86)</td>
<td>0.6</td>
</tr>
<tr>
<td>CKD stage by eGFR, n (%)</td>
<td>1 (25)</td>
<td>2 (7)</td>
<td>3 (11)</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>6 (22)</td>
<td>4 (15)</td>
<td>5 (19)</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>11 (40)</td>
<td>9 (33)</td>
<td>10 (36)</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>5 (19)</td>
<td>6 (22)</td>
<td>7 (25)</td>
<td>0.8</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>165±29</td>
<td>164±25</td>
<td>164±25</td>
<td>1.0</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>103±32</td>
<td>105±30</td>
<td>105±30</td>
<td>0.8</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>43±11</td>
<td>44±11</td>
<td>44±11</td>
<td>0.9</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>137±22</td>
<td>137±22</td>
<td>137±22</td>
<td>1.0</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>30±6</td>
<td>31±6</td>
<td>31±6</td>
<td>1.0</td>
</tr>
<tr>
<td>PCSK9, ng/mL</td>
<td>400±22</td>
<td>386±26</td>
<td>414±22</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Values are predosing mean±SE, mg/dL unless stated. Analysis by ANOVA.

**Table 2. Baseline Lipid Profiles for Each Study Phase**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Nifedipine</th>
<th>ET&lt;sub&gt;α&lt;/sub&gt; Antagonist</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>164±6</td>
<td>167±6</td>
<td>164±6</td>
<td>0.9</td>
</tr>
<tr>
<td>LDL-C</td>
<td>99±6</td>
<td>101±6</td>
<td>109±6</td>
<td>0.6</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44±2</td>
<td>43±2</td>
<td>40±2</td>
<td>0.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>116±16</td>
<td>153±20</td>
<td>137±23</td>
<td>0.8</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>30±6</td>
<td>31±6</td>
<td>30±6</td>
<td>0.9</td>
</tr>
<tr>
<td>PCSK9, ng/mL</td>
<td>400±22</td>
<td>386±26</td>
<td>414±22</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Values are predosing mean±SE, mg/dL unless stated. Analysis by ANOVA.

**Methods**

Data relating to this study are available from the corresponding author on reasonable request. To test the paradigm that selective ETA antagonism can lower circulating lipids, we performed a secondary analysis of a single center, fully randomized, double-blind, 3-phase, and placebo-controlled crossover study in patients with varying degrees of proteinuric, predialysis CKD, a population at significantly increased CVD risk. The full study protocol has been described previously and was performed with subjects’ written consent and South East Scotland research ethics committee approval.

**Patients and Interventions**

Twenty-seven patients were enrolled and randomly assigned to receive the selective ETA receptor antagonist, sitaxentan 100 mg once-daily, matched placebo, or long-acting nifedipine 30 mg once-daily for 6 weeks in addition to their usual medications. Each phase was separated by a minimum 2-week washout period. We included patients aged 18 to 70 years of age with stable CKD stages 1 to 4 and proteinuria >300 mg/d. Patients with diabetes mellitus, nephrotic syndrome, significant cardiorespiratory comorbidity, peripheral vascular disease, liver disease, and women of childbearing potential were excluded.

**Assessments**

Patients underwent assessments at baseline, week 3 and week 6 of each treatment phase, which included blood sampling for biochemical analyses. Total cholesterol, LDL-C, high-density lipoprotein–associated cholesterol (HDL-C), triglycerides, lipoprotein(a) (Lp(a)), and circulating PCSK9 were also assessed at these timepoints (Figure S1 in the online-only Data Supplement).

**Sample Collection and Analysis**

Blood was collected into serum and EDTA tubes, immediately centrifuged at 2500g for 20 minutes at 4°C and stored at –80°C until analysis. Lipid parameters were analyzed from stored serum, while PCSK9 was analyzed from stored plasma. Total cholesterol, LDL-C, HDL-C, and triglycerides were measured by enzymatic colorimetric assays. For total cholesterol, the limit of detection and intra-assay and interassay coefficients of variation (CV) were 0.03 mmol/L, 0.8% and 1.3%, respectively. For LDL-C, the limit of detection was 0.03 mmol/L with intra-assay and interassay CV of 1.4% and 2.2%, respectively. For HDL-C, the limit of detection was 0.06 mmol/L with intra-assay and interassay CV of 1.7% and 5.0%, respectively. For triglycerides, the limit of detection was 0.13 mmol/L with intra-assay and interassay CV of 0.8% and 1.7%, respectively. Lp(a) was quantified using a latex agglutination assay with a limit of detection of 0.83 mg/dL and intra-assay and interassay CV of 1.2% and 3.0%, respectively. PCSK9 was measured using an ELISA (R&D systems) with a limit of detection of 0.096 ng/mL. Mean recovery of PCSK9 was 107%, and cross-reactivity was 0% for LDL-R, PCSK1, 3 and 7. The intra-assay and interassay CV were 4.1% and 5.6%, respectively.
Statistical Analysis

The original study was designed to detect significant changes in proteinuria using data from a prior study, where an ETA receptor antagonist was administered to 22 subjects in a crossover design leading to a reduction in proteinuria of ≈0.7 g/d with an SD of 0.9 g/d. Using these data, the current study size had 80% power to detect such a difference at the 2-sided 5% significance level.

Baseline lipid levels were assessed by repeated measures 1-way ANOVA with Tukey correction for multiple comparisons to assess carryover and period effect at the start of each treatment phase. A repeated measures 3-way ANOVA was used to assess for interactions between time, treatment, and statin use for changes in lipids and PCSK9. Where Mauchly test indicated the sphericity assumption was not met, the Greenhouse-Geisser or Huynh-Feldt correction were used as appropriate. Changes from baseline to week 6 within treatment phases and between treatments phases at all time points were assessed by repeated measures 2-way ANOVA with Sidak and Tukey corrections for multiple comparisons, respectively. Predictors of change in PCSK9 concentrations were modeled by linear regression, adjusting for potential confounders. Data were analyzed with IBMSPSS (version 24) and R (version 3.3.3). Significance was taken at the 5% level.

Results

Baseline patient characteristics are shown in Table 1. Baseline mean (±SEM) total cholesterol was 165±29 mg/dL, LDL-C 103±32 mg/dL, HDL-C 43±11 mg/dL mmol/L, triglycerides 143±113 mg/dL, and Lp(a) 31±3 mg/dL. There were
In terms of effects on circulating lipids and PCSK9, there were no significant 3-way interactions between time, treatment, and statin use but significant interactions between time and treatment were present and analyzed further (Table S1). Total cholesterol, LDL-C, and HDL-C were unaffected by placebo or nifedipine. In contrast, 6 weeks of ETA antagonism led to a fall in total cholesterol of 18±2 mg/dL, a reduction of 11% (P<0.01 versus baseline; P<0.001 versus nifedipine and placebo at week 6, Figure 1A). The reduction in total cholesterol seen with ETA antagonist comprised a fall in LDL-C of 21±3 mg/dL (≈20% reduction, P<0.001 versus baseline; P<0.001 versus nifedipine and placebo at week 6, Figure 1A) and an increase in HDL-C of 5±1 mg/dL (≈14% increase, P<0.001 versus baseline; P<0.001 versus nifedipine and placebo at week 6, Figure 1C). ETA antagonism also led to reductions in triglycerides of 39±10 mg/dL (≈20% fall, P<0.001 versus baseline; P≈0.05 versus nifedipine and placebo at week 6, Figure 1D) and in Lp(a) of 3.2±0.8 mg/dL (≈15% fall, P<0.05 versus baseline and placebo at week 6, Figure 1E). Detailed effects of ETA antagonist comparison with nifedipine and placebo are shown in Tables S2 through S7 with individual patient responses shown in Figures S2 through S6.

Mean (±SEM) baseline plasma PCSK9 concentration was 400±117 ng/mL and did not differ between the three phases of the study (Table 2). After 6 weeks of ETA antagonist, PCSK9 fell by −81±13 ng/mL (≈20% reduction, P<0.001 versus baseline; P<0.05 versus nifedipine and placebo, Figure 2 and Figure S7). Reductions in circulating PCSK9 during ETA antagonist were observed to occur with simultaneous reductions in total cholesterol, LDL-C, and to a lesser degree with triglycerides, while also associating with increases in HDL-C (Figure 3). No relationship could be demonstrated for the nifedipine and placebo phases.

Figure 2. Change in circulating PCSK9 (proprotein convertase subtilisin/kexin type 9). Bar chart of mean change in plasma PCSK9 from baseline after week 3 and week 6 of dosing with placebo (blue bars), nifedipine (green bars), and selective ETA (endothelin-A) receptor antagonist (red bars). ***P<0.001 for selective ETA receptor antagonist at week 6 versus baseline; analysis by paired t tests. P<0.05 for change at timepoint vs placebo and nifedipine. Analysis by ANOVA. Error bars are SE of mean.

Discussion

Our study has several important findings. We provide new evidence of the broad beneficial effects of selective ETA receptor antagonism on circulating lipids in patients with varying degrees of predialysis CKD and residual proteinuria. Here, medium-term dosing with an ETA antagonist resulted in clinically-relevant reductions in total cholesterol, LDL-C, and triglycerides with a significant increase in HDL-C. In addition, we saw a significant fall in Lp(a). Importantly, these improvements occurred in patients at high CVD risk, the majority of whom were already receiving recommended CVD prevention therapy with a statin and either an ACEi or ARB. Furthermore, we have shown that these lipid-lowering effects occurred with a concurrent reduction in circulating PCSK9. This previously unreported finding supports a link between the endothelin system and cholesterol homeostasis.

Lowering LDL-C has been shown to reduce the risk of major atherosclerotic events in a wide range of patients with CKD.4 However, despite current lipid-lowering treatments, a number of patients fail to achieve target LDL-C.6 This is mirrored in our cohort of patients whose mean baseline fasting LDL-C was above the recommended 100 mg/dL despite a high rate of statin use.6,22 Additionally, of the 18 patients (67%) receiving a statin, 11 were also prescribed the cholesterol-absorption inhibitor, ezetimibe. Thus, from a clinical perspective, it is important that the effects observed with ETA receptor antagonism occurred on top of currently available therapies. Furthermore, suboptimal dosing and discontinuation of statins because of adverse effects remain significant in clinical practice.27 For example, the risk of statin-induced myopathy is increased in patients with impaired renal function.23 Therefore, alternative agents, which might improve lipid profiles in this particularly high-risk group, while conferring broader CVD risk protection, would be of major clinical value.

Previous reports of the lipid-lowering effects of ET receptor antagonism are limited. Kowala et al14 demonstrated that selective ETA antagonism lowered total cholesterol, LDL-C, and triglycerides in hyperlipidemic hamsters, and this reduced aortic arch atherosclerosis. Data from clinical studies are conflicting with some noting an improvement in lipid profiles15,17 whereas others have shown no effect.18,24 Studies in CKD are limited to those with diabetic nephropathy. In a study using the mixed ETA antagonist, avosentan, the authors...
reported a ≈7% reduction in total cholesterol after 12 weeks dosing but found no effect on triglycerides; they did not report on LDL-C or HDL-C. Using the selective ET_A antagonist, atrasentan, de Zeeuw et al showed similar effects after 12 weeks on total cholesterol, LDL-C, and triglycerides to those seen in the current study but no change in HDL-C. Our data add to these studies and also demonstrate a beneficial effect on HDL-C and Lp(a), as well as suggesting a potential mechanism through a reduction of circulating PCSK9. Interestingly, these effects on lipids may relate to the relative ET_A:ET_B receptor selectivity of the drug used: bosentan (nonselective) no effect on cholesterol16; avosentan (ET_A:ET_B ≈ 300:1) ≈7% reduction in cholesterol16; atrasentan (ET_A:ET_B ≈ 1200:1) ≈9% reduction in cholesterol19; and sitaxentan (ET_A:ET_B ≈ 6500:1) ≈11% reduction in cholesterol.25

Beyond its role in cholesterol homeostasis, a link between circulating PCSK9 concentration and CVD risk has emerged. Leander et al26 recently showed in a middle-aged, non-CKD population that a greater circulating PCSK9 was associated with a higher risk of incident CVD, particularly thrombotic events. This remained the case even after adjusting for traditional CVD risk factors including LDL-C and statin use. The mean PCSK9 level in our study (≈400 ng/mL) is comparable to the highest risk quartile identified by Leander et al26 and is similar to that seen in other studies in CKD.27 The greater CVD risk associated with elevated PCSK9 concentrations may be due in part to its positive association with elevated Lp(a), a modified LDL species that can impair endogenous fibrinolysis.28 A recent meta-analysis of >29,000 patients found an independent and near-linear association between both

Figure 3. Change in lipids and circulating PCSK9 (proprotein convertase subtilisin/kexin type 9). Scatter plots of individual percentage changes from baseline in total cholesterol (A), low-density lipoprotein–associated cholesterol (LDL-C); B, high-density lipoprotein–associated cholesterol (HDL-C); C, and triglycerides (D) after 6 weeks of treatment vs individual percentage change in plasma PCSK9. Blue dots denote subjects receiving placebo; green dots denote subjects receiving nifedipine; and red dots denote subjects receiving selective ET_A (endothelin-A) receptor antagonist.
Inhibition of circulating PCSK9 using novel humanized monoclonal antibodies results in marked reductions in LDL-C, and uniquely Lp(a), in clinical trials of patients both on and off statins. These agents bind to circulating PCSK9, lowering plasma levels by ≈90%. However, their widespread use is limited by cost; the current list price of evolocumab is more than $14,000 a year per patient. In our study, ETA receptor antagonism reduced circulating PCSK9 by ≈20%, which was associated with significant improvements in lipids. The pattern of improvement in lipid profiles with ETA receptor antagonism, particularly the significant reductions in Lp(a) (≈16%), is strikingly similar to that observed in clinical trials of PCSK9 inhibitors. Figure 4 (Figure S8) suggesting that these are secondary to a reduction in circulating PCSK9.

Our observed reduction in PCSK9 during ETA antagonism occurred independently of the major recognized vascular and renal effects of this drug class, namely reductions in BP, arterial stiffness, and proteinuria. This suggests novel and specific links between the endothelin system and PCSK9, as proposed in Figure 4. Systemic inflammation, podocyte injury, and proteinuria are features of CKD and in which ETA receptor activation plays a key role. All 3 have also been shown to increase tissue and circulating PCSK9 expression in mice. However, selective ETA receptor antagonism has been shown to ameliorate podocyte injury and proximal tubule ER stress suggesting a potential role in renal PCSK9 expression.
expression after podocyte injury/ablation is also localized to proximal tubular cells.12

Other preclinical data suggest an important role for insulin in reducing hepatic PCSK9 expression by preventing nuclear translocation of HNF1α.13 ET-1 has been shown to promote hepatic insulin resistance15 which can be restored by ETA receptor antagonism in Zucker fatty rats16 and in man17 with a subsequent improvement in glucose metabolism. Finally, inflammation may act as an important shared pathway as vascular smooth muscle cells, the predominant site of ETA receptor expression, have recently been shown to express PCSK941 which can be upregulated by inflammatory stimuli in vitro.42

The collected published data link the endothelin system, PCSK9 and lipid homeostasis (Figure 4) and provide a plausible mechanistic basis for our clinical observations that should be explored further in future studies. We recognize the small size of our study as well as its medium-term duration and observational nature and while our data are secondary analyses, they originate from a well-designed, fully randomized, placebo-controlled clinical trial with no measurable evidence of carryover or period effects. We acknowledge that while the 2-week washout period between phases was designed to ensure adequate drug elimination, persisting effects on cholesterol metabolism cannot be fully excluded, although our detailed analyses show no sign of this. We demonstrate clear, consistent benefits on circulating lipids with ETA antagonism and provide novel insight into links between the endothelin system and cholesterol homeostasis in kidney disease.

Perspectives

Medium-term selective ETa antagonism improves lipid profiles in optimally-managed patients with CKD. Our data suggest that the lipid-lowering effects of ETA antagonism may be achieved through a reduction in circulating PCSK9. Alongside recognized reductions in BP, proteinuria and arterial stiffness, ETA receptor antagonism offers a novel strategy to reduce CVD risk in patients with CKD. Current larger clinical trials of selective ETa antagonism alone43 or in combination with angiotensin II receptor blockade44 in patients with protein-uric CKD should help confirm the current observations.

Acknowledgments

Dr Farrah and Anand drafted the article, performed statistical analysis, and critically revised the article. Dr Gallacher performed statistical analysis and critically revised the article. Dr Kimmitt critically revised the article. E. Carter performed biochemical assays. Drs Dear, Mills, and Webb critically revised the article. Dr Dhaun conceived the study, carried out the primary study, and critically revised the article. All authors approved the final version.

Sources of Funding

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Disclosures

Dr Dhaun has acted as a consultant for Retrophin Inc. The other authors report no conflicts.

References

41. Daly DD Jr, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr. The beneficial effects seen here were in patients at high cardiovascular risk, the majority of whom were already receiving recommended cardiovas- cular disease prevention therapy.

**Summary**

In patients with predialysis chronic kidney disease, selective ET₄ receptor antagonism reduces circulating lipids. These effects are seen on top of statin therapy and may be mediated through a reduction in PCSK9. These previously unreported findings support a link between the endothelin system and cholesterol homeostasis.