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Citation for published version:

Digital Object Identifier (DOI):
10.1161/HYPERTENSIONAHA.119.12919

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Hypertension

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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 ET<sub>A</sub> (endothelin-A) receptor antagonists reduce cardiovascular disease risk factors. Preclinical data suggest that ET<sub>A</sub> antagonism has beneficial effects on circulating lipids. We assessed the effects of selective ET<sub>A</sub> 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 ET<sub>A</sub> 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 ET<sub>A</sub> 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, ET<sub>A</sub> 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 ET<sub>A</sub> antagonism improves lipid profiles in optimally-managed patients with CKD, effects that may occur through a reduction in circulating PCSK9. ET<sub>A</sub> 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.)

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

Chronic kidney disease (CKD) is common and an important independent risk factor for cardiovascular disease (CVD).<sup>1</sup> This increased risk is partly explained by a high prevalence of traditional CVD risk factors, such as diabetes mellitus and hypertension.<sup>2</sup> Dyslipidemia is also common in CKD and contributes to the development of accelerated atherosclerosis and CVD.<sup>3</sup> 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.<sup>4,5</sup> However, despite the use of statins, many patients with CKD continue to have elevated lipids.<sup>6</sup> Furthermore, the side effects associated with these drugs can limit their use.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9,10</sup> Recent preclinical studies have shown that PCSK9 expression increases during systemic inflammation<sup>11</sup> and with podocyte injury.<sup>12</sup> Both are central features of CKD and contributed to by ET-1 (endothelin-1).<sup>13</sup> ET-1 is the most potent endogenous vasoconstrictor and plays an important role in the development and progression of CKD.<sup>13</sup> The major pathological effects of ET-1 are mediated via ET<sub>A</sub> (endothelin-A) receptors.<sup>13</sup> 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.

### 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 measured using an ELISA.

### Results

**Table 1. Baseline Study Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Nifedipine</th>
<th>PXA-021 Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48±12</td>
<td>48±12</td>
<td>48±12</td>
</tr>
<tr>
<td>Male (%)</td>
<td>23 (85)</td>
<td>23 (85)</td>
<td>23 (85)</td>
</tr>
<tr>
<td>CKD stage by eGFR, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (19)</td>
<td>5 (19)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>2</td>
<td>6 (22)</td>
<td>6 (22)</td>
<td>6 (22)</td>
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<td>3</td>
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</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>165±29</td>
<td>165±29</td>
<td>165±29</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>103±32</td>
<td>103±32</td>
<td>103±32</td>
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<tr>
<td>HDL-C, mg/dL</td>
<td>43±11</td>
<td>43±11</td>
<td>43±11</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>143±113</td>
<td>143±113</td>
<td>143±113</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>30±3</td>
<td>30±3</td>
<td>30±3</td>
</tr>
<tr>
<td>PCSK9, ng/mL</td>
<td>400±117</td>
<td>400±117</td>
<td>400±117</td>
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<tr>
<td>Statin, n (%)</td>
<td>18 (67)</td>
<td>18 (67)</td>
<td>18 (67)</td>
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<td>ACEi, n (%)</td>
<td>11 (41)</td>
<td>11 (41)</td>
<td>11 (41)</td>
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<td>β-blocker, n (%)</td>
<td>6 (22)</td>
<td>6 (22)</td>
<td>6 (22)</td>
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<td>Calcium channel blocker, n</td>
<td>3 (11)</td>
<td>3 (11)</td>
<td>3 (11)</td>
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<tr>
<td>Diuretic, n (%)</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
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</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Nifedipine</th>
<th>PXA-021 Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>164±6</td>
<td>167±6</td>
<td>164±6</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>99±6</td>
<td>101±6</td>
<td>109±6</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>44±2</td>
<td>43±2</td>
<td>40±2</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>116±16</td>
<td>153±20</td>
<td>137±23</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>30±6</td>
<td>31±6</td>
<td>30±6</td>
</tr>
<tr>
<td>PCSK9, ng/mL</td>
<td>400±22</td>
<td>386±24</td>
<td>414±22</td>
</tr>
</tbody>
</table>

Values are predosing mean±SE, mg/dL unless stated. Analysis by ANOVA. Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; urine protein-to-creatinine ratio in mg/mmol to mg/g, × 0.113; cholesterol, LDL-C, HDL-C in mg/dL to mmol/L, ×0.02586; and triglycerides in mg/dL to mmol/L, ×0.01129. HDL-C indicates high-density lipoprotein–associated cholesterol; LDL-C, low-density lipoprotein–associated cholesterol; Lp(a), lipoprotein(a); and PCSK9, proprotein convertase subtilisin/kexin type 9.
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 \( \approx 0.7 \) 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
adverse events were recorded during any treatment phase.20

parameters. All patients completed all 3 phases, and no serious

greater extent than nifedipine. Placebo did not affect these

reduction, 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.

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 and placebo are shown in Tables S2 through S7 with indi-

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, avosentan, the authors

Discussion

Our study has several important findings. We provide new
evidence of the broad beneficial effects of selective ETA re-
ceptor antagonism on 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 dem-

onstrated for the nifedipine and placebo phases.

Linear regression modeling indicated that treatment with

selective ETA antagonism remained an independent predictor of change in PCSK9 concentration at 6 weeks after adjustment for change in proteinuria, BP, and pulse wave velocity (Table S9).

Detailed effects of ETA antagonism compared with nifedipine

were present and analyzed further (Table S1). Total cholesterol, LDL-C, and HDL-C were unaffected by

placebo of 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 cho-

lesterol seen with ETA antagonism 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 1B) 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 antagonism compared 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 receptor antagonism, 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 antagonism 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 dem-

onstrated for the nifedipine and placebo phases.

As previously reported,20 6 weeks dosing with a selective ETA antagonist and nifedipine reduced BP and arterial stiff-

ness similarly, but ETA antagonism reduced proteinuria to a
greater extent than nifedipine. Placebo did not affect these parameters. All patients completed all 3 phases, and no serious adverse events were recorded during any treatment phase.20

In terms of effects on circulating lipids and PCSK9, there

were no significant 3-way interactions between time, treat-

ment, 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 cho-

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Detailed effects of ETA antagonism compared 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 receptor antagonism, 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 antagonism 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 dem-

onstrated for the nifedipine and placebo phases.

Linear regression modeling indicated that treatment with

selective ETA antagonism was an independent predictor of change in PCSK9 concentration at 6 weeks after adjustment for age, sex, statin treatment, and baseline CVD risk factors (adjusted β, 73 ng/mL; 95% CI, −131 to −16; P<0.01, Table S8). In addition, selective ETA antagonist remained an independent predictor of change in PCSK9 concentration at 6 weeks after adjustment for change in proteinuria, BP, and pulse wave velocity (Table S9).

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 ET<sub>A</sub> receptor antagonist at week 6 vs 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.
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<sub>A</sub> antagonist, atrasentan, de Zeeuw et al<sup>19</sup> 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<sub>A</sub>:ET<sub>B</sub> receptor selectivity of the drug used: bosentan (nonselective) no effect on cholesterol<sup>18</sup>; avosentan (ET<sub>A</sub>:ET<sub>B</sub> = 300:1) ≈7% reduction in cholesterol<sup>16</sup>; atrasentan (ET<sub>A</sub>:ET<sub>B</sub> = 1200:1) ≈9% reduction in cholesterol<sup>16</sup>; and sitaxentan (ET<sub>A</sub>:ET<sub>B</sub> = 6500:1) ≈11% reduction in cholesterol.<sup>25</sup>

Beyond its role in cholesterol homeostasis, a link between circulating PCSK9 concentration and CVD risk has emerged. Leander et al<sup>26</sup> 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 al<sup>26</sup> and is similar to that seen in other studies in CKD.<sup>27</sup> 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.<sup>28</sup> A recent meta-analysis of >29 000 patients found an independent and near-linear association between both

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**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<sub>A</sub> (endothelin-A) receptor antagonist.
Hypertension August 2019

Elevated baseline and on-statin Lp(a) concentrations and CVD risk. This association holds true in CKD as shown in ≈ 3500 patients with CKD from the Chronic Renal Insufficiency Cohort where a higher concentration of Lp(a) was independently associated with a greater risk of incident myocardial infarction and death during ≈ 7.5 years follow-up. Targeting these 2 novel markers of CVD risk using conventional treatments is challenging as statins increase circulating PCSK9 and are ineffective at lowering Lp(a). Our data suggest that ETA receptor antagonism reduces both.

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 S8) suggesting that these are secondary to a reduction in circulating PCSK9.

Our observed reduction in PCSK9 during ETA antagonist 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 antagonist has been shown to ameliorate podocyte injury and proximal tubule ER stress suggesting a potential role in renal PCSK9 expression.

Figure 4. Proposed pathways linking the endothelin system, PCSK9 (proprotein convertase subtilisin/kexin type 9) expression and cholesterol in chronic kidney disease. The liver is the major site of PCSK9 expression with HNF1α (hepatic nuclear factor 1α) and SREBP2 (sterol regulatory element binding protein 2) its principle promoters. Animals studies have shown that insulin binding to hepatocytes prevents nuclear translocation of HNF1α thus reducing PCSK9 transcription. ET-1 (endothelin-1) impairs hepatocyte insulin sensitivity which can be ameliorated by selective ETA receptor antagonism and so may restore the inhibitory effect of insulin on HNF1α-mediated PCSK9 transcription in hepatocytes. Whether ET-1 has direct effects on HNF1α or SREBP2 in hepatocytes is unknown. Systemic inflammation can increase both hepatic and renal PCSK9 expression with a concurrent reduction in LDL-R (low density lipoprotein receptor) expression and a rise in low-density lipoprotein–associated cholesterol (LDL-C). In the vasculature, ET-1 has proinflammatory effects mediated predominantly through ETA receptor activation. In the kidney, podocyte damage is associated with increased circulating and renal PCSK9 expression, notably localized to proximal tubular cells in murine models. The relevance of renal PCSK9 expression to the circulating PCSK9 pool and lipids needs further clarification. Interestingly, ER (endoplasmic reticulum) stress leads to an upregulation of SREBP2 in renal proximal tubular cells with subsequent apoptosis, but effects on PCSK9 expression here are unexplored. However, selective ETA 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 resistance38 which can be restored by ETα receptor antagonism in Zucker fatty rats39 and in man40 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 ETα 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 ETα antagonism and provide novel insight into links between the endothelin system and cholesterol homeostasis in kidney disease.

Perspectives

Medium-term selective ETα antagonism improves lipid profiles in optimally-managed patients with CKD. Our data suggest that the lipid-lowering effects of ETα antagonism may be achieved through a reduction in circulating PCSK9. Alongside recognized reductions in BP, proteinuria and arterial stiffness, ETα receptor antagonism offers a novel strategy to reduce CVD risk in patients with CKD. Current larger clinical trials of selective ETα antagonism alone43 or in combination with angiotensin II receptor blockade44-46 in patients with proteinuric CKD should help confirm the current observations.

Acknowledgments

Drs Farrah and Amand 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

Dr Farrah is supported by a Clinical Research Training Fellowship from the Medical Research Council (MR/R017840/1). Dr Amand is supported by a Research Fellowship from Chest Heart and Stroke Scotland (15/A163). Dr Mills is supported by the Butler Senior Research Fellowship (FS/16/14/32023) and Chair (CH/09/0002) awards from the British Heart Foundation. Dr Dhaun is supported by a BHF Intermediate Clinical Research Fellowship (FS/13/30/29994).

The original study was funded by Pfizer Inc.

Disclosures

Drs Dhaun has acted as a consultant for Rетrophin Inc. The other authors report no conflicts.

References


Novelty and Significance

What Is New?

- In patients with chronic kidney disease, treatment with a selective ET<sub>A</sub> (endothelin-A) antagonist led to clinically-relevant reductions in circulating lipids.
- Interestingly, these lipid-lowering effects occurred alongside a reduction in circulating PCSK9 (proprotein convertase subtilisin/kexin type 9).

What Is Relevant?

- Patients with chronic kidney disease are at high cardiovascular risk. Dyslipidemia is common and despite the use of statins, many of these patients continue to have elevated lipids.
- The beneficial effects seen here were in patients at high cardiovascular risk, the majority of whom were already receiving recommended cardiovascular disease prevention therapy.

Summary

In patients with predialysis chronic kidney disease, selective ET<sub>A</sub> 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.