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### Title

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### Permalink

<https://escholarship.org/uc/item/2cg1r078>

### Journal

American Journal of Kidney Diseases, 65(5)

### ISSN

0272-6386

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### Publication Date

2015-05-01

### DOI

10.1053/j.ajkd.2014.11.033

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Peer reviewed



## Niacin and Progression of CKD

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Niacin is the oldest drug available for the treatment of dyslipidemia. It has been studied extensively and tested in clinical trials of atherosclerotic cardiovascular disease prevention and regression in the general population, but not specifically in patients with chronic kidney disease (CKD), who are at extremely high residual risk despite current therapy. Despite the current controversy about recent trials with niacin, including their limitations, there may be a place for this agent in select patients with CKD with dyslipidemia. Niacin has a favorable unique impact on factors affecting the rate of glomerular filtration rate decline, including high-density lipoprotein (HDL) particle number and function, triglyceride levels, oxidant stress, inflammation and endothelial function, and lowering of serum phosphorus levels by reducing dietary phosphorus absorption in the gastrointestinal tract. These effects may slow glomerular filtration rate decline and ultimately improve CKD outcomes and prevent cardiovascular risk. This review presents the clinically relevant concept that niacin holds significant potential as a renoprotective therapeutic agent. In addition, this review concludes that clinical investigations to assess the effect of niacin (in addition to aggressive low-density lipoprotein cholesterol lowering) on reduction of cardiovascular events in patients with CKD with very low HDL cholesterol (or those with identified dysfunctional HDL) and elevated triglyceride levels need to be considered seriously to address the high residual risk in this population.

*Am J Kidney Dis.* 65(5):785-798. © 2015 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Niacin; chronic kidney disease; HDL function; hyperphosphatemia; cardiovascular disease; phosphorus absorption.

### INTRODUCTION

It is estimated that >10% of the US population 20 years or older has chronic kidney disease (CKD).<sup>1</sup> The condition is progressive and irreversible, and its presence is associated with a high risk of mortality, cardiovascular disease (CVD) morbidity, and a marked increase in health care expenditures.<sup>2</sup> Progression of CKD is associated with increased risk of CVD events and mortality. A recent meta-analysis reported that mortality increases 1.4 times for each 15-mL/min/1.73 m<sup>2</sup> decrease in glomerular filtration rate (GFR) < 45 mL/min/1.73 m<sup>2</sup>.<sup>3</sup> Consequently, current guidelines recommend interventions for prevention of the progression of CKD. The NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines<sup>4</sup> advise strict glucose control in diabetes, blood pressure control, and use of drugs providing angiotensin-converting enzyme inhibition or angiotensin-2 receptor blockade. Despite these interventions, there has been limited success in preventing the progression of CKD. The effect of glycemic control on CKD progression was not confirmed in recent large trials.<sup>5,6</sup> The very low optimal blood pressure previously recommended for the prevention of progression of CKD<sup>7</sup> is no longer part of the guidelines in view of a lack of evidence of benefit in terms of CVD events<sup>8</sup> or death.<sup>9</sup> Furthermore, studies have shown that angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers decrease GFR decline in patients with proteinuria,<sup>10</sup> but their effectiveness in patients with non-proteinuric CKD has been questioned.<sup>11</sup> Therefore,

additional interventions for decreasing the rate of GFR decline are necessary.

Niacin is the oldest drug available for the treatment of dyslipidemia.<sup>12</sup> It has been studied extensively and tested in clinical trials of CVD prevention<sup>13</sup> and reversal of atherosclerosis (see Table 1). Its place in current therapy has to be viewed in the context of its long clinical history of more than half a century and its useful properties shown in basic research studies. Controversy has followed recent reports. Results of 2

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*Received August 1, 2014. Accepted in revised form November 19, 2014. Originally published online February 21, 2015.*

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0272-6386

<http://dx.doi.org/10.1053/j.ajkd.2014.11.033>

**Table 1.** Clinical Trials Investigating the Cardiovascular Benefit of Niacin Therapy

Study	Intervention	Clinical Events/Total No. of Pts		Results
		Intervention	Control	
CDP <sup>139</sup> (1975)	Niacin	287/1,119	839/2,789	Clinical benefit <sup>a</sup>
CLAS <sup>132</sup> (1987)	Niacin + colestipol	1/94	5/94	Angiographic benefit <sup>b</sup>
STOCKHOLM <sup>140</sup> (1988)	Niacin + clofibrate	72/279	100/276	Clinical benefit
FATS <sup>141</sup> (1990)	Niacin + colestipol	2/48	10/52	Angiographic benefit
UCSF SCOR <sup>142</sup> (1990)	Niacin + colestipol	0/48	1/49	Angiographic benefit
HATS <sup>143</sup> (2001)	Niacin + simvastatin	1/38	5/38	Angiographic benefit
ARBITER 2 <sup>144</sup> (2004)	Niacin	2/87	2/80	Benefit in terms of reduced carotid intima-media thickening
AFREGS <sup>145</sup> (2005)	Niacin + gemfibrozil + cholestyramine	9/71	29/72	Clinical and angiographic benefit
ARBITER 6 <sup>135</sup> (2009)	Niacin extended release vs ezetimibe	2/187	9/176	Benefit in terms of reduced carotid intima-media thickening and clinical benefit
AIM-HIGH <sup>146</sup> (2011)	Niacin extended release	282/1,718	274/1,696	No clinical benefit
HPS2-THRIVE <sup>16</sup> (2014)	Niacin + laropirant	1,696/1,2838	1,758/1,2835	No clinical benefit

Abbreviations: AFREGS, Armed Forces Regression Study; AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes; HPS2-THRIVE, Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events; ARBITER, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; CDP, Coronary Drug Project; CLAS, Cholesterol-Lowering Atherosclerosis Study; FATS, Familial Atherosclerosis Treatment Study; HATS, HDL-Atherosclerosis Treatment Study; STOCKHOLM, Stockholm Ischaemic Heart Disease Secondary Prevention Study; UCSF SCOR, University of California, San Francisco, Arteriosclerosis Specialized Center of Research.

<sup>a</sup>Clinical benefit: reduced number of cardiovascular events.

<sup>b</sup>Angiographic benefit: reduced amount of stenosis as estimated by quantitative angiography.

recent clinical trials to determine whether niacin confers incremental benefit in patients treated optimally for low-density lipoprotein cholesterol (LDL-C) level reduction resulted in negative outcomes.<sup>14-16</sup> These trials have cast doubts about the place of niacin in current therapy for cardiovascular risk reduction. The limitations and implications about which types of patients currently may benefit are discussed later in this review. Importantly, we preface this review by indicating that there is a serious unmet need in therapies to slow CKD progression and reduce the high residual risk for CVD. The role of niacin in CKD management has not been the subject of much inquiry and merits attention despite the recent trials. In pharmacologic doses, niacin's effects on lipid and lipoprotein levels are fairly well known,<sup>17</sup> and its pharmacokinetics in patients with CKD have been documented.<sup>18</sup> In experimental animal models of CKD, niacin reduced kidney injury, 24-hour protein excretion, and the rate of GFR decline.<sup>19</sup>

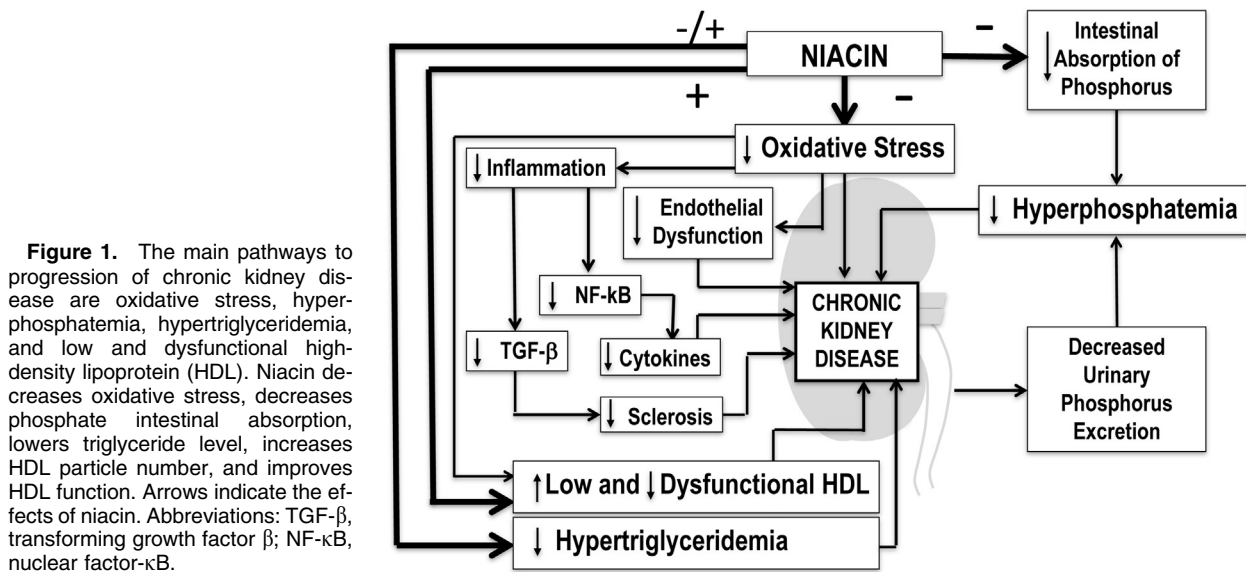
The results of 2 recent studies, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH)<sup>15</sup> and Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)<sup>16</sup> have cast doubt on the safety and efficacy of niacin for reducing CVD events in high-risk patients. We believe it is premature to give up on the use of niacin

for cardiovascular prevention based on these 2 studies, in which heterogeneous groups of patients may have diluted the benefits in selected populations. Many types of patients were not studied in these trials, as acknowledged by the studies' investigators, and only a few patients with CKD were enrolled.

This review presents the clinically relevant concept that niacin may slow the rate of GFR decline in patients with CKD through its effect on HDL cholesterol (HDL-C), triglycerides, oxidative stress, and phosphate absorption (Fig 1).

### NIACIN, TRIGLYCERIDES, HDL CHOLESTEROL, AND CKD

The definition of metabolic syndrome<sup>20</sup> includes elevated serum fasting triglyceride and low HDL-C levels, along with central obesity, hypertension, and impaired fasting glucose level. This definition confers a risk for coronary events, but not more than the sum of its parts.<sup>21</sup> Patients with estimated GFRs (eGFRs) < 60 mL/min/1.73 m<sup>2</sup> are more likely to have metabolic syndrome,<sup>22</sup> and metabolic syndrome also is associated with increased albumin excretion rate (AER).<sup>23</sup> Specifically, a high ratio of triglycerides to HDL-C has an increased prevalence in patients with CKD.<sup>24-26</sup> Triglyceride levels commonly are increased in patients with CKD in multivariate analysis whether studied separately<sup>27,28</sup> or combined with



central obesity as “hypertriglyceridemia waist.”<sup>29</sup> In a recent study,<sup>30</sup> both triglyceride and HDL-C levels were associated independently with CKD.

In most prospective studies, triglyceride and/or HDL-C levels were identified as predictors of the development or progression of CKD whether defined as a GFR threshold, a decrease in GFR, or onset of proteinuria (Table 2). Larger studies also appear more likely to show a positive association between the high triglyceride and/or low HDL-C exposure with the CKD end point.

The mechanism by which high triglyceride and low HDL-C levels increase the risk of CKD progression is not known. Hypertriglyceridemia has been associated with progression of CKD by multiple mechanisms: monocyte activation, glycocalyx degradation, increased permeability of the glomerular filtration barrier, podocyte apoptosis, and mesangial profibrotic changes.<sup>31</sup> The association between HDL-C level and CKD progression is attributed mainly to the fact that HDL particles are one of the main carriers of endogenous antioxidants, and low HDL-C level reflects a deficiency of these important molecules/proteins. Therefore, the total antioxidant defense is diminished irrespective of the capacity for individual HDL particles to carry antioxidants. HDL in patients with CKD is not only reduced, but also dysfunctional.<sup>32,33</sup> Dysfunctional HDL predicts a poor outcome in end-stage renal disease (ESRD).<sup>34</sup> Because dysfunctional HDL is characterized by a reduced capacity to transport antioxidants (in addition to reduced reverse cholesterol transport and endothelial function), its association with progression of CKD will be reviewed further. Hence, if high triglyceride and low HDL levels are associated independently with worse outcomes,

decreasing triglyceride and elevating HDL-C levels may be indicated for kidney protection.

In addition to statin therapy, drugs commonly used to reduce triglyceride levels and/or increase HDL-C levels are fibric acid derivatives (fibrates, such as fenofibrate and gemfibrozil in the United States), omega-3 fatty acids (HDL neutral), and niacin. New unapproved drugs that increase HDL-C levels include cholesteryl ester transfer protein (CETP) inhibitors. Two of these drugs (torcetrapib<sup>35</sup> and dalcetrapib<sup>36</sup>) examined cardiovascular outcomes in patients without CKD and failed to show clinical benefit, raising questions about elevating HDL-C level as a target of therapy to reduce residual cardiovascular risk after statin or LDL-C–based therapy. These drugs have a unique mechanism of action by which cholesterol in HDL is suppressed from transfer to other lipoproteins, thus increasing the cholesterol content in HDL at the possible expense of its removal from the circulation. Despite the controversial mechanism of action of CETP inhibitors, 2 other CETP-inhibitor drugs are in clinical trials (evacetrapib<sup>37</sup> and anacetrapib<sup>38</sup>), and their potential benefit is unknown. Fenofibrate<sup>39–45</sup> and omega 3 fatty acids<sup>46</sup> have been shown to have a modest renoprotective effect in terms of AER reduction or GFR decline. However, fibrates increase the risk for myopathy and rhabdomyolysis<sup>47</sup> in patients with CKD and thus cannot be considered seriously for reducing residual risk in patients with CKD. The mechanisms of action of all these drugs (CETP inhibitors, fibrates, and omega 3 fatty acids) on triglyceride and HDL concentrations and function are unique and very different from niacin. Study results from one drug should not be extrapolated to another.

**Table 2.** Prospective Studies Reporting an Association of Triglycerides and/or HDL-C and CKD End Points

Study	N	Type of Patient	Mean Age (y)	End Point	Follow-up (mo)	Triglycerides	HDL-C	Covariates
Baragetti et al <sup>163</sup> (2013)	176	Mild to moderate decreased kidney function	67	Creatinine > 2× baseline or ESRD	84	+	+	Hemoglobin, eGFR, AER, MAP, BMI, Ca × P, LDL-C
Boes et al <sup>111</sup> (2005)	177	Nondiabetic CKD stages 3-4	46	Creatinine > 2× baseline or ESRD	53	-	-	None
Bonnet et al <sup>147</sup> (2006)	2,738	Nondiabetic, no microalbuminuria	47	CKD	72	-	-	None
Chawla et al <sup>164</sup> (2010)	840	Nondiabetic CKD stages 1-5	52	ESRD	120	-	-	None
Cho et al <sup>165</sup> (2013)	15,401	No CKD	44	CKD	62	+	+	Age, sex, smoking, alcohol, physical activity
Hunsicker et al <sup>166</sup> (1997)	840	eGFR 35-55 mL/min/1.73 m <sup>2</sup>	51	eGFR decline	28	NA	+	AER, PKD, transferrin, MAP, black race
Kitiyakara et al <sup>148</sup> (2007)	2,067	Nondiabetic	42	CKD	144	-	-	Central obesity, blood pressure, FPG
Klein et al <sup>167</sup> (1999)	52	Type 1 diabetes	31	ESRD	120	NA	+	Age at diagnosis, BMI, hypertension, AER, retinopathy, impaired sensation, smoking, alcohol, physical activity
Kurella et al <sup>22</sup> (2005)	10,096	Community	54	CKD	108	+	+	Age, sex, race
Massy et al <sup>168</sup> (1999)	138	CKD stages 3-4	62	ESRD	144	+	-	SBP, smoking, fibrinogen, protein intake, antihypertensive drugs
Muntner et al <sup>169</sup> (2000)	12,728	Creatinine < 2.0 mg/dL in men, <1.8 mg/dL in women	54	Creatinine increase ≥ 0.4	22	+	+	Creatinine, SBP, diabetes, antihypertensive drugs
Navaneethan et al <sup>149</sup> (2013)	25,868	CKD stages 3-4	73	ESRD	26	+	-	Age, race, sex, comorbid conditions, LDL-C, albumin, antihypertensives, eGFR
Obermayr <sup>175</sup> (2008)	17,357	General population	42	CKD	84	-	+	eGFR, AER, BMI, sports, smoking, FPG, SBP, DBP, diabetes, cholesterol, TG
Rahman et al <sup>150</sup> (2014)	3,939	CKD	58	ESRD or 50% decline in GFR	49	-	-	Age, race, sex, BMI, diabetes, blood pressure, statin use, smoking, AER, clinical center, alcohol use, baseline eGFR
Rashidi et al <sup>151</sup> (2007)	4,607	Nondiabetic	40	CKD	36	-	-	Central obesity, blood pressure, FPG
Ravid et al <sup>170</sup> (1998)	574	Type 2 diabetes	48	Diabetic nephropathy	108	+	+	None
Schaeffner et al <sup>171</sup> (2003)	4,483	Creatinine < 1.5 mg/dL	49	Creatinine > 1.5 mg/dL	170	NA	+	Age, smoking, alcohol, diabetes, hypertension, family history, lipid-lowering drugs
Sun et al <sup>152</sup> (2010)	118,924	Nondiabetic	39	CKD	44	+	+	Age, sex, central obesity, blood pressure, FPG
Toda et al <sup>153</sup> (2014)	1,652	Community	52	CKD	60	+	-	Age, sex, BMI, SBP, DBP, LDL-C, HOMA-IR, HbA <sub>1c</sub> , uric acid
Torres et al <sup>172</sup> (2011)	241	Polycystic kidney disease	32	eGFR decline	60	NA	+	None
Tozawa et al <sup>154</sup> (2002)	4,326	No proteinuria	48	Proteinuria, eGFR change	36	+	+	Age, BMI, creatinine, SBP, diabetes, antihypertensive medication, smoking

(Continued)

**Table 2 (Cont'd).** Prospective Studies Reporting an Association of Triglycerides and/or HDL-C and CKD End Points

Study	N	Type of Patient	Mean Age (y)	End Point	Follow-up (mo)	Triglycerides	HDL-C	Covariates
Watanabe et al <sup>155</sup> (2010)	3,679	Community	59	CKD	70	+	+	Age, sex, BMI, eGFR, blood pressure, IGT
Yoshida et al <sup>173</sup> (2008)	485	Nondiabetic CKD stages 1-2	42	eGFR decline	60	-	+	Age, sex, BMI, metabolic syndrome, AER, hypertension, FPG, smoking, ACEi/ARB, CCBs
Zoppini et al <sup>174</sup> (2012)	1,987	Type 2 diabetes	66	CKD	60	-	+	Age, sex, BMI, eGFR, hypertension, diabetes duration, HbA <sub>1c</sub> , antihypertensive, hypoglycemic and lipid-lowering drugs, microvascular complications

Abbreviations and definitions: (+), positive association of exposure with outcome; (-), no significant association found between exposure and outcome; ACEi/ARB, angiotensin-converting enzyme inhibitor or angiotensin-2 receptor blocker; AER, albumin excretion rate; BMI, body mass index; Ca × P, calcium-phosphorus product; CCB, calcium channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FPG, fasting plasma glucose; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; NA, not applicable; PKD, polycystic kidney disease; SBP, systolic blood pressure; TG, triglycerides.

The effect of niacin on kidney function and AER has been studied in experimental kidney disease. Cho et al<sup>19,48</sup> reported that niacin-treated partially nephrectomized rats had marked reductions in 24-hour protein excretion and rate of GFR decline. There is no study reporting a similar effect of niacin in humans. However, a case report of a patient with familial lecithin cholesterol acyltransferase deficiency with moderate CKD showed that daily administration of niacin and fenofibrate resulted in a 75% reduction in albumin-creatinine ratio and stabilization of serum creatinine level.<sup>49</sup> Conversely, derivatives of niacin, such as niceritrol<sup>50</sup> and nicorandil,<sup>51</sup> have been tested in small clinical trials in patients with CKD and proteinuria. Both drugs have shown a significant reduction in AER when the treated group was compared to the respective control group (untreated and placebo, respectively).

In summary, elevated triglyceride and low HDL-C levels are predictors of increased AER and GFR decline, whereas fenofibrate, a drug used to reduce triglyceride and increase HDL-C levels, has a beneficial effect on AER and GFR in diabetic patients. Additionally, niacin has been shown to be renoprotective in experimental CKD. These data support the need for clinical investigations exploring the potential of niacin for renoprotection in patients with CKD and additionally for identifying the profile of patients who may benefit.

**NIACIN, OXIDATIVE STRESS, AND CKD**

Progression of kidney disease is associated with a progressive worsening of oxidative stress attributable to an increased level of reactive oxygen species and a decrease in antioxidant defense mechanism. In the past 12 years, multiple reviews have emphasized the role of oxidative stress in different aspects of the pathophysiology of CKD.<sup>52-55</sup> These reviews explain that oxidative stress is the primary trigger for the inflammation, fibrosis, and impaired endothelial function observed in CKD, and that the level of oxidative stress increases progressively in close association with declining eGFR. Niacin can play a role in ameliorating oxidative stress, inflammation, and endothelial dysfunction.

**Oxidative Stress**

Oxidative stress has been identified as a major factor in the progression of CKD. This pathogenic pathway is documented through animal studies, in vitro studies, small prospective studies, and randomized clinical trials using antioxidants.

In patients with diabetes, oxidative stress mediates high glucose-induced activation of nuclear factor-κB (NF-κB) and NF-κB-dependent monocyte chemoattractant protein 1 (MCP-1) expression.<sup>56</sup> Upregulation of MCP-1 is considered to be one of the mechanisms

involved in the development and progression of diabetic nephropathy.<sup>57</sup> In early stages of diabetic nephropathy in type 1 diabetes, hyperfiltration is associated with oxidative stress biomarkers independent of age at disease onset, glycated hemoglobin levels, and microalbuminuria.<sup>58</sup> In patients with established CKD, levels of markers of oxidative stress increase and antioxidative enzyme levels decrease as GFR declines.<sup>59</sup> In patients with immunoglobulin A nephropathy, advanced oxidation protein product concentration predicted worse kidney outcomes in multivariate analysis<sup>60</sup> and correlated strongly with the slope of GFR decline over the next 3 to 10 years.<sup>61</sup>

In the past 5 years, myeloperoxidase (MPO) has emerged as a main mediator of tissue injury induced by reactive oxygen species<sup>62-66</sup> and as a main pathway for generating dysfunctional HDL.<sup>67</sup> In patients with CKD, MPO is considered to be a primary link between oxidative stress, inflammation, and endothelial dysfunction.<sup>68,69</sup> In mice with CKD, MPO deficiency is associated with decreased levels of inflammatory and profibrotic markers, less proteinuria, and slower course of glomerular lesions.<sup>70</sup> In patients with diabetic nephropathy, MPO is elevated and correlates significantly with albumin-creatinine ratio.<sup>71</sup> MPO levels in patients with CKD are elevated compared with healthy controls,<sup>72</sup> but their association with eGFR has been reported to be both positive<sup>73</sup> and negative.<sup>74</sup> In dialysis patients, MPO levels are more than 20-fold higher than in predialysis patients.<sup>75</sup> In these patients, MPO levels are associated with mortality, cardiovascular events, and reduced kidney function.<sup>76</sup> A study of the gene polymorphism for MPO G-463A showed that the allele G, which is associated with higher MPO levels, also is associated with progression of diabetic nephropathy, expressed as either increased AER or decreased eGFR.<sup>77</sup> Recent research from our laboratory has indicated that niacin significantly decreases the release of MPO by leukocytes and prevents HDL from becoming dysfunctional.<sup>78</sup>

In the past 15 years, various attempts were made to decrease antioxidant stress by drug intervention in order to provide renoprotection or cardioprotection for patients with CKD at risk. The agents tested were acetylcysteine<sup>79,80</sup>; vitamin E, 800 IU/d<sup>81</sup>; and probucol.<sup>82</sup> A Cochrane analysis reported that antioxidants decreased the progression of CKD.<sup>53</sup> This analysis was based mostly on a 52-week randomized placebo-controlled study, Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM).<sup>83</sup> Unfortunately, clinical trials for this antioxidant were discontinued because of safety concerns.<sup>84,85</sup>

HDL is one of the main carriers of antioxidants in serum and has impaired antioxidant activity in CKD.<sup>32</sup> In studies of humans, niacin significantly

reduced oxidative stress in patients with hypercholesterolemia and low HDL levels.<sup>86</sup> An antioxidant effect of niacin also was demonstrated in cultured human aortic endothelial cells.<sup>87</sup> In this study, niacin decreased mediators of oxidative stress and LDL oxidation, which resulted in reductions in MCP-1 and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), NF- $\kappa$ B activation, and vascular cell adhesion molecule 1 (VCAM-1) levels and secretion. Production of nicotinamide adenine dinucleotide phosphate oxidase enzyme complex and activated reactive oxygen species particles also was inhibited significantly by niacin.<sup>78</sup>

### Inflammation

As CKD progresses, amplification of oxidative stress is associated with increased inflammatory markers such as C-reactive protein (CRP) and fibrinogen.<sup>88</sup> In the ARIC (Atherosclerosis Risk in Communities) Study, the risk of incident CKD increased with increasing baseline quartiles of white blood cell count and fibrinogen.<sup>89</sup> In other prospective studies, level of CRP, the most commonly used marker of inflammation, predicts doubling of baseline serum creatinine level and/or the onset of ESRD<sup>90</sup> and increase in creatinine level<sup>91</sup> and rate of GFR decline.<sup>92</sup> In the CARE (Cholesterol and Recurrent Events) Study, among survivors of myocardial infarction with CKD, higher baseline CRP and soluble TNF receptor II levels were associated independently with more rapid loss of kidney function.<sup>93</sup>

Other biomarkers of inflammation, including TNF receptor I<sup>94</sup>; circulating matrix metalloproteinases-2, -3 and -9<sup>95</sup>; and soluble CD40 ligand,<sup>96</sup> have been associated independently with progression of CKD. The anti-inflammatory properties of niacin are mediated in part by the niacin-specific receptor GPR109A<sup>13</sup> and are independent from its lipid-modifying effects.<sup>97,98</sup> In studies of humans, niacin has demonstrated its anti-inflammatory potential by decreasing fibrinogen,<sup>99,100</sup> CRP,<sup>101,102</sup> and soluble CD40 ligand levels.<sup>103</sup>

### Endothelial Dysfunction

Endothelial dysfunction also increases with progression of CKD. Markers of endothelial dysfunction, such as asymmetric dimethylarginine (ADMA), which is a natural inhibitor of nitric oxide production by the endothelium,<sup>104,105</sup> and von Willebrand factor,<sup>106</sup> have been shown to increase across advancing stages of CKD. Conversely, with progression of CKD, the ability of cultured endothelial progenitor cells to express nitric oxide synthase decreases.<sup>107</sup>

Prospective data show that endothelial dysfunction contributes to the deterioration of kidney function. The effect of endothelial dysfunction on progression of CKD was demonstrated by showing that increased

**Table 3.** Effect of Niacin Extended Release or Niacin/Laropiprant on Serum Phosphorus

Study	Type of Patient	N	Phosphate (mg/dL; mean $\pm$ SD)		P
			Before Niacin	After Niacin	
Sampathkumar et al <sup>130</sup>	Hemodialysis	34	7.7 $\pm$ 1.5	5.6 $\pm$ 1.0	<0.001
Muller et al <sup>156</sup>	Dialysis	17	7.2 $\pm$ 0.5	5.9 $\pm$ 0.6	0.015
Restrepo et al <sup>157</sup>	Dialysis	9	6.5 $\pm$ 0.5	4.0 $\pm$ 0.8	<0.01
Ahmadi et al <sup>158</sup>	Hemodialysis	20	7.3 $\pm$ 1.1	5.6 $\pm$ 1.6	0.004
Hu et al <sup>159</sup>	No CKD	29	3.2 $\pm$ 0.5	2.7 $\pm$ 0.5	0.003
Maccubbin et al <sup>160</sup>	No CKD	1,102	3.3 $\pm$ 0.5	3.2 $\pm$ 0.5	<0.001
Bostom et al <sup>161</sup>	Diabetes $\pm$ CKD	446	3.6 $\pm$ 0.5	3.2 $\pm$ 0.5	<0.001
Ix et al <sup>162</sup>	Stage 3 CKD	177	3.4 $\pm$ 0.5	3.2 $\pm$ 0.5	<0.001

Abbreviations: CKD, chronic kidney disease; SD, standard deviation.

acetylcholine-stimulated forearm blood flow, a gold-standard test for endothelial function, is associated independently with decreased eGFR slope.<sup>108</sup> This report is supported by data addressing markers of endothelial dysfunction. Increased levels of soluble VCAM-1 and plasminogen activator inhibitor 1 were reported to be correlated strongly with steeper eGFR decline in patients with type 1 diabetes.<sup>109</sup> In another study in patients with type 1 diabetes, after adjustment for well-known confounders including baseline eGFR, there was a significant increase in risk for ESRD when comparing upper and lower median ADMA levels.<sup>110</sup> Moreover, in patients with mild to moderate nondiabetic CKD, Cox regression analysis revealed that baseline ADMA level was an independent predictor of CKD progression.<sup>111</sup>

The effect of niacin on endothelial function was documented in the INEF (Impact of Niacin on Endothelial Function) trial.<sup>112</sup> In this study, extended-release niacin treatment improved endothelial dysfunction in patients with coronary artery disease who had low HDL-C levels, but not in those with normal HDL-C levels. In another study, niacin treatment reduced ADMA levels by a clinically significant margin.<sup>113</sup>

### NIACIN, CKD, AND HYPERPHOSPHATEMIA

Hyperphosphatemia is a non-GFR marker of CKD. The concept that high phosphorus level is associated with the rate of CKD progression was proposed first from dietary and animal studies.<sup>114</sup> In 2006, Schwarz et al<sup>115</sup> showed in male veterans with CKD that higher serum phosphorus concentrations were associated with higher risk of the composite end point of doubling of serum creatinine level or ESRD. Another study<sup>116</sup> reported that increases in phosphorus levels in patients with stage 4 CKD were associated with increases in kidney function decline. Other studies reported that in patients with moderate CKD, higher serum phosphate levels were associated independently with progression to ESRD or death.<sup>117-119</sup>

Moreover, higher dietary phosphorus burden in the form of higher phosphorus to protein ratio in food is associated with higher mortality in advanced CKD.<sup>120</sup> The slope of GFR decline obtained from prospective data also has been shown to be associated with increasing serum phosphorus levels.<sup>121,122</sup> In patients with normal kidney function, high plasma phosphorus levels are associated with increased likelihood for ESRD outcome.<sup>123</sup> In addition, hyperphosphatemia is associated with overt proteinuria in nondiabetic patients with advanced CKD,<sup>124</sup> and a strong interaction was reported between serum phosphate level and phosphaturia with an antiproteinuric response to a very low-protein diet.<sup>125</sup>

These studies provide strong evidence that hyperphosphatemia precedes and predicts the progression of CKD. Although it is assumed that lowering serum phosphorus levels should have a favorable effect on progression of CKD, a retroactive analysis of non-dialysis-dependent patients with CKD treated with phosphate binders showed a steeper slope of GFR decline than for untreated patients,<sup>126</sup> and another study showed that phosphorus binders may have a paradoxically deleterious effect on vascular calcification.<sup>127</sup> These data indicate the need for new approaches to address hyperphosphatemia and vascular calcification in CKD.

The phosphorus-reducing properties of niacin and its derivatives, including nicotinamide, were reported first by Shimoda et al.<sup>128</sup> The mechanism of action is attributed to inhibition of type IIb sodium-dependent phosphate cotransporter in the intestinal brush-border membranes.<sup>129</sup> The first report of extended-release niacin use for treatment of hyperphosphatemia in CKD was published in 2006.<sup>130</sup> Subsequently, other authors reported on the phosphorus-lowering effects of niacin or niacin/laropiprant in patients with CKD receiving hemodialysis, non-dialysis-dependent patients with CKD, and patients without CKD (Table 3). All these studies confirmed significant lowering of serum phosphorus levels in treatment arms, which



was consistent among subgroups and associated with minimal adverse events. In summary, hyperphosphatemia is associated with an increased rate of GFR loss in CKD, and niacin has been uniformly reported to reduce serum phosphorus concentration.

### NIACIN, CKD, AND ATHEROSCLEROTIC CVD

This review is presented at a time when the use of niacin in clinical practice is controversial. The AIM-HIGH study enrolled 3,414 patients with coronary artery disease, low HDL-C levels (men, <40 mg/dL; women, <50 mg/dL), high triglyceride levels (>150 mg/dL), and LDL-C level lowered to 40 to 80 mg/dL with simvastatin and ezetimibe if necessary. Study results showed no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up despite significant improvements in HDL-C and triglyceride levels. A subgroup analysis from the AIM-HIGH trial showed a significant decrease in primary events in 439 patients with triglyceride levels  $\geq 200$  mg/dL and HDL-C levels  $\leq 32$  mg/dL.<sup>131</sup> This finding suggests that the cardioprotective effect of niacin could have been attributable to triglyceride level lowering and/or HDL-C concentration increase, in addition to niacin's other lipid and nonlipid properties. A larger trial, HPS2-THRIVE, compared niacin/laropiprant to placebo in statin-treated patients with atherosclerotic CVD who were recruited without regard for lipid levels and failed to show incremental benefit.<sup>14,16</sup> These patients had normal HDL-C (mean, 44 mg/dL) and triglyceride levels (mean, 126 mg/dL), and all patients' LDL-C levels in this study were controlled with simvastatin. Patients with this type of lipid profile have not been indicated for treatment with niacin. In addition, by trial design, patients in this study were heterogeneous in terms of racial origin and lipid profiles, so that any subgroup that may have benefitted was diluted by results from the rest of the study cohort.

Because of the limitations of these studies, we believe the clinical benefit and safety of niacin deserves to be investigated further, particularly in patients with CKD. Niacin use in combination with other lipid-lowering drugs consistently has resulted in reversal of atherosclerosis, expressed as increased carotid intima thickness, femoral atherosclerosis, and coronary stenosis.<sup>132-135</sup> A 2010 meta-analysis reported that niacin significantly reduced major coronary events by 25%, stroke by 26%, and any cardiovascular events by 27%.<sup>136</sup> Another meta-analysis including 9,959 patients showed a 34% reduction in the composite end points of any CVD event and a 25% reduction in major coronary heart disease events.<sup>137</sup>

Based on current considerations, we are proposing that a randomized clinical trial of niacin versus placebo on statin background therapy should be undertaken in patients with non-dialysis-dependent CKD with triglyceride levels  $\geq 200$  mg/dL and HDL-C levels  $\leq 35$  mg/dL. Based on numbers provided by the Veterans Administration (VA) database, we approximate that 10% of non-dialysis-dependent patients with CKD would qualify for enrollment based on these HDL-C and triglyceride criteria. In addition, in order to identify additional suitable patients for this study, we may include criteria that patients have elevated CRP levels, endothelial dysfunction, elevated MPO levels, dysfunctional HDL, and/or reduced HDL particle number.

In preparation for this trial, we currently are conducting a retrospective analysis in the VA database of more than 650,000 patients with incident CKD, of whom more than 50,000 were treated with niacin. We aim to explore the safety of niacin in order to further refine the inclusion criteria of our proposed trial. Recent published trials have raised concerns that need to be explored carefully in patients with CKD. In both AIM-HIGH<sup>39</sup> and HPS2-THRIVE,<sup>16</sup> there was a significantly increased risk of nonspecific infection, which is an important complication for patients with CKD. In addition, a significant increase in risk of gastrointestinal bleeding was seen in HPS2-THRIVE, but not in AIM-HIGH. This bleeding has been attributed mainly to the effect of niacin on platelets.<sup>16</sup> Niacin in vitro affects platelet activity by a unique inhibiting effect on aggregation and by stimulating significant prostaglandin release, while major platelet receptor expression remains mostly intact.<sup>138</sup> This niacin effect on platelets is considered to be mild. Moreover, bleeding has not been seen with niacin in other trials. The increased risk of gastrointestinal bleeding found in HPS2-THRIVE raises the question of whether laropiprant (used in this trial and not AIM-HIGH) had a role in this adverse event. Exploring large databases to confirm that niacin is not associated with bleeding complications is essential.

In addition, our group is exploring methods of evaluating HDL function. We believe that niacin's main mechanism of action is altering HDL function, and results from this study may further identify CKD subgroups that will benefit from niacin treatment in conjunction with aggressive LDL-C reduction therapy with statins.

### CONCLUSIONS

To our knowledge, the effects of niacin on rate of GFR decline have never been explored in either cohort studies or randomized clinical studies. Niacin has a favorable impact on multiple risk factors affecting the rate of GFR decline, such as HDL concentration and

function, triglyceride level, oxidant stress, inflammatory markers, endothelial function, and serum phosphorus level. In addition, recent evidence<sup>135</sup> indicates that niacin may be most effective in reducing cardiovascular events in certain subgroups of statin-treated patients with high triglyceride and very low HDL-C levels, a pattern similar to that seen in patients with CKD. Thus, in patients with CKD, treatment with niacin (in addition to intense LDL-C-lowering therapy) may contribute to lowering the rate of GFR decline and amelioration of atherosclerosis, which is the primary cause of death in these patients. The large body of evidence presented in this review strongly suggests that clinical investigations are needed to assess the effect of niacin (in addition to aggressive LDL lowering) on GFR loss and possibly on reduction of atherosclerosis CVD end points in select groups of patients with CKD; in particular, those with very low HDL-C levels (or identified dysfunctional HDL) and with elevated triglyceride levels who have a very high residual risk and for whom there is no other viable therapy available.

### ACKNOWLEDGEMENTS

*Support:* Dr Kalantar-Zadeh is funded by the National Institute of Diabetes, Digestive and Kidney Disease of the National Institutes of Health (R01 DK078106) and a philanthropic grant from Mr Harold Simmons. Dr Kashyap is funded by the VA Merit Review Award.

*Financial Disclosure:* Drs Kovesdy, Kalantar-Zadeh, and Kashyap are employees of the US Department of Veterans Affairs. Opinions expressed in this article are those of the authors and do not necessarily represent the opinion of the Department of Veterans Affairs. Dr Kashyap currently has research grant support as Principal Investigator (PI) or sub-PI through the VA from Abbvie, AstraZeneca, Sanofi-Aventis, Merck, Eli-Lilly, Amgen, Amylin, and Arisaph. The remaining authors state that they have no relevant financial interests.

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