

# Optimizing Outcomes in Patients With Cardiovascular Disease and Chronic Kidney Disease

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**C**hronic kidney disease (CKD) affects 26 million people in the United States, and another 20 million are at risk of developing CKD.<sup>1,2</sup> Cardiovascular disease (CVD) continues to be the leading cause of death in both men and women in the United States.<sup>3</sup> CKD is an independent risk factor for the development of CVD; therefore, the National Kidney Foundation (NKF), American Heart Association (AHA), and the American College of Cardiology consider it a coronary heart disease (CHD) risk equivalent.<sup>4</sup> In addition, most of the traditional CVD risk factors (eg, diabetes mellitus, hypertension, and dyslipidemia) are highly prevalent in the CKD population.<sup>4</sup> The NKF defines CKD as kidney damage for greater than 3 months, as confirmed by biopsy or markers of damage such as microalbuminuria (with or without a decrease in glomerular filtration rate [GFR]) or a GFR less than 60 ml/min/1.73 m<sup>2</sup> for greater than 3 months.<sup>4</sup> The end-stage renal disease (ESRD) population has a CVD mortality rate 10 to 30 times higher than the general population.<sup>5,6</sup>

Traditional cardiovascular (CV) risk factors (eg, hypertension and dyslipidemia) often occur in high rates in the CKD population, and therefore are logical therapeutic targets in clinical trials.<sup>7,8</sup> In addition, there are many nontraditional risk factors (eg, high homocysteine levels) associated with higher CVD risk in patients with CKD.<sup>9</sup> The focus of this review is on evaluating the clinical trial evidence supporting antihypertensive and lipid-lowering therapy (LLT) in the CKD population to prevent CV outcomes.

## Current US Hypertension and Dyslipidemia Guidelines

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) was published in 2003.<sup>10</sup> These guidelines set a blood pressure target of less than 130/80 mm Hg in patients with CKD. In 2004, the NKF Kidney Disease Outcomes Quality Initiative (NKF KDOQI) group published guideline recommendations for hypertension treatment in the CKD population (which also targeted a blood pressure goal of <130/80 mm Hg).<sup>11</sup> In 2007, the AHA developed a scientific statement on treating hypertension and designated the CKD population as a high coronary artery disease (CAD) risk group and recommended a blood pressure goal of less than 130/80 mm Hg.<sup>12</sup> **Table 1** summarizes

## Abstract

Chronic kidney disease (CKD) is an independent risk factor for the development of cardiovascular disease (CVD). Often, CKD and CVD coexist, and patients warrant optimal pharmacotherapy to reduce the risk of future cardiovascular (CV) events. Randomized trials have evaluated the role of antihypertensive therapy and lipid-lowering therapy as means to reduce CVD in patients with CKD. Many clinical trials support the role of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in the CKD population. In addition, many clinical trials have evaluated the role of statin therapy in reducing CV events in early- and late-stage CKD. The struggle with interpreting results from these trials is that there are a number of different CV composite end points and a lack of consistency in defining CKD, especially in some post hoc subanalyses. Overall, ACEI/ARB therapy is supported by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) hypertension guidelines and statin therapy is supported by the Adult Treatment Panel (ATP) III and NKF KDOQI dyslipidemia guidelines to optimally manage patients with CKD and CV risk factors. Questions remain as to the optimal role of statin therapy in patients with CKD receiving dialysis. JNC 8 and ATP IV guidelines will be available in the next year, and it is expected that there will be specific recommendations on both hypertension and dyslipidemia management in the CKD population.

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For author information and disclosures, see end of text.

■ **Table 1.** National US Guidelines for Managing Hypertension in Chronic Kidney Disease<sup>10-12</sup>

	NKF KDOQI	JNC 7	AHA
	2003	2003	2007
Lifestyle Modifications <sup>a</sup>	All	All	All
ACEI or ARB Preferred	Diabetic kidney disease Nondiabetic kidney disease With spot protein-to-creatinine ratio ≥200 mg/g	All	1st line option in addition to calcium channel blocker or thiazide
BP Goals	<130/80 mm Hg Lower if spot protein-to-creatinine ratio 500-1000 mg/g	<130/80 mm Hg	<130/80 mm Hg

ACEI indicates angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; BP, blood pressure; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

<sup>a</sup>Lifestyle modifications include weight reduction, Dietary Approaches to Stop Hypertension (DASH) diet, dietary sodium restriction, physical activity, and moderation of alcohol consumption.

the blood pressure goals and treatment recommendations for patients with CKD. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are preferred antihypertensive agents in patients with CKD per the NKF KDOQI and JNC 7 guidelines. AHA recommends these agents as first-line options, but does not give specific recommendations for drug therapy in these patients.

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) published recommendations for the management of dyslipidemia in 2001 and an update in 2004.<sup>13,14</sup> In 2003, the NKF KDOQI group published guidelines for the management of dyslipidemia in patients with CKD.<sup>15</sup> **Table 2** summarizes the key recommendations from the NKF KDOQI guidelines. The primary target of dyslipidemia management in patients with CKD is low-density lipoprotein cholesterol (LDL-C). The guidelines recommend an LDL-C target less than 100 mg/dL in patients with CKD (all stages), unless their triglycerides are above 500 mg/dL.

**Cardiovascular Outcome Trials With Antihypertensive Therapy in the CKD Population**

Treatment with antihypertensive therapy to prevent CV outcomes in the CKD population has been investigated in patients with established CVD and diabetes mellitus. Five CVD trials of hypertensive management with ACEI or ARB therapy have focused on patients at high CV risk, with a subanalysis of the patients with CKD. Three other trials in type 2 diabetes mellitus (T2DM) specifically assessed patients with CKD or nephropathy. The focus of this review is on trials which evaluated ACEIs and ARBs as initial or added therapy in patients with CKD. **Table 3** provides a summary of the antihypertensive trials evaluating CV outcomes in the CKD population.

**ACEI Therapy**

The DIABHYCAR (non-insulin-dependent DIABetes, HYpertension, microalbuminuria or proteinuria, Cardiovascular events, and Ramipril) trial was a randomized, double-blind, parallel group, placebo-controlled trial in 4912 patients with T2DM and microalbuminuria or proteinuria who were randomized to ramipril 1.25 mg daily or placebo and followed for 4 years.<sup>16</sup> The primary CV outcome was the composite outcome of CV death, nonfatal myocardial infarction (MI), stroke, heart failure leading to hospital admission, and ESRD. No difference in the primary CV outcome was observed between ramipril and placebo. See Table 3 for complete trial details.

The HOPE (Heart Outcomes Prevention Evaluation),<sup>17</sup> EUROPA (The EUROpean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease),<sup>18</sup> and PEACE (Prevention of Events with ACE inhibition)<sup>19</sup> trials all evaluated patients with established CVD and determined the benefit of ACEI therapy in this population. A post hoc subanalysis of each study evaluated whether CV event reduction occurred in patients with CKD treated with ACEI therapy. The HOPE trial was a randomized, double-blind, placebo-controlled study; data were analyzed from 980 patients with CAD, stroke, peripheral vascular disease, or diabetes plus at least 1 additional CV risk factor and a serum creatinine level of at least 1.4 mg/dL who received ramipril 10 mg daily or placebo and were followed for 5 years.<sup>17</sup> The primary CV outcome was the composite of CV death, nonfatal MI, or stroke. In patients with renal insufficiency, there was a 19.3% primary event rate versus 25.5% in the ramipril and placebo groups, respectively. Patients with renal insufficiency had an increased risk of CV death (11.4% vs 6.6%) and total mortality (17.8% vs 10.6%) (*P* <.001). EUROPA was a randomized, double-blind, placebo-controlled study; data from

■ **Table 2.** National Kidney Foundation Guidelines for Managing Dyslipidemia in Chronic Kidney Disease<sup>15</sup>

Lipid Abnormality	Goal	Initial Therapy	Secondary Therapy	Alternative Therapy
TG $\geq$ 500 mg/dL	TG <500 mg/dL	TLC	TLC + fibrate or niacin	Fibrate or niacin
LDL-C 100-129 mg/dL	LDL-C <100 mg/dL	TLC	TLC + low-dose statin	Bile acid sequestrant or niacin
LDL-C $\geq$ 130 mg/dL	LDL-C <100 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Bile acid sequestrant or niacin
TG $\geq$ 200 mg/dL and non-HDL-C $\geq$ 130 mg/dL	non-HDL-C <130 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Fibrate or niacin

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TLC, therapeutic lifestyle changes. Reprinted with permission from Kidney Disease Outcomes Quality Initiative (KDOQI) Group. *Am J Kidney Dis.* 2003;41(suppl 3):S1-S91.

6295 patients with stable CAD without heart failure and an estimated GFR (eGFR) of less than 75 ml/min/1.73 m<sup>2</sup> were analyzed.<sup>18</sup> Patients were randomized to perindopril 8 mg daily or placebo and followed for an average of 4.2 years. The primary CV outcome was the composite of CV death, nonfatal MI, and resuscitated cardiac arrest. The composite end point occurred in 7.9% versus 10.0% of patients with eGFRs of at least 75 and less than 75, respectively. The PEACE trial was a randomized, double-blind, placebo-controlled study; data from 1355 patients with stable CAD without heart failure and an eGFR less than 60 ml/min/1.73 m<sup>2</sup> were used for the subanalysis.<sup>19</sup> Patients were randomized to trandolapril 4 mg daily or placebo and followed for an average of 4.8 years. The primary CV outcome was the composite of CV death, nonfatal MI, and coronary revascularization. No difference in the primary CV outcome was observed between trandolapril and placebo. Further trial results are located in Table 3.

PROGRESS (Perindopril Protection Against Recurrent Stroke Study) evaluated patients with a history of stroke or transient ischemic attack and determined the benefit of ACEI therapy in this population.<sup>20</sup> Of note, there was a significant lowering of blood pressure by 9/4 mm Hg in the perindopril arm over the 4-year study. The subanalysis used data from 1757 patients with an estimated creatinine clearance (eCrCl) less than 60 ml/min who were randomized to perindopril 4 mg daily or placebo for 4 years. The primary CV outcome was fatal and nonfatal stroke, but the composite outcome of CV death, nonfatal MI, or stroke was also evaluated. In patients with an eCrCl less than 60 ml/min there was a 30% relative risk reduction with perindopril versus placebo in the CV composite outcome.

### ARB Therapy

HIJ-CREATE (Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease) was a randomized, double-blind, placebo-controlled study; data from 1025 patients with CAD and hypertension and an eCrCl less than 60 ml/min were included in the subanalysis.<sup>21</sup> Patients were randomized to candesartan 4 mg

to 12 mg daily or placebo and followed for an average of 4.2 years. The primary CV outcome was the composite of CV death, nonfatal MI, unstable angina, heart failure, stroke, and CV events requiring hospitalization. An 11% lower rate in the composite CV outcome was observed with candesartan versus placebo. There was also a lower rate of hospitalization for unstable angina in patients with CKD given candesartan compared with those given placebo.

IDNT (Irbesartan Diabetic Nephropathy Trial) was a randomized, double-blind, placebo-controlled study; data from 1715 patients with T2DM and nephropathy (defined as a urinary albumin to creatinine ratio [UACR] greater than 900) were used in the subanalysis.<sup>22</sup> Patients were randomized to irbesartan 300 mg, amlodipine 10 mg, or placebo daily and followed for 2.6 years. The primary CV outcome was the composite of CV death, MI, congestive heart failure, stroke, and coronary revascularization. There was no difference in the primary CV outcome among irbesartan, amlodipine, and placebo. RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) was a randomized, double-blind, placebo-controlled trial; data from 1513 patients with T2DM with nephropathy (defined as a UACR greater than 300) who received losartan 50 mg or 100 mg daily or placebo for an average of 3.4 years were analyzed.<sup>23</sup> The primary CV outcome was the composite of fatal or nonfatal CV events. There was no significant difference in the CV composite event rates between losartan and placebo (32.9% and 35.2%, respectively [ $P = .26$ ]).

### Cardiovascular Outcome Trials With Lipid-Lowering Therapy in the CKD Population

Treatment with LLT to prevent CV outcomes in the CKD population has been investigated in trials with patients with established CVD or diabetes mellitus. Three Cochrane reviews of statin use in patients with CKD not requiring dialysis, those requiring dialysis, and kidney transplant recipients showed a significant reduction in composite CV end points only in the non-dialysis CKD population (ie,

**Table 3.** Antihypertensive Trials Targeted to Reduce Cardiovascular Outcomes in Patients With Chronic Kidney Disease<sup>16-23</sup>

Study	Population	Design (n)	Primary End Point	Duration (years, mean)	Treatment	RR/HR (95% CI)
<b>ACEI Trials</b>						
DIABHYCAR <sup>16</sup>	T2DM + UACR >20 mg/L + SCr <2.0 mg/dL	RCT (4912)	CV death, MI, stroke, HF hospitalization, ESRD	3.9	Ramipril 1.25 mg/day vs placebo	0.97 (0.85-1.11)
EUROPA <sup>18</sup>	CAD + eGFR <75	RCT subanalysis (6295)	CV death, MI, resuscitated cardiac arrest	4.2	Perindopril 8 mg/day vs placebo	0.84 (0.72-0.98)
HOPE <sup>17</sup>	>55 y/o + CAD, stroke, PVD, or DM + ≥1 CV RF + CrCl ≤65	RCT subanalysis (980)	CV death, MI, stroke	5.0	Ramipril 10 mg/day vs placebo	0.75 (0.64-0.89)
PEACE <sup>19</sup>	CAD + eGFR <60	RCT subanalysis (1355)	CV death, MI, coronary revascularization	4.8	Trandolapril 4 mg/day vs placebo	1.18 (0.98-1.42)
PROGRESS <sup>20</sup>	Cerebrovascular disease + CrCl <60	RCT subanalysis (1757)	CV death, CHD, stroke	4.0	Perindopril 4 mg/day +/- indapamide vs placebo	0.70 (0.58-0.86)
<b>ARB Trials</b>						
HIJ-CREATE <sup>21</sup>	CAD + HTN + CrCl <60	RCT subanalysis (1022)	CV death, MI, stroke, hospitalization for HF, UA, or CV event	4.2	Candesartan 4-12 mg/day vs non-ARB therapy	0.79 (0.63-0.99)
IDNT <sup>22</sup>	T2DM + nephropathy + SCr (1.0-3.0 mg/dL) + BP >135/85	RCT (1715)	CV death, MI, CHF, stroke, coronary revascularization	2.6	Irbesartan 300 mg/day vs amlodipine 10 mg/day vs placebo	0.90 (0.74-1.10) irbesartan vs placebo 1.00 (0.83-1.21) amlodipine vs placebo 0.90 (0.74-1.10) irbesartan vs amlodipine
RENAAL <sup>23</sup>	T2DM + nephropathy + SCr (1.3-3.0 mg/dL)	RCT (1513)	CV death, MI, stroke, hospitalization for HF or UA, coronary or peripheral revascularization	3.4	Losartan 50 mg or 100 mg/day vs placebo in addition to standard antihypertensive treatment at baseline	0.90 (CI not reported)
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; HTN, hypertension; MI, myocardial infarction; PVD, peripheral vascular disease; RCT, randomized controlled trial; RF, risk factor; RR, relative risk; SCr, serum creatinine; T2DM, type 2 diabetes mellitus; UA, unstable angina; UACR, urine albumin to creatinine ratio.						

those not receiving dialysis or having undergone a kidney transplant).<sup>24,26</sup> LLT trials focusing on CVD event reduction in early- to late-stage CKD are reviewed in **Table 4**.

**Statin Therapy**

*Patients Not Requiring Dialysis*

PREVEND IT (Prevention of Renal and Vascular End Stage Disease Intervention Trial) was a randomized, double-blind, placebo-controlled study in 1439 patients with microalbuminuria and an eGFR of at least 60 ml/min/1.73 m<sup>2</sup> who

were randomized to pravastatin 40 mg daily or placebo and followed for an average of 3.8 years.<sup>27</sup> The primary CV composite outcome in this trial was CV death, hospitalization for stroke, unstable angina, or arterial revascularization. A non-significant 13% reduction in the CV event rate was observed in the pravastatin treatment arm versus placebo (*P* = .649).

Four post hoc subanalyses of the major statin trials, ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm),<sup>28</sup> CARE (Cholesterol And Recurrent Events),<sup>29</sup> HPS (Heart Protection Study),<sup>30</sup> and JUPITER

**Table 4.** Lipid-Lowering Therapy Trials Targeted to Reduce Cardiovascular Outcomes in Patients With Chronic Kidney Disease<sup>27-37</sup>

Study	Population	Design (n)	Primary End Point	Duration (years, mean)	Treatment	HR/RR (95% CI)
<b>Statin Trials (patients not requiring dialysis)</b>						
ASCOT-LLA <sup>28</sup>	HTN + renal dysfunction	RCT subanalysis (6517)	CV death, nonfatal MI	3.3	Atorvastatin 10 mg/day vs placebo	0.61 (0.44-0.84)
CARE <sup>29</sup>	CHD + eGFR <75	RCT subanalysis (1711)	CV death, symptomatic nonfatal MI	4.9	Pravastatin 40 mg/day vs placebo	0.72 (0.55-0.95)
HPS <sup>30</sup>	CHD, DM, or other CVD + ↑ SCr <sup>a</sup>	RCT subanalysis (1329)	Death, major vascular event	5.0	Simvastatin 40 mg/day vs placebo	0.72 (0.56-0.82)
JUPITER <sup>31</sup>	Male >50 years old or female >60 years old + LDL-C <130 mg/dL + hsCRP ≥2 mg/dL + eGFR <60	RCT subanalysis (3267)	CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or arterial revascularization	1.9	Rosuvastatin 20 mg/day vs placebo	0.55 (0.38-0.82)
PREVEND IT <sup>27</sup>	Microalbuminuria <sup>b</sup> + eGFR ≥60	RCT (1439)	CV death, hospitalization	3.8	Pravastatin 40 mg/day vs placebo	0.87 (0.49-1.57)
SHARP <sup>32</sup>	Pre-dialysis, HD or PD	RCT (6247 pre-dialysis and 3023 dialysis)	CV death, nonfatal MI, fatal or nonfatal stroke, or revascularization	4.4	Simvastatin 20 mg/day + ezetimibe 10 mg/day vs placebo	0.84 (0.75-0.93)
<b>Statin Trials (dialysis)</b>						
4D <sup>33</sup>	T2DM + chronic HD	RCT (1255)	CV death, fatal stroke, nonfatal MI, or nonfatal stroke	4.0	Atorvastatin 20 mg/day vs placebo	0.92 (0.77-1.10)
AURORA <sup>34</sup>	Chronic HD	RCT (2776)	CV death, nonfatal MI, or nonfatal stroke	3.8	Rosuvastatin 10 mg/day vs placebo	0.96 (0.84-1.11)
<b>Statin Trials (kidney transplant)</b>						
ALERT <sup>35</sup>	Kidney transplant recipient	RCT (2102)	CV death, nonfatal MI, CV procedure	5.0	Fluvastatin 40-80 mg/day vs placebo	0.83 (0.64-1.06)
<b>Other Lipid-Lowering Therapy Trials</b>						
VA-HIT <sup>36</sup>	CHD + CrCl ≤75 ml/min	RCT subanalysis (1046)	CV death, nonfatal MI	5.0	Gemfibrozil 1200 mg/day vs placebo	0.73 (0.56-0.96)
OPACH <sup>37</sup>	CHD + chronic HD	RCT (206)	Total CV events and all-cause death	2.0	Omega-3 PUFA 1.7 g/day vs placebo	1.03 (0.72-1.48)

CHD indicates coronary heart disease; CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; RR, relative risk; PD, peritoneal dialysis; SCr, serum creatinine; T2DM, type 2 diabetes mellitus.

<sup>a</sup>Serum creatinine in the range of 1.3-2.3 mg/dL.

<sup>b</sup>Urinary albumin concentration >10 mg/L in 1 early morning spot urine sample and a concentration of 15 to 300 mg/24 hours in two 24-hour urine samples at least once.

(Justification for the Use of statins in primary Prevention: an Intervention Trial Evaluating Rosuvastatin)<sup>31</sup> were performed in the CKD population. In all trials, significantly lower CV composite end points were observed with statins compared

with placebo. The ASCOT-LLA trial included 6517 patients with hypertension and reduced GFR at baseline and showed a 39% relative risk reduction (RRR) in CV death and nonfatal MI with atorvastatin 10 mg daily versus placebo ( $P = .0025$ )

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at 3.3 years.<sup>28</sup> The CARE trial included 1711 patients with CHD and an eGFR of 75 ml/min/1.73 m<sup>2</sup> or less; pravastatin 40 mg daily was associated with a 28% RRR in CV death and nonfatal MI versus placebo ( $P = .02$ ) at 4.9 years.<sup>29</sup> HPS included 1329 patients with CHD, diabetes, or other occlusive arterial disease and serum creatinine levels between 1.3 and 2.3 mg/dL.<sup>30</sup> The study showed a 28% RRR in all-cause mortality and major CV events with simvastatin 40 mg daily compared with placebo ( $P < .05$ ) at 5.0 years. The most recent subanalysis was from JUPITER.<sup>31</sup> This trial included 3267 patients with an LDL-C level less than 130 mg/dL, a high-sensitivity C-reactive protein level greater than 2 mg/L, and an eGFR  $<60$  ml/min/1.73 m<sup>2</sup>. Rosuvastatin 10 mg daily showed a 45% RRR in composite of CV death, nonfatal MI, stroke, hospitalization for unstable angina, and arterial revascularization versus placebo ( $P = .002$ ) at 1.9 years.

Based on the numerous results from subanalyses of data from major statin trials, there was a need to perform a large prospective trial in patients with CKD. The SHARP trial was a randomized, double-blind, placebo-controlled study in 9270 patients (6247 not requiring dialysis and 3023 on hemodialysis [HD] or peritoneal dialysis) without a history of MI or coronary revascularization.<sup>32</sup> Patients were randomized to simvastatin/ezetimibe 20 mg/10 mg daily or placebo and were followed for 4.9 years. The prespecified primary CV composite was CV death, nonfatal MI, nonhemorrhagic stroke, or arterial revascularization. During the study, the steering committee changed the primary CV composite to coronary death, nonfatal MI, nonhemorrhagic stroke, or arterial revascularization. Simvastatin/ezetimibe 20 mg/10 mg daily was associated with a 17% RRR in the revised CV composite versus placebo ( $P = .002$ ) in the entire patient population. This was the first large prospective trial to show significant reductions in CV events with statins in a pure CKD population.

### Dialysis

4D (Deutsche Diabetes Dialyse Studie) was a randomized, double-blind, placebo-controlled trial in 1255 patients with T2DM receiving HD who were randomized to atorvastatin 20 mg daily or placebo for 4 years. The primary CV composite was CV death, nonfatal MI, or stroke. There was not a significant difference in the primary CV composite among atorvastatin and placebo (hazard ratio [HR] 0.92 [0.77-1.11],  $P = .37$ ).<sup>33</sup> Atorvastatin was associated with a significant reduction in all CV events (secondary end point) compared with placebo (HR 0.82 [0.68-0.99],  $P = .03$ ). This secondary composite end point was mainly driven by the increased need for coronary artery bypass grafting and percutaneous transluminal coronary angioplasty in the placebo group.

AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) was a randomized, double-blind, placebo-controlled trial in 2755 patients receiving chronic HD who were randomized to rosuvastatin 10 mg or placebo daily and followed for an average of 3.8 years.<sup>34</sup> The primary CV composite outcome was CV death, nonfatal MI, or nonfatal stroke. No significant differences were observed among rosuvastatin and placebo in the primary CV end point (HR 0.96 [0.84-1.11],  $P = .59$ ).<sup>34</sup>

A subanalysis of results from the SHARP trial used data from 3023 patients receiving HD or peritoneal dialysis.<sup>32</sup> The study was not powered to make comparisons among those who received dialysis and those who did not. However, when evaluating the CV outcome of coronary death, nonfatal MI, non-hemorrhagic stroke, or arterial revascularization in dialysis patients, there was not a significant difference between simvastatin/ezetimibe 20 mg/10 mg and placebo. In the dialysis subgroup, simvastatin/ezetimibe 20 mg/10 mg daily resulted in a nonsignificant RRR compared with placebo (RR 0.90 [0.75-1.08]). These results, along with those from the 2 other HD trials previously discussed, have left questions about the CV event-lowering benefits of statin treatment in dialysis patients.

### Kidney Transplant

The ALERT (Assessment of Lescol in Renal Transplant) trial was a randomized, double-blind, placebo-controlled trial in 2102 kidney transplant patients who were randomized to fluvastatin 40 to 80 mg/day or placebo for 5 years.<sup>35</sup> The primary CV composite was CV death, nonfatal MI, or coronary intervention. A nonsignificant 17% RRR in the CV composite was observed in the fluvastatin treatment arm versus placebo ( $P = .139$ ). However, there was a significant RRR (35%) in the composite of CV death and nonfatal MI in the fluvastatin group compared with placebo ( $P = .005$ ).

### Non-Statin Lipid-Lowering Therapy

VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial) was a double-blind, placebo-controlled trial in which patients were randomized to receive gemfibrozil 1200 mg or placebo daily and followed for 5 years. In a subanalysis, data from 1046 patients with CHD and an eCrCl less than 75 ml/min were assessed.<sup>36</sup> The primary CV composite was CV death and nonfatal MI. A significant 27% RRR in the CV composite end point was observed in the gemfibrozil treatment arm versus placebo ( $P = .02$ ).

The OPACH (Omega-3 Fatty Acids as Secondary Prevention Against Cardiovascular Events in Patients Who

Undergo Chronic Hemodialysis) trial was a randomized, double-blind, placebo-controlled study in 206 patients with CHD receiving HD.<sup>37</sup> Patients were randomized to receive 1.7 g of omega-3 fatty acids or placebo daily for 2 years. The primary CV composite outcome was all-cause mortality and CV events. There was no significant difference in the primary end point between treatment and placebo (HR 1.03 [0.72-1.48]).

### Other Therapies

No trials evaluating CV morbidity and mortality as a primary end point with niacin or bile acid sequestrants have been conducted in the CKD population. These LLTs have been studied in clinical trials where patients with CKD were included, but no subanalyses in this population have been published. As noted in the KDOQI 2003 guidelines, there are roles for these therapies based on the lipid abnormality.

### Discussion

Among antihypertensive medications, ACEI and ARB therapy has the most prospective trial data evaluating CV outcome benefit in the CKD population. There are reasons to use ACEI or ARB therapy beyond preventing CV events (eg, delaying progression of nephropathy), and these need to be considered when determining optimal medical therapy in patients with CKD. Antihypertensive guideline recommendations from JNC 7, NKF KDOQI, and AHA should be followed as they relate to hypertension target goals and preferred treatment options in the CKD population.<sup>10-12</sup> Recent data from the National Health and Nutrition Examination Surveys (NHANES) 1999-2004 indicate that only 34% and 37% of patients with stage 3 to 4 CKD without and with established CVD, respectively, were at their target blood pressure goal of less than 130/80 mm Hg.<sup>38</sup> These numbers are alarming given the many CV and non-CV benefits known to occur with optimal blood pressure management. In addition, only 28% and 44% of patients with stage 3 to 4 CKD without and with CVD, respectively, were on ACEI or ARB therapy in the NHANES data.<sup>38</sup> The Eighth Report of the JNC (JNC 8) is highly anticipated and is scheduled to be published in 2012.<sup>39</sup>

Statin therapy has been shown to reduce CV events across a broad range of patients, from those with early CKD to those post kidney transplant. Most positive CV event-lowering data were observed in patients with CKD not requiring dialysis. Questions remain about the benefit of statin therapy in the dialysis population. The recent SHARP study has shown that benefits in the CKD population can occur by targeting a lower LDL-C level than US guidelines currently recommend. The SHARP study achieved a mean LDL-C level of 75 mg/

dL at a median of 4.4 years.<sup>32</sup> Results with this low LDL-C level help support a lower LDL-C goal of less than 100 mg/dL, as recommended by the ATP III and NKF KDOQI guidelines.<sup>13,15</sup> Recently, the European Society of Cardiology and the European Atherosclerosis Society published updated guidelines on the management of dyslipidemia.<sup>40</sup> In this update, patients with CKD are considered at very high risk of CV events and an LDL-C goal of less than 70 mg/dL is recommended.<sup>40</sup>

In the NHANES survey, only 22% and 55% of patients with stage 3 or 4 CKD without and with CVD, respectively, were on LLT.<sup>38</sup> The new ATP IV guidelines are scheduled to be published in 2012 and are highly anticipated given the recent study findings of the SHARP trial and the potential for a more aggressive LDL-C target in the CKD population.<sup>41</sup>

### Conclusions

Evidence has demonstrated that antihypertensive therapy and statin therapy significantly reduce major CV events in patients with CKD with or without established CVD. The struggle with interpreting these trial results is that there are a number of different CV composite end points and a lack of consistency in defining CKD, especially in some of the post hoc subanalyses. Cardiovascular event reductions with antihypertensive therapy have been confirmed with ACEI and ARB therapy in the CKD population. ACEI and ARB therapy is supported by JNC 7 and NKF KDOQI hypertension guidelines. Statin therapy has shown significant reductions in CV events across most stages of CKD, but questions still remain as to the optimal role of statin therapy in patients with CKD receiving dialysis. JNC 8 and ATP IV guidelines will be out in the next year, and it is expected that there will be specific recommendations on hypertension and dyslipidemia management in the CKD population.

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