as dogs. In its virulent forms, leptospirosis may lead to liver failure, renal failure, severe pulmonary hemorrhage, myocarditis, and death. In 2012, the Dominican Republic's Minister of Agriculture died of leptospirosis. Even today, 5% to 10% of patients with leptospirosis in the Caribbean may die from the disease.

Some patients may present with flu-like symptoms, but others patients may be relatively asymptomatic or have insidious symptoms making the onset difficult to discern. When patients present with fewer than 8 days of symptomatology, Dr. Resiere recommends a polymerase chain reaction (PCR) test for diagnosis; this has been available in Martinique since 2006.

If leptospirosis is diagnosed, physicians should evaluate for new LV systolic dysfunction (ejection fraction <50%) as the complication of myocarditis can be devastating. In patients presenting with cardiogenic shock, mortality approaches 40%. Practioners evaluating patients with leptospirosis should also have a high degree of suspicion for meningitis, encephalitis, and other neurological manifestations, which occur in 5% to 10% of patients.

Treatment of leptospirosis includes not only antibiotics but supportive therapy (eg, including fluid and electrolyte regulation) and monitoring for new complications.

To evaluate cases of leptospirosis in a single institution, Dr. Resiere and colleagues conducted a retrospective analysis, looking at data from 82 patients admitted to University Hospital in Martinique, 29% of whom were admitted prior to the institution of PCR tests for diagnosis, from 2001 to 2006, and 63% of whom were admitted between 2006 and 2010. Of 32 patients admitted to the intensive care unit for leptospirosis, the most frequent abnormal vital sign was tachycardia. He also noted that <10 of the 20 patients admitted to the hospital with this diagnosis after 2006 required intensive care [Mehdaoui H et al. *Critical Care* 2012].

Greater awareness could vastly reduce the mortality associated with leptospirosis in the Caribbean improving the timing of diagnosis and early institution of care. Physicians should carefully consider leptospirosis in those presenting with symptoms. For those with symptoms <8 days, the physician should perform a PCR test for the early diagnosis of leptospirosis, if available. In cases where leptospirosis has been confirmed, the physician should not merely prescribe antibiotic and supportive therapy, but should evaluate for cardiac involvement as myocarditis is associated with high mortality rate and requires specialized care.

CKD, CVD, and Lipids: Insights From the SHARP Trial

Written by **Mary Mosley**

Robert P. Giugliano, MD, SM, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA, discussed the relationship between chronic kidney disease (CKD) and cardiovascular disease (CVD), and provided an overview of the SHARP trial, the largest study of lipid-lowering therapy in patients with CKD and CVD.

The National Kidney Foundation (NKF) defines CKD as kidney damage for ≥3 months with structural or functional abnormalities of the kidney, manifested either on pathology, or by clinical markers of kidney damage (eg, elevated creatinine). The patient may have a reduced glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 months as well. In the United States, the vast majority of CKD patients are equally split between NKF Stages 1, 2, and 3 (GFR >90, 60 to 89, and 30 to 59 mL/min/1.73 m^2, respectively), with only ~0.3% falling into Stages 4 and 5 (GFR of 15 to 29 and <15 mL/min/1.73 m^2, respectively).

Diabetes and hypertension are the traceable causes of CKD in about two thirds of cases in the United States [http://www.kidney.org/kidneydisease/aboutckd.cfm. Accessed August 22, 2013]. Renal disease itself raises CV risk, and the severity of CKD is associated with the severity of CV risk.

According to data from the Kaiser Permanente Renal Registry of 1,120,295 adults, kidney function showed a linear increase in the adjusted risk of any CV event as the estimated GFR (eGFR) decreased [Go AS et al. *N Engl J Med* 2004].

The link between CKD and CV death is even stronger, with exponential increases in risk.

A GFR of 60 is associated with a 2-fold risk of CV death, while a GFR of 30 carries a 4-fold increase in risk. There is a 10- to 30-fold increased risk in patients on dialysis.

AGGRESSIVE LIPID LOWERING IN CKD

The results of three different observational studies have suggested that patients with CKD should receive aggressive lipid-lowering therapy. The US Renal Data System Morbidity and Mortality Wave 2 study reported a 36% reduction in CV death (RR, 0.64; 95% CI, 0.45 to 0.91) in the 9.7% of patients on a statin [Seliger SL et al. *Kidney Int* 2002]. The prospective, observational Dialysis Outcomes and Practice Patterns Study from dialysis centers across seven countries showed a significant 23% reduction in cardiac mortality (p=0.03) in the 11.8% of patients taking a statin [Mason NA et al. *Am J Kidney Dis* 2005]. Finally, the Pravastatin Pooling Project, a meta-analysis of clinical trials with pravastatin versus placebo, found a reduction in the composite of coronary heart disease death, myocardial infarction (MI), or revascularization (HR, 0.77; 95% CI, 0.68

to 0.86) and a decrease in total mortality (HR, 0.86; 95% CI, 0.74 to 1.00; p=0.045) in 4991 patients with Stage 3 CKD [Tonelli M et al. *Circulation* 2004]. Although the results from each study were hypothesis-generating, Dr. Giugliano maintained that they did not provide definitive evidence.

However, two double-blind, placebo-controlled clinical trials of statin therapy in patients with CKD have been conducted. The 4D study of 1255 diabetic patients (aged 18 to 80 years) on dialysis <2 years showed a 42% reduction in low-denisity lipoprotein cholesterol (LDL-C) with atorvastatin 20 mg daily, but demonstrated no significant difference for the primary outcome of cardiac death, MI, or stroke at 4 years (RR, 0.92; 95% CI, 0.77 to 1.10; p=0.37) [Wanner C et al. *N Engl J Med* 2005]. The AURORA study also showed a reduction in LDL-C, by 43% with rosuvastatin 10 mg, but there was no significant reduction in the primary endpoint of CV death, MI, or stroke at 4 years (HR, 0.96; 95% CI, 0.84 to 1.11; p=0.59) [Fellström BC et al. *N Engl J Med* 2009]. The AURORA study patients, with or without diabetes, were older on average (aged 50 to 80 years) and had been on dialysis >3 months. There were no significant differences for any of the individual endpoints in either study.

THE SHARP TRIAL OF LIPID-LOWERING IN CKD

The Study of Heart and Renal Protection [SHARP] evaluated a broader population of CKD patients [SHARP Collaborative Group. *Am Heart J* 2010]. Only about one third of patients were on dialysis. Eligible patients were aged ≥40 years, had CKD, had an elevated creatinine on at least two occasions (if not receiving dialysis; men ≥1.7 mg/dL; women ≥1.5 mg/dL), and had no history of MI or coronary revascularization. Equipoise was required, as LDL-lowering treatment was not indicated, nor was it contraindicated.

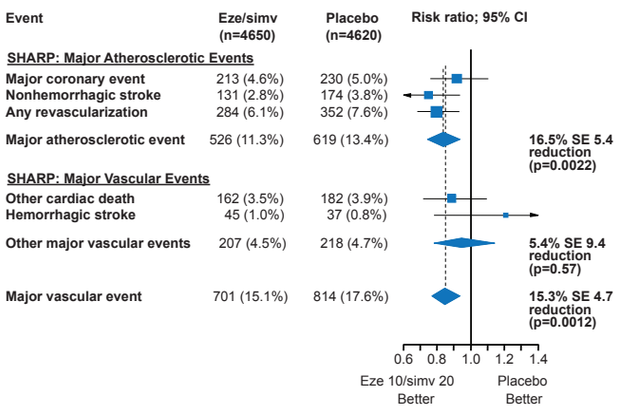
Patients were randomized to a combination of ezetimibe 10 mg plus simvastatin 20 mg daily (eze/simv; n=4193) or placebo (n=4191). For 1 year, 1054 patients received simvastatin 20 mg daily alone to assess safety, and were then randomized to eze/simv. The final analysis included 4650 patients on eze/simv and 4620 patients on placebo at a median follow-up of 4.9 years.

The study population was typical for moderate to severe renal disease. They had a mean age of 62 years, and were mildly hypertensive (139/79 mm Hg) and overweight (body mass index 27 kg/m^2). Of the 6247 patients not on dialysis, the mean eGFR was 27 mL/min/1.73 m^2 and 80% had albuminuria. Women comprised 37% of the study population.

The primary outcome—major atherosclerotic events (coronary death, MI, nonhemorrhagic stroke, or any revascularization)—was significantly reduced with eze/simv compared with placebo (HR, 0.83; log-rank 2-sided p=0.0022) [Baigent C et al. *Lancet* 2011]. The events accrued at a very stable pace of about 3% to 4% per year.

Among the treatment group, consistent effects were seen across all primary and subsidiary outcome measures, including major vascular events (overall reduction of 15.3%; p=0.0012; Figure 1). Howevr, there was no effect on hemorrhagic stroke.

Figure 1. Results for the Primary Outcome and Major Vascular Events in SHARP

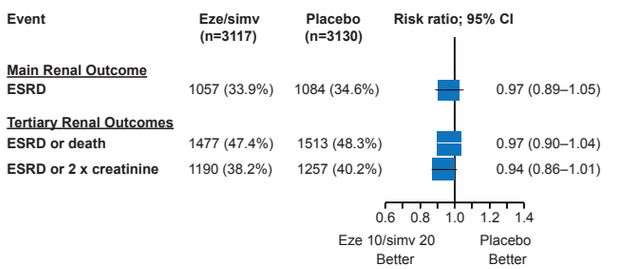


Eze/simv=ezetimibe 10 mg plus simvastatin 20 mg daily.

Reproduced from Baigent C et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;377(9784):2181-2192. With permissionfrom Elsevier.

Eze/simv did not affect renal function, regardless of dialysis status, as measured by end-stage renal disease (ESRD), ESRD or death, or ESRD or a 2-fold increase in creatinine (Figure 2). No statistical heterogeneity was found between dialysis and nondialysis patients (p=0.25).

Figure 2. Renal Outcomes in the SHARP Study



Eze/simv=ezetimibe 10 mg plus simvastatin 20 mg daily.

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There were no significant differences in safety outcomes between the two groups, and there were no signals of cancer (HR, 0.99; 95% CI, 0.87 to 1.13; log-rank 2-sided p=0.89).

Adherence to the eze/simv regimen was maintained by about two thirds of patients. The study investigators calculated that full adherence with eze/simv would reduce the risk of the primary outcome by 25%, avoiding 30 to 40 events for every 1000 patients treated over 5 years.

Dr. Giugliano noted that the results of the IMPROVE-IT study [NCT00202878], expected to be available in late 2014, should provide further evidence about the benefits of adding ezetimibe to a statin. The study is comparing eze/simv 10/40 mg and simvastatin 40 mg in patients with recent acute coronary syndrome.

First Caribbean Experience: Abbott's Experimental Bioresorbable Stent

Written by John Otrompke

The first Caribbean studies to examine the performance of Abbott's experimental bioresorbable vascular scaffold (BVS) indicate that the device is feasible to be used in clinical practice, according to a presentation by Ingrid Valdez, MD, Los Centros de Diagnóstico y Medicina Avanzada y de Conferencias Médicas y Telemedicina (CEDIMAT), Santo Domingo, Dominican Republic.

As of July 2013, eight patients in the Dominican Republic, who are the first in the Caribbean to receive the device for use, have been treated with the bioresorbable stents. Dr. Valdez presented data from the first five patients for whom 30-day follow-up is available.

Bioresorbable stents are absorbed by the vessel wall over time and evidence of the coronary stent disappears. Thus, it is possible that the normal vascular functions of the vessel can be restored once the stent is absent. The results presented demonstrated the use of the experimental device in four men and one woman. The patients were aged between 39 and 75 years, and all had multivessel coronary artery disease. Dyslipidemia was the most frequent risk factor and was found in 80% of the patients. Hypertension was present in 60% of the patients, and 20% of the patients had diabetes. Ongoing tobacco abuse was present in 20%. Additional angiographic characteristics are outline in Table 1.

For most patients, it was necessary to use more than one device of varying diameters to cover the entire lesion (Figure 1). In one patient, there was one complication: a perforation caused by the guidewire during the predilation phase. In that case, Dr. Valdez noted, physicians performed a double coil implantation, and then successfully performed the remainder of the stenting procedure.

Table 1. Angiographic Characteristics

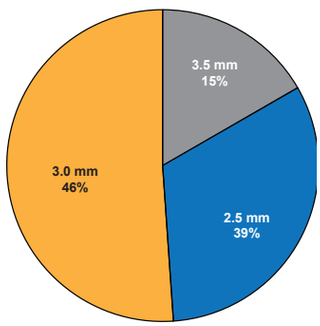
5/5 MVD	3/5 PCI <6 months
3/5 Severe calcification	2/5 Previous AMI
5/5 Diffuse LAD disease	3/5 Guided by IVUS
4/5 SYNTAX score >23	5 Bifurcations
1/5 SYNTAX score >33*	100% Device success
5/5 LAD was treated	100% Procedure success

AMI=acute myocardial infarction; IVUS=intravascular ultrasound; LAD=left anterior descending; MVD=microvascular disease; PCI=percutaneous coronary intervention.

*Discussed by the heart team and rejected for bypass, because of bad beds.

Figure 1. Number of BVSs Used

Case Number	Total Number of BVS	Diameters of BVS 2.5 mm	3.0 mm	3.5 mm
1	2	1	1	0
2	3	0	3	0
3	3	2	1	0
4	2	1	0	1
5	3	1	1	1



BVS=bioresorbable vascular scaffold.

Reproduced with permission from I Valdez, MD.

Like the XIENCE V which is a drug-eluting stent using a traditional scaffold, the Abbott BVS serves as a vehicle for everolimus. The efficacy of everolimus with stenting for reducing restenosis has demonstrated in trials of the XIENCE V stent. The delivery platform of the Abbot BVS is the same as the XIENCE V. Although the biosorbable scaffold is not yet approved by the United States Food and Drug Administration, 12-month data from the Spirit I, II, and III trials in more than 2000 patients have demonstrated bioresorbable stents to be noninferior to the Xience V (MACCE at 12 months) [Serruys PW et al. *Eurointervention* 2005, 2006; Stone GW et al. *JAMA* 2008].

Initial experience with the Abbott BVS demonstrate that implantation is possible even in some complex cases. Thus, these results from the first-ever trials of the device in the Caribbean are consistent with prior studies that have found use of the bioresorable devices to be feasible. Further studies are needed to better understand the long-term clinical outcomes in patients treated with bioresorbable stents.