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Impact of Chronic Renal Insufficiency on Clinical Outcomes in Patients Undergoing Saphenous Vein Graft Intervention With Drug-Eluting Stents: A Multicenter Southern Californian Registry

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Objectives: To evaluate the clinical outcomes in patients with chronic renal insufficiency (CRI) who undergo saphenous vein graft (SVG) intervention with drug-eluting stents (DES). Background: Patients with CRI have higher rates of major adverse cardiac events (MACE) after percutaneous revascularization. SVG intervention is associated with increased rates of MACE compared with percutaneous revascularization of native arteries. However, the impact of CRI on SVG intervention with DES has not been well delineated. Methods: Consecutive patients who underwent SVG intervention with DES at five medical centers from April 2003 to December 2007 were included in this analysis. Results: A total of 172 patients, 39 patients with CRI and a serum creatinine $\geq$1.5 mg dL^{-1}, and 133 patients without CRI, underwent SVG intervention with DES. Patients with CRI were more often older, diabetic, and had a longer mean total stent length. At 1 year, patients with CRI had a higher MACE rate (35.9% vs. 15.8%, hazard ratio [HR] 2.48, 95% confidence interval [CI] 1.26–4.88, log rank $P = 0.009$), mainly driven by higher mortality (20.5% vs. 9.8%, HR 3.41, 95% CI 1.10–10.58, log rank $P = 0.024$). There was a trend toward higher rates of target vessel revascularization in the CRI group (21.8% vs. 10.3%, HR 2.42, 95% CI 0.94–6.24, log rank $P = 0.059$). Stent thrombosis rates were not different between patients with and without CRI (2.6% vs. 2.3%, $P = 0.8$). Multivariable analysis revealed that CRI was the only significant predictor of 1-year MACE (HR 2.2, 95% CI 1.1–4.3; $P = 0.03$). Conclusions: Patients with CRI who underwent SVG intervention with DES had higher risks of MACE and death compared with patients with preserved renal function. Further treatment strategies are needed in this high-risk group who undergo SVG intervention with DES. © 2010 Wiley-Liss, Inc.

Key words: drug-eluting stent; renal insufficiency; saphenous vein graft

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INTRODUCTION

Saphenous vein grafts (SVG) degenerate over time due to the development of large, lipid-rich, soft, and friable plaque comprised of necrotic debris, cholesterol crystals, foam cells, blood elements, and often thrombus. Approximately 50% of SVG develop significant stenosis and 40% are occluded by 5–10 years after coronary artery bypass graft surgery [1–7].

SVG intervention is associated with worse short- and long-term clinical outcomes, including a higher incidence of in-stent restenosis, when compared to percutaneous coronary intervention of native vessels [8–10]. Cellular hyperplasia, local inflammatory reaction to stent struts, thrombosis and progression of atherosclerosis outside the stented area may account for the high restenosis rates observed after SVG intervention [11–13]. Similarly, patients with chronic renal insufficiency (CRI) have higher rates of major adverse cardiac events after percutaneous coronary intervention compared with patients with normal renal function [14–17].

Drug-eluting stents (DES) significantly reduce the rate of in-stent restenosis and the need for repeat revascularization in patients with relatively simple native coronary artery lesions [18–20]. However, most randomized trials have excluded patients with SVG disease. Furthermore, the impact of CRI in patients undergoing SVG intervention with DES is unclear. Therefore, this study was undertaken to assess the impact of CRI on cardiovascular outcomes in patients undergoing SVG intervention with DES.

METHODS

Study Patients

This multicenter retrospective analysis included consecutive patients who underwent SVG intervention with Cypher (Cordis, Miami Lakes, FL) and Taxus stents (Boston Scientific, Minneapolis, MN) from April 2003 to December 2007 at UCLA Medical Center (Los Angeles, CA) (82 patients), Harbor-UCLA Medical Center (Torrance, CA) (20 patients), UCSD Medical Center (San Diego, CA) (18 patients), VA San Diego Healthcare System (San Diego, CA) (28 patients), and Santa Barbara Cottage Hospital (Santa Barbara, CA) (24 patients). The Institutional Review Board approved the analysis of this database.

Percutaneous Coronary Intervention

Standard techniques for SVG intervention were used. The choice of anticoagulation (unfractionated heparin or bivalirudin), use of glycoprotein IIb/IIIa antagonists, the decision to predilate or postdilate the lesions, use adjunctive intravascular ultrasound (Boston Scientific Corp.), use of intra-aortic balloon counterpulsation, use of distal embolic protection device, and the decision to use Cypher or Taxus stents were at the discretion of the operators. All patients received aspirin 81 or 325 mg a day^{-1} indefinitely. Clopidogrel at a dose of 75 mg daily was administered for at least 3–6 months after a loading dose of 300 or 600 mg. Routine measurements of cardiac enzymes (creatine kinase and CK-MB) were not performed unless there was clinical suspicion of myocardial ischemia.

Data Collection and Follow-Up

Baseline characteristics and clinical events were obtained from prospectively collected databases, procedural medical records, and outpatient clinic notes of referring physicians. Follow-up angiography was performed when clinically indicated.

End Points

The primary end point was major adverse cardiac events (MACE), defined as all death, myocardial infarction, or target vessel revascularization, at 1-year follow-up. Death was defined as any death from any cause. Myocardial infarction was defined as ischemic symptoms associated with increase of creatine kinase more than two times the upper limit of normal value with an elevated MB fraction and troponin I level. Target vessel revascularization (TVR) was defined as a repeat revascularization (percutaneous or surgical) for ischemia due to stenosis >50% of the luminal diameter on follow-up angiography either within the stent or SVG.

The academic research consortium definition of stent thrombosis was used [21]. Definite/confirmed stent thrombosis is defined as acute coronary syndrome and angiographic confirmation of stent thrombus or occlusion or pathologic confirmation of acute stent thrombosis. Probable stent thrombosis is defined as any unexplained death within 30 days or as target vessel myocardial infarction without angiographic confirmation of thrombosis or other identified culprit lesion. Possible stent thrombosis is defined as unexplained death after 30 days of the index procedure.

Statistical Analysis

Continuous data are expressed as mean ± SD, and categorical variables are presented as percentages. Continuous variables were compared by Student's *t* test. Categorical variables were compared by chi-square or Fisher's exact tests. Kaplan–Meier event-free survival

TABLE I. Baseline Clinical Characteristics

	CRI ($n = 39$)	No CRI ($n = 133$)	P value
Age (yrs ± SD)	74 ± 10	69 ± 11	0.02
Men (%)	77	87	0.21
Diabetes (%)	68	42	0.006
Hypertension (%)	95	82	0.07
Hypercholesterolemia (%)	87	92	0.33
Chronic obstructive pulmonary disease (%)	13	15	>0.9
Peripheral vascular disease (%)	40	24	0.10
Previous myocardial infarction (%)	40	57	0.15
Left ventricular ejection fraction (% ± SD)	48 ± 15	49 ±14	0.80
Presentation with myocardial infarction (%)	37	57	0.56

SD = standard deviation

TABLE II. Baseline Angiographic and Procedural Characteristics

	CRI ($n = 39$)	No CRI ($n = 133$)	P value
Cypher (%)	56	60	0.71
Stents per patient	1.9 ± 1.1	1.6 ± 1.1	0.19
Total stent length (mm)	39 ± 25	30 ± 21	0.01
Glycoprotein IIb/IIIa antagonist (%)	23	26	0.84
Distal embolic protection (%)	56	54	0.88
Intravascular ultrasound (%)	3	6	0.69
Intra-aortic balloon pump (%)	5	2	0.31

curves were constructed, and groups were compared with the log-rank test. The following variables were entered into a stepwise Cox proportional hazard regression model for 1-year MACE: age of patient, gender, hypertension, diabetes, CRI, chronic obstructive pulmonary disease, peripheral vascular disease, presentation with myocardial infarction, history of stroke, administration of glycoprotein IIb/IIIa antagonists, use of distal embolic protection, and stent type. A P value <0.05 was considered to be significant. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 172 patients, 39 patients with CRI and serum creatinine $\geq$1.5 mg dL^{-1}, and 133 patients without CRI underwent SVG intervention with DES. The baseline clinical characteristics of these patients are presented in Table I. Patients with CRI were older and more likely to be diabetic. Otherwise, the two groups were well matched.

Baseline Angiographic and Procedural Characteristics

The majority of the patients was treated with Cypher stents in both groups (CRI, 56% vs. no CRI, 60%, $P = 0.71$) (Table II). Although there was no difference in stents per patient (CRI, 1.9 ± 1.1 vs. no CRI, 1.6 ± 1.1, $P = 0.19$), the mean total stent length was longer in the CRI group (39 ± 25 mm vs. 30 ± 21 mm, $P = 0.01$). The use of intravascular ultrasound and intra-aortic balloon pump was low in both groups.

Thirty-Day Clinical Outcomes

In the CRI group, only one MACE (2.6%) occurred in a patient with acute myocardial infarction who died the following day from cardiogenic shock. In the group without CRI, MACE occurred in two patients (1.5%). One patient died unexpectedly on day 5 from probable stent thrombosis while the second patient had acute myocardial infarction and TVR due to subacute stent thrombosis on day 14.

One-Year Clinical Outcomes

At 1 year, patients with CRI had a higher MACE rate (35.9% vs. 15.8%, hazard ratio [HR] 2.48, 95% confidence interval [CI] 1.26–4.88, log rank $P = 0.009$; Fig. 1), mainly driven by higher mortality (20.5% vs. 9.8%, HR 3.41, 95% CI 1.10–10.58, log rank $P = 0.024$; Fig. 2). There was a trend toward higher TVR in the CRI group (21.8% vs. 10.3%, HR 2.42, 95% CI 0.94–6.24, log rank $P = 0.059$; Fig. 3).

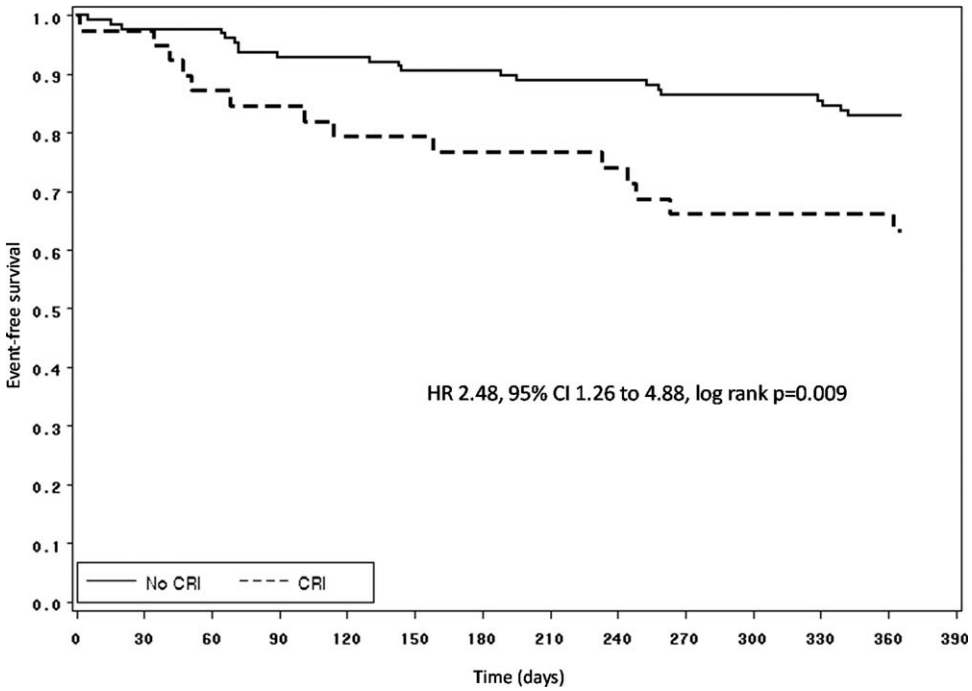

Fig. 1. Kaplan–Meier estimates of the probability of MACE-free survival in patients with and without chronic renal insufficiency.

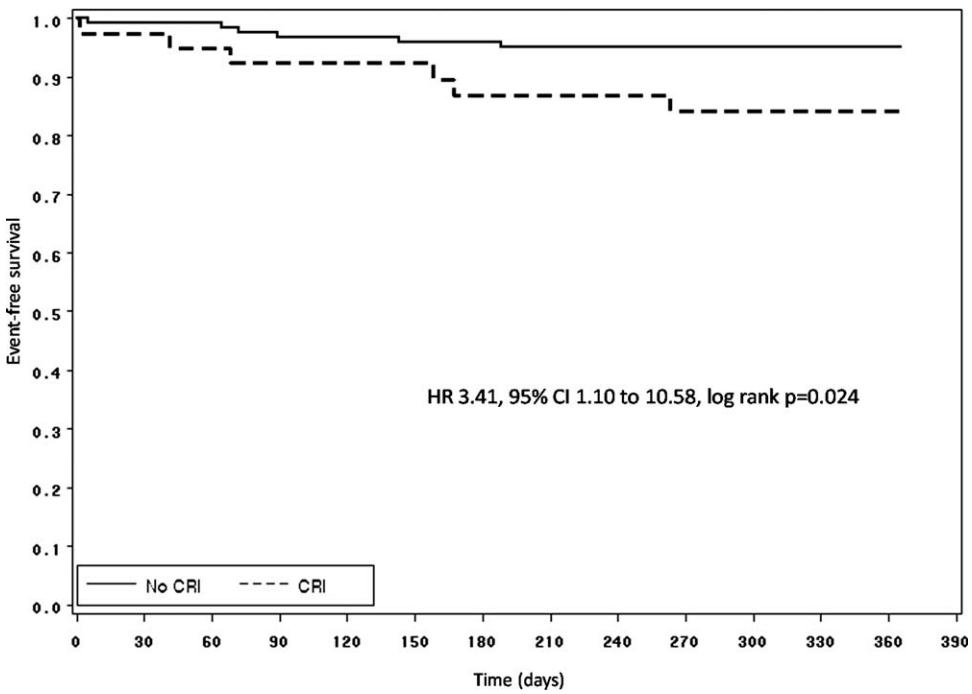

Fig. 2. Kaplan–Meier estimates of the probability of survival in patients with and without chronic renal insufficiency.

Stent Thrombosis

The rate of stent thrombosis at 1 year was similar in the CRI and no-CRI group (2.6% vs. 2.3%, $P = 0.8$). Two patients, who did not have CRI, had subacute stent thrombosis. One patient who had probable stent thrombosis died suddenly on day 5 and another patient had a stent thrombosis on day 14. Two patients had late stent thrombosis (on days 229 [CRI group] and

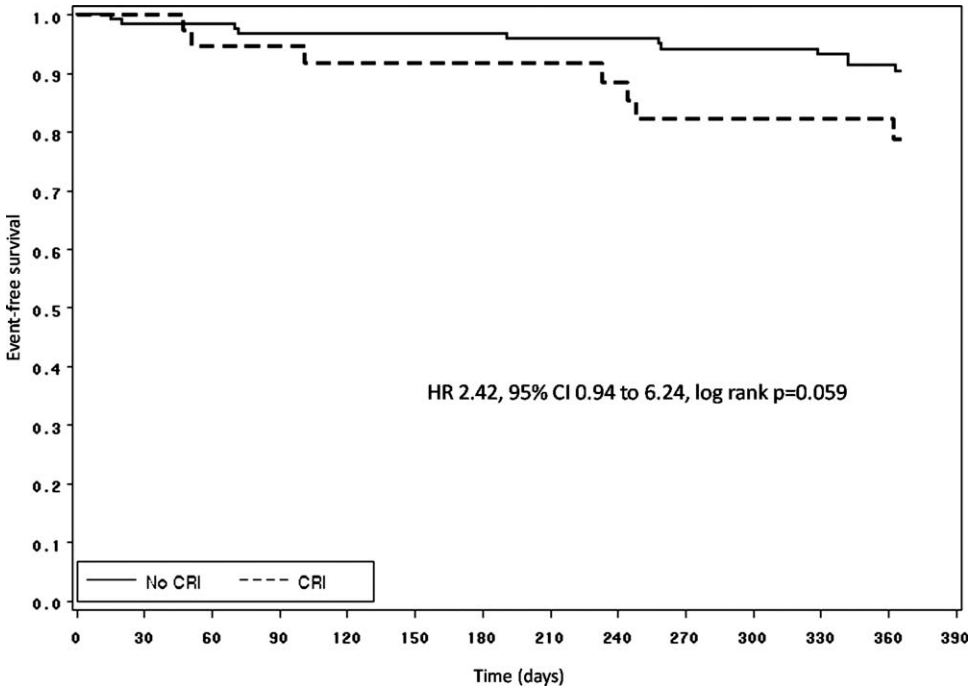

Fig. 3. Kaplan–Meier estimates of the probability of freedom from TVR in patients with and without chronic renal insufficiency.

365 [no-CRI group]). Three patients who had definite stent thrombosis underwent successful repeat SVG intervention.

Predictors of 1-Year MACE

By Cox regression analysis, CRI was the only independent predictor of 1-year MACE (HR 2.2, 95% confidence interval 1.1–4.3; $P = 0.03$).

DISCUSSION

The results of this study highlight the high incidence of MACE in patients with CRI who undergo SVG intervention with DES. In this study, patients with CRI who underwent SVG intervention with DES have higher MACE and mortality rates compared with patients with normal renal function. CRI was the only independent predictor of MACE at 1 year, even though these patients were older, more likely to have diabetes, and were treated with a longer total stent length.

Saphenous vein grafts remain suboptimal graft conduits because they degenerate over time with 50% of SVG developing significant stenosis within 10 years [1–7]. Because of higher morbidity and mortality associated with repeat coronary artery bypass graft surgery, percutaneous revascularization is the preferred treatment of SVG failure [22]. However, SVG intervention is associated with high rates of restenosis, progression of atherosclerosis outside the stented area leading to a failure rate of 35–40% over the next 12–18 months [8–13], as well as a high incidence of death and myocardial infarction [11,23,24].

Cardiovascular disease remains the primary cause of death in patients with CRI [25,26]. Similar to other studies, in the present study, patients with CRI had a high proportion of diabetics [16,21]. Patients with CRI are also more likely to have diffuse, extensive, and heavily calcified lesions [27,28], which makes percutaneous revascularization more technically demanding. Patients with CRI who develop acute coronary syndrome have a poor prognosis with over 70% mortality at 2 years [14]. In that study, percutaneous coronary intervention was associated with improved long-term survival when compared with medical therapy alone. Bonello et al. reported a graded increase in the rate of 1-year MACE with decreasing renal function in 2,357 patients with acute coronary syndrome who underwent percutaneous revascularization [17]. Patients with CRI treated with Cypher stents had increased rates of MACE at 6 months [16] and restenosis at 1 year [21]. Patients with CRI treated with Cypher stents who required hemodialysis had even higher in-segment restenosis rates, death, and target lesion revascularization rates compared with patients who did not require hemodialysis at 2 years [29].

The present study identifies patients with CRI who undergo SVG intervention with DES as a very high-

risk group for adverse cardiovascular events. At 1 year, the mortality rate was 20.5% while 35.9% of the treated patients experienced a MACE despite the use of DES. Furthermore, CRI was identified as the only independent predictor of 1-year mortality and MACE. Though the high MACE rates may be related to the increased risk of SVG atherosclerotic plaque disruption and occlusion in patients with CRI [30], the methodology of the current study does not allow confirmatory evidence of that hypothesis.

This study is limited by its retrospective nonrandomized design which is subject to bias toward patient selection, technique, and operator skill level. Postprocedural markers of myocardial injury in asymptomatic patients were not routinely measured at all sites but the clinical relevance of asymptomatic periprocedural myocardial necrosis is debatable. In fact, the results of this study are strengthened by only reporting hard clinical endpoints as components of MACE. Angiographic follow-up was not routinely performed on all patients but only in patients with clinical evidence of ischemia. Therefore, the rate of angiographic restenosis remains unknown while ischemia-driven TVR is reported.

CONCLUSION

This study shows that SVG intervention with DES is associated with worse outcomes in patients with CRI compared with patients with preserved renal function. The presence of CRI is associated with increased 1-year mortality and MACE in this high-risk group of patients undergoing SVG intervention with DES. The high clinical event rates reinforce the need for improved device and pharmacotherapy in patients with CRI who undergo SVG intervention. Prospective randomized studies with long-term follow-up are also required to identify the ideal revascularization strategy for these patients.

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