Risk of target lesion revascularization after coronary stenting in patients with and without chronic kidney disease

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Abstract

Background. Rates of restenosis following percutaneous coronary intervention with stent placement are high in patients with advanced renal failure. Whether mild to moderate chronic kidney disease (CKD) is associated with a similarly increased need for short or long-term target lesion revascularization (TLR) following coronary stenting is uncertain.

Methods. We analysed results from 1228 patients enrolled in four separate, randomized, controlled clinical trials who underwent elective coronary angioplasty with stenting and were prospectively followed for 5 years after the index procedure. Cox proportional hazards regression was used to correct for confounding and to estimate the short and long-term risks of target lesion revascularization in patients with vs without mild to moderate CKD.

Results. During a median follow-up of 5 years, 205 patients (16.7%) required TLR with 59 (4.8%) requiring TLR after the first year. Mild (HR 1.07, 95% CI 0.74–1.53) and moderate (HR 0.95, 95% CI 0.55–1.64) CKD were not associated with an increase in the adjusted, overall-risk of TLR. However, mild to moderate CKD was associated with a non-significantly increased risk of late TLR (HR 1.40, 95% CI 0.73–2.69).

Conclusions. Coronary stenting appears to be similarly effective in patients with mild to moderate CKD and patients with normal renal function. While target lesion revascularization is rarely needed beyond the first year after revascularization, long-term results of coronary stenting may be less-favourable in patients with CKD.

Keywords: angioplasty; chronic kidney disease; coronary artery disease; percutaneous coronary intervention; restenosis; revascularization

Introduction

Both end-stage renal disease (ESRD) and lesser degrees of renal dysfunction are associated with accelerated rates of atherosclerosis and a high incidence of cardiovascular morbidity and mortality [1–4]. Percutaneous angioplasty is an effective therapy for symptomatic coronary atherosclerosis, but in patients with advanced chronic kidney disease it is associated with high complication rates and poor long-term outcomes [3–7].

In patients with normal renal function, placement of coronary stents reduces the frequency of restenosis compared to angioplasty alone [8], and their routine use during percutaneous coronary intervention has reduced the need for reintervention after coronary procedures. Results of percutaneous intervention in patients with severe renal disease remain suboptimal despite the increased use of coronary stents. In patients with ESRD rates of target vessel as well as target lesion revascularization (TLR) after coronary stenting are high [9]. Whether less-severe renal impairment is associated with a similarly elevated rate of repeat revascularization after coronary angioplasty with stenting is controversial. Analyses of outcomes after coronary stenting in pre-dialysis CKD patients have typically examined mortality or recurrent myocardial infarction (MI) rates after stenting [3,4,10]. The relationship between CKD and the need for revascularization after stenting has been analysed previously, but most studies focused on the need for target vessel revascularization [11,12] rather than target lesion revascularization. Target vessel revascularization, however, is a suboptimal measure of the effectiveness of the initial intervention when comparing patients with and without CKD because it includes interventions outside of the target lesion performed to...
treat atherosclerotic plaques as well as interventions done within the target lesion to treat neo-intimal hyperplasia resulting in in-stent restenosis. Thus, comparisons using target vessel revascularization rates are likely to be heavily influenced by the high burden of atherosclerosis in patients with CKD and are likely to underestimate the usefulness of percutaneous procedures for treating isolated, symptomatic coronary lesions in the CKD population. More recent studies have examined TLR rates in patients with CKD, but none have followed patients for longer than 1 year [3,13,14] or simultaneously analysed short and long-term risk of TLR after percutaneous coronary intervention with stenting. Thus, whether long-term TLR risk differs in patients with and without CKD remains uncertain. To better understand these risks, we studied 1228 patients who underwent elective coronary angioplasty with stenting who were prospectively followed for 5 years after the index procedure.

Subjects and methods

Subjects

Subjects were patients with long-term follow-up enrolled in the experimental arms of three randomized stent vs stent trials (ASCENT-ACS Multilink™ stent, NIRVANA-NIR™ stent and SMART-AVE Micro II™ stent) and one non-randomized registry (AVE-GFX™ stent) [15–18]. Each of these trials was FDA-regulated and used similar inclusion and exclusion criteria as shown in Table 1. Although not excluded from these trials, patients with marked elevations in serum creatinine were rarely enrolled. In each, objective evidence of coronary ischaemia in the absence of recent myocardial infarction was required. Angiographic follow-up at 6–9 months was performed in 519 (42%) patients per protocol. After conditional device approval, the FDA mandated 5-year follow-up of all Multilink and NIR patients and a randomly selected subset of 75% of Micro II and GFX patients. Data used in this analysis were derived from the 1228 patients with long-term follow-up. Consenting patients were followed annually for the occurrence of death, MI, repeat revascularization and cardiac hospitalization.

Definitions

Deaths and cardiovascular events were adjudicated by an independent clinical events committee. Target lesion revascularization was defined as clinically indicated percutaneous or surgical revascularization of the index lesion during follow-up. Revascularization was considered clinically indicated if there was >70% diameter stenosis on angiography or >50% stenosis together with a positive stress test or ischaemic symptoms.

In the primary analysis, renal function was estimated with the Cockroft–Gault estimating equation [19] using a serum creatinine drawn prior to the index procedure. We chose the Cockroft–Gault equation, because missing values for race precluded use of the MDRD equation in 233 participants. Mild CKD was defined as an estimated creatinine clearance of 60–89 ml/min, and moderate CKD was defined as an estimated creatinine clearance <60 ml/min. We assessed the sensitivity of our results to our definition of CKD by conducting secondary analyses using thresholds of estimated creatinine clearance as defined by the abbreviated MDRD equation and using uncorrected serum creatinine. In the latter analysis mild CKD was defined as a serum creatinine ≥1.3 and <1.6 mg/dl in men or ≥1.0 and <1.2 in women and moderate CKD as baseline serum creatinine ≥1.6 in men and ≥1.2 in women. We chose these thresholds because they reliably detect inulin clearances below 80 or 60 ml/min, respectively [20].

Analysis and statistics

Missing continuous variables were imputed as the study mean or median, depending on normality. Except for ejection fraction (missing in 158 patients), all other continuous variables were missing in well less than 5% of patients. Serum creatinine was missing in 14 patients but was not imputed because it was the primary variable of interest. Indicator variables were created for missing race, which was the only discrete variable with >5% missing values. Associations between degree of renal impairment
and other baseline covariates were examined using ANOVA for continuous variables and chi-square tests for discrete variables. Heterogeneity between the four studies was evaluated for key baseline variables using key baseline variables using Student’s t-test or Wilcoxon Rank-Sum tests for continuous variables. No significant differences were detected at the P < 0.05 level. Rates of TLR were determined using the Kaplan–Meier survival method, and univariate time-to-event analyses were conducted with the log-rank test or univariate Cox models.

Cox proportional hazards regression was used to adjust for potentially confounding variables. Model fit was assessed through the use of likelihood ratio testing, and the proportional hazards assumptions were tested by fitting time varying covariates. Variables used in the multi-variable analyses were chosen because of their known association with the use of cardiac catheterization or TLR or because of univariate associations (P < 0.20) with TLR in this dataset. Variables included in the final model were age, trial, sex, race (black vs non-black), reference vessel size, post-procedure minimal luminal diameter (MLD), diabetes, stent length, cigarette smoking, body mass index, left anterior descending intervention and prior MI [23–31]. A minimum of 39 sites and a maximum of 50 sites were used in each trial. Given this large number of sites and the small number of patients enrolled at each site, site was not included in the final models. After fitting this model, terms for CKD were added to generate the final model. We assessed for effect modification by the presence or absence of diabetes. All statistical analyses were performed using SAS for Windows version 9.1 (SAS Institute, Cary, NC) or Power Source for Windows (Vanderbilt University, Memphis, TN).

Using three categories of renal impairment as defined earlier, we had 80% power to detect a HR of 2.1 in the group with moderate CKD, and a HR of 1.7 in the group with mild CKD. For renal function categorized into two groups (<60 and >60) based upon Cockcroft–Gault estimation, we had 80% power to detect a 1.3-fold increase in the hazard of TLR.

Results

Patient characteristics

The median follow-up interval was 1830 days (5.0 years) with follow-up of at least 2 years in 90.8% of patients and beyond 4 years in 86% of patients. Serum creatinine was missing in 14 patients. Of the remaining patients, 981 (79.9%) had normal renal function, 178 (12.7%) had mild CKD and 77 (6.3%) had moderate or worse CKD. In 17 patients serum creatinine was ≥2.0 mg/dl. Baseline characteristics of the patients are summarized in Table 2. Those with mild or moderate CKD were older (66.1 and 68.9 vs 61.6 years, P < 0.001), more likely to be female (53.9 and 57.1% vs 52.3%, P < 0.001), more likely to be black (4.5 and 6.5% vs 1.9%, P < 0.003) and more likely to have hypertension (67.5 and 79.2% vs 53.5%, P < 0.001), but they were less likely to be smokers (16.0 and 13.0% vs 23.9%, P < 0.003).
Index lesion characteristics

There were no significant differences in the lesion characteristics when stratified by baseline renal function (Table 2). LAD location accounted for 41.5% of lesions. Average reference vessel diameter was 3.0 ± 0.5 mm. Average lesion length was 12.4 ± 6.8 mm and average stent length was 20.3 ± 9.2. Mean post-procedure minimal luminal diameter was 2.5 ± 0.5 mm.

Crude associations of baseline characteristics on risk of restenosis

During follow-up, 92 patients died and 71 underwent coronary artery bypass grafting of either a target or non-target lesion. In total, there were 205 TLRs during follow-up. Most (n = 146) of these occurred during the first year with the remaining (n = 59) occurring during the long-term follow-up. Diabetes (HR 1.46, 95% CI 1.08–1.99), reference vessel diameter (HR 0.46, 95% CI 0.34–0.61), stent length (HR 1.01, 95% CI 1.00–1.03) and post-procedure minimal luminal diameter (MLD) (HR 0.45, 95% CI 0.33–0.61) were significantly associated with the risk of TLR. Prior MI, gender and lesion length had borderline significant associations with the risk of TLR.

There were 95 TLRs in patients with normal renal function, 79 in those with mild CKD and 30 in subjects with moderate CKD. Renal function was not a significant predictor of TLR. As shown in Figure 1, the univariate association between renal function and TLR was non-significant. The hazard ratio for mild CKD (HR 1.01 (95% CI 0.67–1.51) and 0.95 (95% CI 0.55–1.62) for mild and moderate CKD, respectively. The relationship between creatinine clearance and renal function remained null when creatinine clearance was entered into the models as a continuous variable (HR for each 1 ml/min change 1.0, 95% CI 1.00–1.00).

Short vs long-term risk of TLR

Because the risk of angiographic restenosis is greatest during the first 6–9 months after stenting and because the threshold for performing repeat angiography might correlate with renal function, we explored whether the risk of TLR was different in the first year than in ensuing years. There were 146 TLRs during the first year and 59 events during late follow-up. Because of the small number of events in each time period, renal impairment was defined dichotomously as normal (>90 ml/min) or impaired for these analyses. In univariate analysis, there was no evidence for a significant relation between renal function and TLR during early or late follow-up. Adjusting for potential confounders had no impact on the relative hazard of TLR during the first year (HR 0.94 95% CI 0.61–1.45, P = 0.79). However, after the first year, the risk of TLR was non-significantly higher (HR 1.40, 95% CI 0.73–2.69) in patients with at least mild CKD.
Among 1228 patients who received elective coronary angioplasty with stenting, we found no association between the presence of mild and moderate chronic renal impairment and the risk of target lesion revascularization. Our results were robust and the 95% confidence intervals suggest that mild and moderate CKD are unlikely to be associated with an HR of TLR greater than 1.7 or 1.3, respectively. This is one of the largest studies to date to examine renal function as a risk factor for revascularization of a previously stented atherosclerotic lesion, and has a markedly longer follow-up than any previously reported study.

Relatively few studies have examined revascularization following percutaneous coronary intervention with stenting in patients with CKD, whether specifically addressing target lesion revascularization, or target vessel revascularization (which includes but is not limited to target lesion revascularization). In one such study, Sadeghi et al. analysed 2082 patients from the CADILLAC trial who received primary PTCA for acute MI. Consistent with our findings, they found that a Cockroft–Gault estimated creatinine clearance \( \leq 60 \text{ ml/min} \) was not associated with target vessel revascularization; however, in 584 patients who underwent routine angiographic follow-up, severe restenosis (21 vs 12%) or reocclusion (15 vs 7%) of the target lesion occurred significantly more frequently in those with an estimated GFR \( \leq 60 \text{ ml/min} \). Notably, less than 60% of the patients in that study received stents [10].

Gruberg reported the impact of chronic renal failure (creatinine \( \geq 1.4 \text{ mg/dl in women or } \geq 1.5 \text{ mg/dl in men} \)) among participants of the WRIST trials which were aimed at assessing the efficacy of intracoronary radiation [13]. Among 120 participants who did not receive intracoronary radiation, TLR occurred more frequently among those with chronic renal failure (71 vs 59%, \( P = 0.34 \)) as did TVR (79 vs 60%, \( P = 0.18 \)), but this was not statistically significant. There was no difference between those with or without CKD when intracoronary radiation was used. Gruberg subsequently published findings from a retrospective cohort study of 10 076 who underwent percutaneous angioplasty with stenting, and our results are consistent with these findings.

### Table 3. Univariate predictors of target lesion revascularization

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hazard ratio (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockroft–Gault estimated creatinine clearance (ml/min)</td>
<td></td>
<td></td>
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<tr>
<td>( \geq 90 )</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>60–89</td>
<td>0.96 (0.71–1.30)</td>
<td>0.80</td>
</tr>
<tr>
<td>&lt;60</td>
<td>0.80 (0.53–1.20)</td>
<td>0.27</td>
</tr>
<tr>
<td>MDRD eGFR (ml/min/1.73 m(^2))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 90 )</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>60–89</td>
<td>0.95 (0.64–1.40)</td>
<td>0.80</td>
</tr>
<tr>
<td>&lt;60</td>
<td>0.86 (0.52–1.41)</td>
<td>0.54</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>0.99 (0.87–1.12)</td>
<td>0.86</td>
</tr>
<tr>
<td>Female</td>
<td>0.78 (0.57–1.07)</td>
<td>0.12</td>
</tr>
<tr>
<td>Black race</td>
<td>0.98 (0.40–2.38)</td>
<td>0.96</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.46 (1.08–1.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.14 (0.86–1.51)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>0.84 (0.64–1.12)</td>
<td>0.24</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.71 (0.70–4.16)</td>
<td>0.23</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.83 (0.59–1.18)</td>
<td>0.31</td>
</tr>
<tr>
<td>Prior MI</td>
<td>0.73 (0.55–1.03)</td>
<td>0.07</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>0.88 (0.52–1.49)</td>
<td>0.64</td>
</tr>
<tr>
<td>BMI (per m/kg(^2))</td>
<td>1.02 (0.99–1.04)</td>
<td>0.17</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
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<tr>
<td>45–54</td>
<td>1.14 (0.82–1.57)</td>
<td>0.44</td>
</tr>
<tr>
<td>&lt;45</td>
<td>1.05 (0.67–1.64)</td>
<td>0.83</td>
</tr>
<tr>
<td>Lesion characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD lesion</td>
<td>1.21 (0.92–1.60)</td>
<td>0.17</td>
</tr>
<tr>
<td>Reference vessel diameter (per mm)</td>
<td>0.46 (0.34–0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lesion length (per mm)</td>
<td>1.02 (1.00–1.04)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stent length (per mm)</td>
<td>1.01 (1.00–1.03)</td>
<td>0.04</td>
</tr>
<tr>
<td>Excess stent length (per mm)</td>
<td>1.01 (0.99–1.02)</td>
<td>0.37</td>
</tr>
<tr>
<td>Post-procedure MLD (per mm)</td>
<td>0.45 (0.33–0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-procedure stenosis (%)</td>
<td>1.00 (0.99–1.01)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

**Note:** Baseline characteristics of the patients and coronary lesions. MI, myocardial infarction; CABG, coronary artery bypass grafting; LAD, left anterior descending coronary artery; MLD, minimal luminal diameter. Excess stent length is defined as the difference between stent length and lesion length.
coronary intervention with or without stenting for a variety of indications. In that study, the occurrence of TLR was similar between 786 patients with moderate chronic renal impairment (defined as creatinine concentration ≥1.8 mg/dl) and 9195 patients with ‘normal’ renal function (25 vs 26%, P = 0.46). However, that result was not adjusted for potential confounders, nor is it clear from their report how TLR was adjudicated [3]. A recent report has examined the impact of CKD on outcomes of patients in the TAXUS trials and found no difference in 1 year TLR rates [14]. These results are consistent with our 1 year results despite the use of a single-stent platform in the TAXUS trials and multiple different stents in the current report. Long-term follow-up of the patients in the TAXUS trial is not yet available.

We did not find a statistically significant interaction between time of TLR following stenting and CKD, but our results suggested that there may be higher rates of late TLR among those with chronic kidney disease. As with all secondary analyses, this finding should be cautiously interpreted, particularly as it is possible that the late TLR represents de novo atherosclerosis rather than restenosis. However, emerging evidence suggests that restenosis continues to occur at a low frequency between the first and second year after coronary stenting—a process that does not seem to be substantially altered by the use of drug-eluting stents [32]. Our findings merit further investigation in larger databases, but suggest that patients with CKD should at least be monitored for the late occurrence of restenosis after stenting.

The apparent discrepancy between the accelerated atherosclerosis in chronic renal impairment and our finding that rates of (early) TLR are not increased in this setting may be due to the unique biological processes that mediate in-stent restenosis [33,34]. Risk factors for restenosis may be distinct from risk-factors for atherosclerosis and this may explain why renal impairment confers an increased risk for long-term morbidity and mortality after angioplasty [12] without increasing the risk of restenosis. Alternatively, it is possible that the biological risks of restenosis are greater in patients with CKD than in those with normal renal function but that lower rates of restenosis are observed in patients with CKD because they are more likely than those with normal renal function to die prior to the development of clinically significant restenosis. However, our results were unchanged when we restricted the analysis to patients who survived for the duration of follow-up (data not shown). Furthermore, with only 22 deaths among patients with advanced CKD in our cohort, the increased risk of death in CKD patients would be unlikely to fully account for our findings.

Strengths of our study include its large sample size, the large number of events, the use of multiple stents in some patients, and the relatively uniform indications for intervention all of which should increase the generalizability of our findings. Nevertheless, our study’s findings must be considered within the context of its design. The presence of acute renal failure is unlikely to have produced significant misclassification of CKD status since the uniform exclusion of patients with acute myocardial infarction ensured that most procedures were performed electively rather than emergently. However, creatinine-based methods for estimating GFR do carry substantial degrees of inaccuracy [21,22] that may be magnified when serum creatinine is not calibrated against a uniform standard [21]. Thus, it is possible that some patients were misclassified among categories of renal function. However, we assessed renal function in multiple ways (three categories vs dichotomous, creatinine and sex-based definitions vs Cockcroft–Gault or MDRD estimates), and the results were robust regardless of the manner in which renal function was classified. Furthermore, the large sample size provides some assurance that an important association was unlikely to be missed, despite the possibility of a degree of non-differential misclassification.

Second, if patients with CKD are less likely to present with anginal symptoms, then an increased rate of restenosis may not translate into increased TLR, as has been previously observed in smokers [31]. Alternatively, physicians may be less willing to perform repeat angiography or to intervene on restenosis in patients with kidney disease due to the risks of contrast nephropathy and the increased mortality in these patients [12]. However, patients in this study were included because they had already exceeded clinical and symptomatic barriers to coronary angiography and intervention, and we feel that these factors are unlikely to have unduly influenced our findings. Additionally, the vast majority of patients in our study had serum creatinines under 2 mg/dl, and many of the patients with renal impairment had values close to the ‘normal’ range. It is unlikely that angiography was routinely withheld in this setting.
Finally, as with all analyses of clinical trials data, the possibility that the randomized patients differed in important ways from the general population has to be considered. Since patients with CKD are less likely than those with normal renal function to undergo coronary angiography [35], we agree that the results of our analysis of a cohort of patients uniformly deemed to be suitable candidates for both coronary angiography and inclusion in a clinical trial should be generalized to the overall CKD population with caution. However, the results should be applicable to patients who meet the inclusion criteria in Table 1 and are likely to apply to other CKD patients deemed to be clinically acceptable candidates for coronary revascularization.

In conclusion, we did not find any association between mild or moderate renal impairment and the risk of target lesion revascularization in patients who have undergone prior coronary angioplasty with stenting. Whether renal impairment is associated with an increased need for late revascularization of the target lesion merits further study.

Conflict of interest statement. None declared.

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