Impact of Chronic Kidney Disease on the Efficacy of Drug-Eluting Stents: Long-term follow-up Study

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Abstract

Background: Patients with chronic kidney disease (CKD) submitted to coronary angioplasty have higher rates of target lesion revascularization (TLR) and mortality. Drug-eluting stents (DES) are associated with a lower rate of restenosis, compared to bare metal stents (BMS), although data on DES efficacy and safety is limited in patients with CKD.

Objective: We sought to evaluate the safety and efficacy of DES in patients with significant CKD as compared to patients without normal renal function in a real world registry.

Methods: 504 patients who underwent percutaneous coronary intervention with DES in two centers were included. Outcomes were stratified based on the presence of CKD, defined as a baseline glomerular filtration rate (GFR) < 60 ml/min/1.73 m².

Results: The mean follow-up was 22.7 months. CKD was present in 165 patients (32.7%). Patients with CKD were older, had a higher incidence of hypertension and diabetes. CKD patients presented an increased incidence of death (12.3% vs 2.4%, p < 0.001) and myocardial infarction (MI) (7.4% vs 3.3%, p = 0.04) compared to patients without CKD. TLR rates were similar between groups (4.8% vs 5.6%, p = 0.7, CKD and no CKD patients, respectively). Independent predictors of death were CKD (HR 6.93; 2.4 - 19.5, p < 0.001), current smoking (HR 3.66; 1.20 - 11.10, p = 0.02) and diabetes (HR 2.66; 1.03 - 6.60, p = 0.045).

Conclusion: In this registry, coronary intervention with DES in patients with CKD was associated with similar TLR compared to patients without CKD, demonstrating the efficacy of DES in preventing in-stent restenosis in this patient population. CKD was related to significantly increased MI and mortality rates. (Arq Bras Cardiol. 2011; [online].ahead print, PP.0-0)

Keywords: Renal insufficiency, chronic; drug-eluting stents; efficacy; follow-up studies.

Introduction

Chronic kidney disease (CKD) is an important worldwide public health issue. There is a strong association between CKD and coronary artery disease (CAD) prevalence and mortality¹. Among patients with end-stage renal disease (ESRD), cardiac mortality is 10 to 30 times higher than in the general population. The mechanism of this association is not entirely known, but a higher prevalence of traditional risk factors in this population such as advanced age, hypertension and diabetes, contributes to accelerated atherosclerosis ²⁻⁴.

After percutaneous coronary intervention (PCI) with bare-metal stents (BMS), CKD patients had an increased incidence of restenosis and cardiac events when compared to patients without renal dysfunction⁵⁻⁷. However, even considering the limited results, PCI is a very important alternative in the treatment of CKD patients who may have increased surgical risk and present limiting angina despite of optimal medical treatment⁸.

Drug-eluting stents (DES) have been found to reduce the incidence of restenosis and the need for future revascularization compared to BMS. There is a paucity of data on safety and efficacy of DES in CKD patients, as this population is often excluded from large clinical trials⁹⁻¹⁰.

The aim of this study was to evaluate the efficacy and safety of DES in patients with significant CKD as compared to patients with normal renal function in a real-world registry.

Methods

Study population

The study population consisted of 611 consecutive patients who underwent PCI with DES between June of 2002 and June of 2006 in two tertiary hospitals in Porto Alegre, Brazil. A total of 504 patients were included in this analysis, as they had available serum creatinine measurements up to 30 days before the coronary intervention.
CKD was defined as the calculated glomerular filtration rate (GFR) < 60 ml/min/1.73 m², a cut-off value previously proposed by the National Foundation’s Kidney Disease Outcome Quality Initiative Advisory Board (K/DOQI) to identify patients with moderate renal failure. In accordance, patients were divided into 2 groups: 1) patients with GFR ≥ 60 ml/min/1.73 m² and 2) patients with GFR < 60 ml/min/1.73 m².

The GFR was calculated by the equation of the modification of the diet in the renal disease (MDRD): Estimated GFR = 186 x (serum creatinine)⁻¹.¹⁵⁶ x (age)⁻⁰.²⁰⁵ x (0.742 if female) x (1.210 if black), where creatinine is measured in mg/dl, age in years and GFR is expressed as ml/min/1.73 m².¹²,¹³

This study was approved by the local Institutional Research and Ethics Committee of both hospitals.

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**Endpoint definitions and clinical follow-up**

Myocardial infarction (MI) was defined as an elevation of the creatinine kinase-MB fraction of 3 times the upper limit of normal range. Target vessel revascularization (TVR) was defined as repeated percutaneous or surgical revascularization of the treated vessel. Target lesion revascularization (TLR) was defined as percutaneous or surgical revascularization of the index lesion during follow-up. A major adverse cardiac event (MACE) was defined as a composite end-point of cardiac death, non-fatal MI or TVR during follow-up. The stent thrombosis definition was based on criteria set by the Academic Research Consortium (ARC).

Angiographic success was defined as stenosis < 20% and TIMI 3 flow at the end of the procedure. Clinical success was defined as angiographic success and absence of clinical complications such as death, MI, urgent revascularization and stroke.

For patients with more than one intervention during the follow-up period of the study, only the first intervention was considered for endpoint analysis.

The type of DES used during the coronary procedure was left to the discretion of the intervention cardiologist.

The clinical follow-up was obtained by telephone interviews with the patient, from outpatient record review and contact with the assistant physician. All clinical events were adjudicated by analysis of source documentation by a cardiologist blinded for the remaining clinical data.

**Quantitative coronary angiographic analysis**

Coronary angiograms obtained at baseline and post-procedure were analyzed by an experienced cardiologist. Off-line quantitative coronary angiography of the index intervention was performed using the guiding catheter for magnification calibration (CardioNow Websend DICOM Study Sharing Software, HeartLab, Inc., Westerly, Rhode Island). Minimal luminal diameter and reference vessel diameter were measured before and after the intervention from a single matched view showing the smallest luminal diameter.

**Statistical analysis**

The statistical analysis was performed using SPSS 13.0 software (SPSS Inc, Chicago, Illinois). Categorical data were presented as frequencies (%) and compared by chi-square test. Continuous variables were presented as mean ± standard deviation (SD) and compared using the Student t-test or Mann-Whitney U-test when appropriate. Clinical outcomes were calculated by chi-square. The time to occurrence of death, MI, thrombosis and revascularization in the 2 groups are presented as Kaplan-Meier curves and compared using the log-rank test. Significant baseline characteristics predictive of death and TLR were identified using Cox multivariate analyses, selecting variables by the Backward Wald method. For all analyses, a 2-sided p value of < .05 was considered as significant.

**Results**

The mean clinical follow-up was 22.6 ± 13.0 months, ranging from 6.0 to 63.5 months and was available in 98.2% of patients. There were 181 females and 323 males. The mean age of the study population was 63.7 ± 11.0 years, ranging from 30 to 90 years. The mean serum creatinine and GFR levels were 1.22 mg/dl and 69.8 ml/min/1.73 m², respectively.

Of 504 patients included in this analysis, 339 (67.3%) presented GFR ≥ 60 ml/min/1.73 m², and 165 (32.7%) presented GFR < 60 ml/min/1.73 m². Ten patients had end-stage renal disease on dialysis. The average serum creatinine of the groups was 0.95 ± 0.17 mg/dl and 1.76 ± 1.38 mg/dl, respectively.

The clinical features of both groups are shown in Table 1. Patients with CKD, compared to non-CKD patients, were significantly older (68.6 ± 10 years vs 61.2 ± 9 years, p < 0.001), more likely to be female (50.3% vs 28.9%, p < 0.001), had hypertension (88.8% vs 72.8%, p < 0.001), diabetes (47.5% vs 31.5%, p = 0.001), and were less likely to use aspirin (74.5% vs 87.4%, p < 0.001), or to be currently smokers (5.7% vs 10%, p = 0.02).

Angiographic and procedural characteristics of the two groups are presented in Table 2. The angiographic success rate was high and similar in both groups. Compared to non-CKD patients, those with CKD were more likely to undergo direct stenting (26.6% vs 35.7%, p = 0.05). By quantitative coronary angiography, minimal luminal diameter tended to be larger at baseline (0.9 ± 0.72 mm vs 1.0 ± 0.42 mm, p = 0.06) and after stenting (2.7 ± 0.48 mm vs 2.8 ± 0.49 mm, p = 0.05) in CKD patients, but the acute gain was similar. Other lesion characteristics were similar between groups.

The incidence of adverse cardiovascular events during hospitalization was higher in CKD patients. Patients with CKD had reduced clinical success (92.1% vs 98.2%, p = 0.001), with increased rates of MI (3.7% vs 0.6%, p = 0.01) and death (3.7% vs 0.3%, p = 0.003). No patient present stroke during hospitalization.

Long-term clinical outcomes are presented in Table 3. Kaplan-Meier survival analysis for death, myocardial infarction, target lesion revascularization and definite stent thrombosis are presented in Figure 1. Patients with CKD presented higher incidence of death and cardiac death (12.3% vs 2.4%, p <...
Table 1 - Baseline clinical characteristics and medical treatment of patients with baseline renal function data

| Clinical features                  | GFR ≥ 60 ml/ min/1.73 m² (n = 339) | GFR < 60 ml/ min/1.73 m² (n = 165) | p   |
|-----------------------------------|------------------------------------|-----------------------------------|-----|
| Age, years                        | 61.2 ± 10                          | 68.6 ± 9                          | < 0.001 |
| Female sex                        | 28.9%                              | 50.3%                             | < 0.001 |
| Diabetes                          | 31.5%                              | 47.5%                             | 0.001 |
| On Insulin                        | 9.2%                               | 21.4%                             | < 0.001 |
| Hypertension                      | 72.8%                              | 88.8%                             | > 0.001 |
| Hypercholesterolemia              | 74.4%                              | 78.8%                             | 0.3   |
| Current smoking                   | 10%                                | 5.7%                              | 0.02  |
| Previous PCI                      | 29.3%                              | 26.4%                             | 0.5   |
| Previous CABG                     | 9.2%                               | 13%                               | 0.2   |
| Level of GFR                      |                                     |                                   |       |
| ≥ 60 ml/min                       | 339                                 |                                   |       |
| 30 - 59 ml/min                    | -                                  | 148                               |       |
| 15 - 59 ml/min                    | -                                  | 7                                 |       |
| < 15 ml/min                       | -                                  | 10                                |       |
| Medical therapy at follow up      |                                     |                                   |       |
| ASA                               | 87.4%                              | 74.5%                             | 0.001 |
| Clopidogrel / ticlopidine         | 52.5                                | 54.8                              | 0.6   |
| Statin                            | 86.5%                              | 84.9%                             | 0.6   |
| ACE inhibitor                     | 39.7%                              | 37.7%                             | 0.7   |
| Betablocker                       | 59.7%                              | 61%                               | 0.8   |
| Diuretic                          | 27.1%                              | 46.1%                             | < 0.001 |

*GFR - glomerular filtration rate; † PCI - percutaneous coronary intervention; ‡ CABG - coronary artery bypass grafting; § MI - myocardial infarction; ASA - acetylsalicylic acid.

0.001, and 6.1% vs 1.2%, p = 0.002, respectively), when compared to non-CKD patients. The incidence of MI was also higher in CKD patients (7.4% vs 3.3%, p = 0.04). However, the TVR and TLR rates were similar between groups (12.5%, vs 11.3%, p = 0.7, and 4.8% vs 5.6%, p = 0.7, respectively CKD and non-CKD patients). The rate of definite stent thrombosis was similar in both groups (1.9% vs 1.2%, p = 0.21, respectively CKD and non-CKD patients).

To determine whether CKD was an independent predictor of TLR and death after DES, we performed backward multivariable analysis using the Cox proportional hazards model. Variables considered for the model included CKD, age, gender, diabetes mellitus, current smoking, hypertension, hypercholesterolemia, lesion length, minimal luminal diameter, number of vessels with coronary artery disease. Lesion length (HR 1.06; 95% CI 1.007 - 1.070, p = 0.02) was the only independent predictor of subsequent target lesion revascularization. Independent predictors of death were CKD (HR 6.93; 95% CI 2.4 - 19.5, p < 0.001), current smoking (HR 3.66; 95% CI 1.20 - 11.10, p = 0.02) and diabetes (HR 2.66; 95% CI 1.03 - 6.60, p = 0.045).
**Discussion**

This is a registry of consecutive patients from two centers who underwent PCI with DES, with no exclusion criteria, and therefore represents the “real-world” practice. To the best of our knowledge, the present study has the longest follow-up of patients with CKD after DES implantation.

The major finding of this study is that, although CKD patients present higher incidence of death, MI and MACE compared to patients with preserved renal function, there is no association between the presence of CKD and the risk of revascularization after DES implantation. This demonstrates that the use of DES remains as effective in CKD as in non-CKD patients for up to five years.

Patients with CKD have accelerated atherosclerosis, higher incidence of CAD risk factors and more severe CAD. Several previous studies found that mild-to-moderate CKD is associated with increased rates of death from any cause and cardiovascular death. After PCI, mortality has been found to be directly related to the severity of CKD. Moreover, moderate CKD increases the risk of contrast-induced nephropathy, recurrent MI, heart failure and arrhythmias. Our study found an increased prevalence of diabetes, hypertension, and older age associated with

**Table 3 - Cumulative events during follow-up**

| Event                                    | GFR* ≥ 60 ml/min/1.73 m² (n = 339) | GFR* < 60 ml/min/1.73 m² (n = 165) | p   |
|------------------------------------------|-----------------------------------|-----------------------------------|-----|
| Death                                    | 2.4%                              | 12.3%                             | <0.001|
| Cardiac death                            | 1.2%                              | 6.1%                              | 0.002 |
| Target vessel revascularization          | 11.3%                             | 12.5%                             | 0.7  |
| Target lesion revascularization          | 5.6%                              | 4.8%                              | 0.7  |
| Myocardial infarction                    | 3.3%                              | 7.4%                              | 0.04 |
| MACE†                                    | 15.6%                             | 25%                               | 0.01 |
| Stent thrombosis                         |                                    |                                   |     |
| Definite                                 | 1.2%                              | 1.9%                              | 0.21 |
| Definite + probable                      | 2.1%                              | 3.7%                              | 0.3  |

* GFR - glomerular filtration rate; † MACE - major cardiac events.

**Figure 1 - Kaplan-Meier survival analysis for death, myocardial infarction, target lesion revascularization, and definite stent thrombosis.**
increased mortality among CKD patients. Multivariate analysis confirmed CKD, current smoking, and diabetes as independent predictors of all-cause mortality.

Previous studies comparing CKD and non-CKD patients undergoing PCI with DES, found that mortality is uniformly higher in CKD patients. In addition, patients with CKD have increased mortality regardless of the use of DES or BMS. Only one study reported a lower mortality rate in CKD patients undergoing PCI with DES at 1 year.

We found that MACE was higher in CKD patients, primarily because of higher rates of mortality and MI. This finding differed from study by Nakazawa, where the higher incidence of MACE following DES implantation in CKD patients was mainly due to an increased incidence of TVR. In that study, routine angiographic follow-up was performed at 8 months post-stenting and might have contributed to an increase in the revascularization rate.

Few studies have examined restenosis and revascularization rates following percutaneous coronary intervention with DES in CKD patients. Meta-analyses of large randomized trials were not able to address this issue, given the fact that most studies excluded patients with renal failure. Likewise, larger network meta-analyses preclude subgroup analysis due to the lack of individual patient data.

In our study, the TLR rate was low regardless of the renal function. This finding is similar to other studies on patients with moderate CKD that reported decreased incidence of revascularization after DES implantation as compared to BMS. A sub-analysis of the TAXUS-IV trial, of patients with baseline moderate renal failure (GFR < 60 ml/min) randomized to paclitaxel-eluting stent (n = 123) or BMS (n = 100) demonstrated significantly lower TLR (3.3% vs 12.2%, p = 0.01) and TVR rates (6.6% vs 15.2%, p = 0.04). On the other hand, one small case-control study including CKD patients presented similar rates of revascularization with DES or BMS.

Kuchulakanti et al., in a study involving 76 patients with CKD and 1,466 controls reported low revascularization rates after DES implantation in both groups. The TVR rate at 6 months was significantly higher in CKD than in non-CKD patients (7% vs 4%, p < 0.001). Another study evaluating revascularization involved patients who were divided in 3 groups: GFR ≥ 60 ml/min; GFR < 60ml/min and patients on hemodialysis. Angiographic follow-up was performed at 8 months. After DES implantation, the TVR rate was significantly increased in hemodialysis patients in comparison to moderate CKD patients and patients without CKD (32.3%, 13% and 9.8%, p = 0.002 respectively).

CKD has been shown to be an independent risk factor for stent thrombosis after DES implantation in some, but not all studies. In our study, we found that the incidence of stent thrombosis was not significantly increased in CKD patients. It is conceivable that the lack of significance observed in our study was related to the reduced statistical power to assess this low-incidence event.

A recently published study, although limited to US patients and not exclusively DES procedures with 1 year of follow-up presented similar results to our study. Patients with CKD had higher incidence of death and MI and TLR and stent thrombosis rates were not influenced by the presence of CKD.

Study limitations
The findings of this study have to be interpreted in light of some limitations. The number of patients with end-stage renal disease on hemodialysis was very small and thus, no conclusions can be drawn regarding the safety and efficacy of DES in this population. In addition, the lack of a control group of bare metal stent does not allow us to compare the results between DES and BMS. Finally, as patients did not undergo mandatory follow-up with stress test or coronary angiography, silent ischemia and restenosis could have been underdiagnosed.

Conclusion
In this real-world registry, PCI with DES in CKD patients was associated with similar rates of target lesion revascularization, as compared to non-CKD patients, indicating that DES preserve the beneficial effect in preventing in-stent restenosis in this high-risk population. Nevertheless, CKD was associated with higher MI and mortality rates, demonstrating that clinical outcomes in patients with CKD, even after successful percutaneous coronary intervention, depend on the interplay of other comorbidities.

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