IMPACT OF CHRONIC KIDNEY DISEASE ON OUTCOME OF PERCUTANEOUS CORONARY INTERVENTION IN ACUTE CORONARY SYNDROME

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ABSTRACT

Objectives: We aim to study the impact of chronic kidney disease (CKD) on short and long term outcome of percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS).

BACKGROUND: Renal impairment (RI), even if mild, is a known independent predictor of cardiovascular events, but the effects of various grades of RI on PCI outcomes is not well established.

Methods: 427 patients with ACS treated within 24 hours with PCI were subjected to ECG, echocardiography, repeated measurements of cardiac troponin I (cTNI), cardiac isoenzyme of creatine kinase (CK-MB), serum creatinine and estimation of creatinine clearance (eCrCl) by Cockcroft, Gault equation which classified patients into 4 groups as per K/DOQI guidelines. Major adverse cardiovascular events (MACE) comprising death, new myocardial infarction (MI) and target vessel revascularization (TVR) were recorded during early (30 days) and late (up to 5 years) follow up period.

RESULTS: Advanced RI was associated with a significant increase in number of affected vessels, percentage of C type lesions and a significant decrease in culprit artery TIMI flow. eCrCl correlated positively with EF and negatively with number of vessels affected and number of late MACE. Patients with advanced RI had an increased risk of TVR in first month after PCI and an increased risk of death, MI and total MACE on long-term follow up.

Conclusion: CKD is associated with an increased need for TVR during the first 30 days, and increased death, MI and total MACE during later follow up in PCI treated ACS patients.

Key Words: Acute myocardial infarction, Acute coronary syndrome, Coronary angioplasty, Contrast agents, Chronic kidney disease.

INTRODUCTION

It is well known that impairment of renal function (RF) is an independent risk factor for cardiovascular disease (CVD) events, even if it is mild.(1-4) Among ACS patients, CKD is an independent predictor of MACE, and is associated with less frequent use of proven medical therapies.(5-7) Despite the increased incidence of bleeding and stent thrombosis in PCI treated CKD patients presenting with ACS,(8,9) subjects with more advanced grades of renal dysfunction were generally excluded from clinical trials evaluating new CVD therapeutics.(10,11) The impact of CKD on mortality and morbidity in ACS patients is apparently underappreciated(12) and the optimal therapeutic modality in CKD patients presenting with ACS has not been well defined.(13) Therefore, we studied the impact of various grades of CKD, including end stage renal disease (ESRD), on the short and long term outcome of PCI done for a cohort of ACS patients.

MATERIALS AND METHODS

This study was conducted in 3 referral centers in Jeddah, KSA: King Faisal Specialist Hospital, Ibn Sina National Medical College Hospital and New Jeddah Clinic Hospital. It enrolled 427 consecutive patients presenting with ACS [214 patients with unstable angina (UA), 144 patients with non ST segment elevation myocardial infarction (NSTEMI) and 69 patients with St segment myocardial infarction (STEMI)] treated with PCI within 24 hours over the period from January 2008 to June 2013. An informed written consent was obtained from each patient according to the declaration of Helsinki and the ethical committee of all included hospitals. All patients were subjected to full history taking, clinical examination, ECG and echocardiograph to assess left ventricular ejection fraction (LVEF). Diabetes mellitus, hypertension, dyslipidemia, stable angina, unstable angina, acute coronary syndrome and heart failure were defined according to the American Heart Association definitions for measuring the clinical management and outcomes of patients with ACS.(14) Laboratory studies included CBC, blood urea, serum creatinine, electrolytes, fasting blood sugar and lipid profile. Serum cTNI and CKMB were recorded on admission and every 8 hours during hospital admission time. The maximum values for cTNI and CK-MB were used for comparisons. The eCrCl, based on serum creatinine value on admission, was calculated using the Cockcroft and Gault equation.(15) It classified patients into 4 groups as per Kidney Disease Outcomes Quality

Initiative (K/DOQI) guidelines on classification of CKD:(16)

- Group 1 (Normal RF): eCrCl > 90 ml/min.
- Group 2 (Mild RI): eCrCl 60 – 89 ml/min (equivalent to K/DOQI CKD stage 2).
- Group 3 (Moderate RI): eCrCl 30 – 59 ml/min (equivalent to K/DOQI CKD stage 3).

Group 4 (Severe RI): eCrCl < 30 ml/min, or treatment with regular haemodialysis (equivalent to K/DOQI CKD stages 4 and 5).

The protocol of patient diagnosis and management was based on the 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for PCI,(17) and the following updates.(18,19) Angiographic analysis for assessment of severity of coronary stenosis was done by two observers using visual assessment. The number of diseased coronary arteries was defined by the number of major coronary arteries with luminal diameter stenosis >70% (or ≥50% stenosis in the left main coronary artery). The culprit artery was defined as the vessel responsible for the ACS. The culprit artery TIMI flow grading system was used for semi quantitative evaluation of myocardial perfusion before and after PCI.(20) One to three intra-coronary stents were inserted in most patients; they were mostly of the drug eluting types. The morphologic types of the coronary stenotic lesions were recorded according to the modified ACC/AHA classification of the primary target stenosis.(21) PCI procedural success was defined as successful stent placement at the desired position with < 30% residual stenosis.(22) Prevention of contrast- induced nephropathy (CIN) was implemented according to the European Society of Urogenital Radiology guidelines,(23) including assessment of baseline RF, adequate hydration, use of the minimal possible dose of low osmolar agents and occasionally the administration of N-acetylcysteine. Patients with baseline serum creatinine > 1.8 mg/dl and not on dialysis were given the dye in one third dilution and put on IV isotonic saline at a rate of 1 ml/Kg/hour for 6 hours before and 6 hours after angiography.(24,25) Daily monitoring of urea, creatinine and fluid chart was employed for 5 days post- contrast injection and dialysis was instituted if indicated. CIN was defined as an impairment in RF (an increase in serum creatinine > 0.5 mg/dl or > 25 % compared to baseline) occurring within 3 days following intravascular administration of contrast media, in absence of alternative etiology.(26) MACE were defined as the combined end point of death (of cardiac or procedure related origin), newly developed

myocardial infarction, and clinically driven target vessel revascularization (TVR).(27) TVR was defined as repeat PCI or CABG (coronary artery bypass graft) performed for revascularization of a stenosis in the vessel originally treated. Restenosis was defined as a luminal diameter stenosis > 50% at follow up. MACE were subdivided into early MACE (recorded during the initial hospital stay and within one month from PCI) and late MACE (during the follow up which was done monthly and included repeat clinical and laboratory evaluation, medication review and, if indicated, TVR). The follow up period ranged from 39 to 70 months with an average of 49 months. Patients who presented with cardiogenic shock, acute renal failure, those in whom PCI was unsuccessful and those lost from follow up in less than 3 years were excluded from the study.

Statistical analysis was performed with SPSS 13.0 statistical package. Continuous data were expressed as mean ± standard deviation (SD) and categorical data as percentages. Associations between degree of renal impairment and other variables were assessed using ANOVA for continuous variables and Chi square test for categorical variables. Correlation coefficient (r) was used to study the relation between 2 continuous variables. The composite end- point (MACE) was determined using the Kaplan-Meyer survival method then time-to-event analysis was conducted using the log-rank test. A P value < 0.05 was considered statistically significant. A P value < 0.01 was considered as highly significant.

RESULTS

The baseline characteristics of the 4 study groups (Table I) showed no statistically significant difference regarding sex, prevalence of diabetes mellitus, hypertension and dyslipidemia and mean duration of follow up. The patients with moderate and severe RI had statistically significant older age and lower body mass index. The use of antiplatelets of the GPIIa/IIIb inhibitor group was significantly less in patients with more advanced degrees of RI.

There was no statistically significant difference between the 4 study groups regarding the maximum levels of CK-MB and cTNI before and after PCI (Table II-A). The mean values of the maximal levels of both cardiac markers declined after PCI in all study groups (Table II-B), but the decline was statistically significant only for CK-MB in patients with normal RF.

The mean number of vessels affected was statistically higher in patients with more advanced RI (Table III). So, instances of triple vessel disease showed a significant clustering in patients

with severe RI (Table IV). The grade of culprit artery TIMI flow following PCI and the percent dilatation of the culprit lesion (Table III) were both significantly lower in patients with higher grades of RI. No statistically significant difference in the number of stents inserted in the different groups was observed. Over the whole study cohort, we found a statistically significant positive correlation between eCrCl and both EF and percent dilataion of the most stenotic lesion (Table V). There was a statistically significant negative correlation between eCrCl and both the number of vessels affected and the number of late MACE.

Table (VI) and figure (1) reveal that type A lesions (most mild) were relatively more frequently encountered in patients with normal RF ormild RI compared with patients with moderate

and severe RI. The reverse was true for type C lesions (most severe) which were relatively more frequently seen in patients with more advanced CKD.

The need for TVR was significantly more frequent in patients with severe RI compared to other groups (Table VII-A). Death, MI and total early MACE were not significantly different among the study groups. A highly significant increase in frequencies of late (up to 5 years) death, MI and total late MACE in patients with severe RI was observed compared to other groups (Table VII-B). Log rank test applied for comparison of Kaplan Meyer curves of MACE free survival in different study groups (Figure 2) showed a statistically significant steady decline in survival with each drop in the RF sector. ($X2 = 15.84$, P = 0.001)

Table (I): Baseline Characteristics, Use of GPIIb/IIIa inhibitors and Follow Up Duration of the Study Patients

	Normal Renal Function (n = 165)	Mild Renal Impairment (n = 109)	Moderate Renal Impairment (n = 115)	Severe Renal Impairment (n = 38)	Test Statistic	P
Sex (Male No, %)	133 (80.6 %)	86 (78.9 %)	84 (73 %)	25 (65.8 %)	$\chi^2 = 5.11$	0.164 (NS)
Age (Years)	56.5 $\pm$ 9.4	58.4 $\pm$ 7.8	60.3 $\pm$ 11.4	58.3 $\pm$ 10	F = 3.509	0.015 (S)
Body Mass Index (Kg/m$^{2)}$)	28.4 $\pm$ 5	24.9 $\pm$ 3.6	25.1 $\pm$ 4.5	24.5 $\pm$ 3	F = 21	< 0.001 (HS)
Diabetes Mellitus	80 (48.5 %)	55 (50.5 %)	65 (56.5 %)	18 (47.4 %)	$\chi^2 = 2.034$	0.565 (NS)
Hypertension	98 (59.4 %)	74 (67.9 %)	79 (68.7 %)	24 (63.2 %)	$\chi^2 = 3.334$	0.343 (NS)
Dyslipidemia	118 (71.5 %)	79 (72.5 %)	87 (75.7 %)	21 (55.3 %)	$\chi^2 = 5.93$	0.115 (NS)
Use of GPIIb/IIIa inhibitors	101 (61.2 %)	76 (69.7 %)	54 (47 %)	17 (44.7 %)	$\chi^2 = 15.359$	0.002 (HS)
Follow up Duration (Months)	49.2 $\pm$ 6.7	50.2 $\pm$ 7.2	47.7 $\pm$ 6.6	48.7 $\pm$ 8.7	F = 2.49	0.06 (NS)

Table (II): Maximum CK-MB and Troponin before and after PCI

(A) Comparison of the values among different renal function groups

	Normal Renal Function (n = 165)	Mild Renal Impairment (n = 109)	Moderate Renal Impairment (n = 115)	Severe Renal Impairment (n = 38)	F	P
Maximum CK-MB before PCI	466.7 ± 962.4	525.7 ± 992.4	501.9 ± 1114.9	457 ± 373.5	0.1	0.96 (NS)
Maximum CK-MB after PCI	219.4 ± 286.4	363.1 ± 714.4	347.6 ± 786.7	319.4 ± 276.3	1.769	0.152 (NS)
Maximum cTNI before PCI	2.92 ± 23.8	1.65 ± 3.1	4.5 ± 22.7	2.44 ± 3.6	0.433	0.73 (NS)
Maximum cTNI after PCI	0.8 ± 1.3	1.25 ± 2.1	2.52 ± 16.3	1.81 ± 3	0.943	0.42 (NS)

CK-MB: cardiac isoenzymes of creatine kinasecTNI: cardiac troponin I

(B) Comparison of the values before and after PCI within each renal function group

		Before PCI	After PCI	T	P
Normal Renal Function (n = 165)	CK-MB	466.7 ± 962.4	219.4 ± 286.4	3.163	0.002 (HS)
	cTNI	2.92 ± 23.8	0.8 ± 1.3	1.141	0.255 (NS)
Mild Renal Impairment (n = 109)	CK-MB	525.7 ± 992.4	363.1 ± 714.4	1.388	0.167 (NS)
	cTNI	1.65 ± 3.1	1.25 ± 2.1	1.106	0.27 (NS)
Moderate Renal Impairment (n = 115)	CK-MB	501.9 ± 1114.9	347.6 ± 786.7	1.213	0.227 (NS)
	cTNI	4.5 ± 22.7	2.52 ± 16.3	0.762	0.447 (NS)
Severe Renal Impairment (n = 38)	CK-MB	457 ± 373.5	319.4 ± 276.3	1.825	0.072 (NS)
	cTNI	2.44 ± 3.6	1.81 ± 3	0.828	0.411 (NS)

CK-MB: cardiac isoenzymes of creatine kinase cTNI: cardiac troponin I

Table (III): Angiographic and PCI Data

	Normal Renal Function (n = 165)	Mild Renal Impairment (n = 109)	Moderate Renal Impairment (n = 115)	Severe Renal Impairment (n = 38)	F	P
Number of Vessels Affected	1.255 $\pm$ 0.56	1.34 $\pm$ 0.6	1.313 $\pm$ 0.54	1.579 $\pm$ 0.79	3.194	0.023 (S)
Number of Stents Inserted	1.582 $\pm$ 0.83	1.844 $\pm$ 0.92	1.722 $\pm$ 0.95	1.684 $\pm$ 0.81	1.964	0.119 (NS)
Culprit Artery TIMI Flow	1.533 $\pm$ 0.69	1.752 $\pm$ 0.76	1.53 $\pm$ 0.74	1.421 $\pm$ 076	3.027	0.029 (S)
Percent dilatation of the culprit lesion	91.33 $\pm$8.7	92.84 $\pm$9.1	88.35 $\pm$10.6	85.53 $\pm$10.6	8.257	< 0.001 (HS)

Table (IV): Extent of Coronary Artery Involvement
In Different Groups of Renal Function

Coronary Involvement	Renal function Group			
	Normal RF (n = 165)	Mild RI (n = 109)	Moderate RI (n = 115)	Severe RI (n = 38)
Single Vessel	133 (80.6 %)	78 (71.6 %)	83 (72.2 %)	22 (57.9 %)
Double Vessels	22 (13.3 %)	26 (23.9 %)	28 (24.3 %)	11 (28.9 %)
Triple Vessels	10 (6.1 %)	5[*] (4.6 %)	4 (3.5 %)	5[*] (13.2 %)

* One patient has 4 vessel disease
χ^2 = 14.412
P = 0.025 (Significant)

**Table (V): Some Statistical Correlations of Creatinine Clearance
With Other Study Parameters**

Parameter Correlated with Creatinine Clearance	r	P
LVEF	0.332	< 0.001 (HS)
Maximum CK-MB before PCI	0.002	0.97 (NS)
Maximum CK-MB after PCI	- 0.077	0.113 (NS)
Maximum cTNI before PCI	- 0.01	0.845 (NS)
Maximum cTNI after PCI	- 0.054	0.265 (NS)
Number of Vessels Affected	- 0.099	0.041 (S)
Number of Stents Inserted	- 0.046	0.279 (NS)
Percent dilatation of the most stenotic lesion	0.0034	0.361 (NS)
Number of Early MACE	0.065	0.179 (NS)
Number of Late MACE	- 0.232	< 0.001 (HS)

LVEF: left ventricular ejection fraction.
PCI percutaneous intervention.
CK-MB: cardiac isoenzymes of creatine kinase.
cTNI: Cardiac troponin I.
MACE: Major Adverse cardiac events.

**Table (VI): Frequency of Different Angiographic Types of Coronary Artery Lesions
In Different Groups of Renal Function**

Lesion Type	Renal Function Group			
	Normal RF (n = 165)	Mild RI (n = 109)	Moderate RI (n = 115)	Severe RI (n = 38)
A	41 (24.8 %)	27 (24.8 %)	11 (9.6 %)	8 (21.1 %)
B1	35 (21.2 %)	25 (22.9 %)	22 (19.1 %)	12 (31.6 %)
B2	63 (38.2 %)	50 (45.9 %)	56 (48. %)	23 (60.5 %)
C	65 (39.4 %)	44 (40.4 %)	(52.2 %)	34 (89.5 %)

The frequencies are presented as number and (percentage).
Number: Number of patients who have at least one lesion of the specified type
Percentage: Percentage of the above number to the total number of patients within the specified renal function group
$\chi^2 = 17.918$
P = 0.036 (Significant)

Table (VII): Major Adverse Cardiac Events (MACE)
At 30 Days and 5 Years After PCI

(A) Mean Number of Early MACE (Within 30 Days after PCI)

Total 424 patients	Normal Renal Function (n = 165)	Mild Renal Impairment (n = 109)	Moderate Renal Impairment (n = 115)	Severe Renal Impairment (n = 38)	F	P
Death	0.006 ± 0.08	0.009 ± 0.1	0.0 ± 0.0	0.026 ± 0.16	0.976	0.404 (NS)
Myocardial Infarction	0.006 ± 1041	0.018 ± 0.13	0.17 ± 0.13	0.053 ± 0.23	1.407	0.24 (NS)
Target Vessel Revascularization	0.012 ± 0.11	0.009 ± 0.1	0.017 ± 0.13	0.079 ± 0.27	2.843	0.037 (S)
Total Early MACE	0.024 ± 0.22	0.037 ± 0.27	0.035 ± 0.26	0.158 ± 0.59	2.197	0.088 (NS)

(B) Mean Number of Late MACE (Up to 5 Years after PCI)

Total 424 patients	Normal Renal Function (n = 164)	Mild Renal Impairment (n = 108)	Moderate Renal Impairment (n = 115)	Severe Renal Impairment (n = 37)	F	P
Death	0.024 ± 0.15	0.056 ± 0.23	0.096 ± 0.3	0.243 ± 0.43	8.24	< 0.001 (HS)
Myocardial Infarction	0.03 ± 0.17	0.056 ± 0.23	0.148 ± 0.36	0.108 ± 0.31	4.98	0.002 (HS)
Target Vessel Revascularization	0.049 ± 0.22	0.083 ± 0.28	0.07 ± 0.26	0.108 ± 0.31	0.759	0.218 (NS)
Total Late MACE	0.104 ± 0.34	0.194 ± 0.44	0.313 ± 0.61	0.459 ± 0.69	7.548	< 0.001 (HS)

Figure 1. Frequency of different coronary lesions in each renal function group.
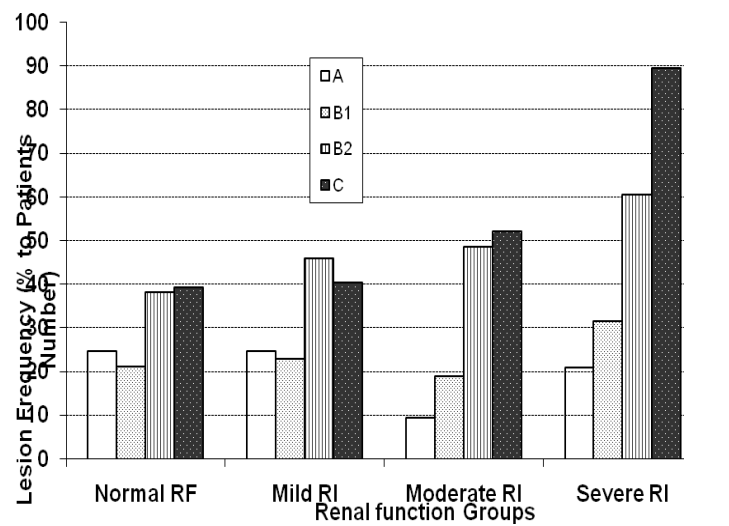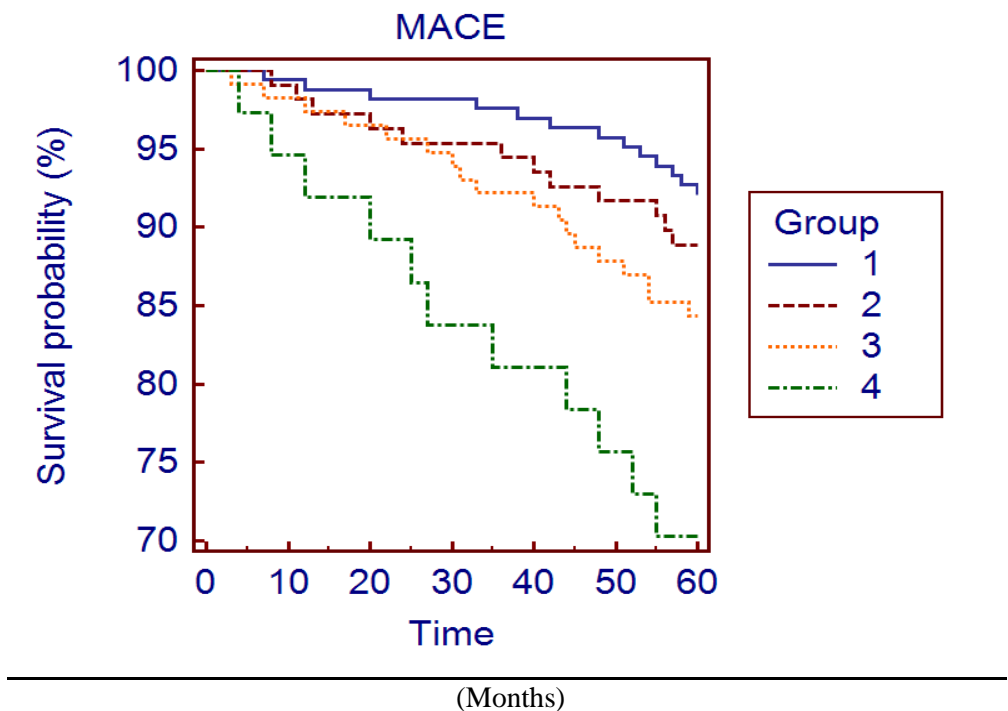
Figure 2. Showing Caplan Mayer curve of late MACE after PCI.

(Months)

MACE: Major Adverse Cardiac Events.
Group1: Normal renal function.   Group 2: Mild renal Impairment.
Group3: Moderate renal Impairment.   Group 2: Severe renal Impairment.

DISCUSSION

CKD is a worldwide public health problem with poor outcomes and high cost.(1) Individuals with CKD are more likely to die of CVD than to develop kidney failure.(28) RI has consistently been found to be an independent risk factor for CVD outcomes and all cause mortality in patients undergoing PCI; it appears that the increased risk is present even with mild reductions in kidney function.(1-4) ACS patients with RI have generally been systemically excluded from large cardiovascular trials.(29) It was perceived that PCI is inappropriately underutilized in ACS patients with concomitant RI.(30)

Therefore, with advances in PCI techniques and overall improvements in outcome, we decided to explore the impact of CKD on PCI outcome in a cohort of patients presenting with ACS. The categorization of the study patients was based on eCrCl at presentation as per K/DOQI guidelines.(16) This was similarly adopted in other studies addressing the effect of CKD on PCI outcome.(31,32) We included patients covering the whole spectrum of CKD, including ESRD patients. Patients with some degree of RI constituted 262/427 (61 %) of the study population, which was very close to the ratio reported by Freeman et al (32) (62 %), but higher than the ratio reported by Inrig et al (33) (40 %) who excluded patients with severe CKD (eCrCl < 30ml/min). Patients with baseline RI were significantly older (Table I), as reported in other studies.(32,33)

The significantly higher BMI in patients with baseline normal RF (Table I) may be explained by freedom from the wasting/cachexia syndrome in CKD patients which consists of anorexia, increased energy expenditure and decreased protein stores.(34) Many studies found diabetes mellitus and hypertension to be more prevalent in CKD patients compared to patients with normal RF. The association of CKD with dyslipidaemia was inconsistent.(2,32,33,35) Patients with RI in the present study did not have more known baseline CVD risk factors (apart from RI itself). Even in studies revealing increased prevalence of DM, HTN and dyslipidaemia, the association of RI with increased MACE was independent of all other measured variables.(2,32,33,35)

The underutilization of cardiac medications and interventions in CKD patients presenting with ACS might be attributed to increased bleeding complications with the use of antiplatelets(32) and fear of CIN following coronary angiography(33).

In the present study, the use of GPIIb/IIIa inhibitors was significantly less in patients with more advanced grades of RI. Winkelmayer et al(36) found that the use of aspirin is limited in elderly dialysis patients after AMI. The problem may be further compounded by blunted response to the antiplatelet agent within the uraemic milieu, as reported for clopidogrel(37). Shlipak et al(38) has found that RI is associated with lower use of PCI, antiplatelets and β-blockers both during hospitalization for AMI and after discharge.

The maximum values of CK-MB and cTNI before and after PCI encompassed a wide range with high standard deviations and so they showed no statistically significant differences among the 4 study groups (Table II-A). Also, we found no significant correlation between these biomarkers and eCrCl (Table V). These results were concordant with those of Li et al(31) who found no significant relationship between status of RF and biomarkers of myocardium necrosis and presumed that acute STEMI caused such a severe damage to the myocardium that eliminated the effects of RF. Within each group, the values became lower after PCI, as expected (table II-B). The decline following PCI was statistically significant only for CK-MB in patients with normal RF. The absence of significant drop in these cardiac markers even after successful PCI may be explained by that RI per se increases serum CK-MB(39) and cardiac troponins(40). Also, comparing only the maximum levels of the biomarkers may be less sensitive for detection of the decline(40).

There was a significant increase in the number of vessels affected in patients with CKD compared to patients with normal RF, with the highest mean number of vessels affected observed in patients with severe RI (Table III). Consequently, patients with triple vessel affection tended to significantly cluster in the severe RI group (Table IV). All over the studied patients, the number of vessels affected showed a statistically significant negative correlation with baseline eCrCl (Table V). In accord with these results, Best et al(2) found triple vessel disease to be more frequent in patients with severe RI or patients on dialysis compared with patients with mild to moderate RI (P < 0.001). Also, Gitt et al 2010(41) found that in patients with ACS, the prevalence of three vessels disease in patients with renal failure was 44.5% compared to 23.8% only in patients without.

The mean number of coronary stents inserted per case was not, however, higher in patients with severe RI compared with the other groups. Similarly, in the study of Best et al (2), the lowest

CrCl group had a greater number of diseased coronary vessels than the higher CrCl group, but had a similar number of vessels treated. These findings may reflect the difficulties in cannulation and stenting of the atherosclerotic/calcified coronary arteries in uraemic patients, who, even in the predialysis stage, are known to have increased arterial stiffness.(42) Coronary angiographic studies have revealed a high prevalence of calcified, tortuous and restenotic lesions in patients with RI (2).

Three other important indicators of the higher technical difficulty and lower procedural success of PCI performed in patients with more advanced grades of CKD in this study are: **(1)** the significantly lower post-dilatation culprit artery TIMI flow, **(2)** the significantly lower percent dilatation of the culprit lesion (Table III), and **(3)** the significant positive correlation between baseline CrCl and percent dilatation of the most stenotic lesion (Table V). These results were concordant with those of Appleby et al (43) who found that culprit artery TIMI flow was significantly lower in patients with CrCl < 60ml/min compared to patients with CrCl > 60ml/min.

Freeman et al(32) found a significantly lower LVEF in patients with RI compared to patients without. In the present study, we found a statistically significant positive correlation between baseline eCrCl and LVEF (Table V). There is increasing evidence that uremic toxins adversely affect cardiac function (44). This may in turn adversely affect the outcome of PCI in uremic patients(45). Best et al (2) found a steady decline of LVEF across the 4 groups of RF that were classified according to baseline CrCl (> 70, 50 – 69, 30 – 49, < 30 ml/min). Patients on dialysis were considered a separate group and they had a relatively increased EF (most probably reflecting a state of hyperdynamic circulation or hyperdynamic heart failure rather than improved myocardial function). However; in our study we excluded all patients on renal dialysis.

We applied the modified ACC/AHA classification of the primary target stenosis to characterize the morphologic types of the coronary lesions (21). This scheme recognizes type A lesions as the most amenable for successful dilatation (>85%), with low risk of abrupt vessel closure. Type C lesions have the least possibility for successful dilatation (< 60 %) and the highest risk of abrupt vessel closure. We found a statistically significant relative increase in type C lesions in patients with more advanced grades of RI (Table VI, Figure 1). Type A lesions, on the other hand, tended to

cluster in patients with normal RF or mild RI. A similar finding was reported by Best et al (2). A similar finding was not detected in another study that excluded patients with serum creatinine >1.8mg/dl (46), denoting that this differential distribution of coronary artery lesions is probably present only with severe degrees of RI. Utilizing integrated backscatter intravascular ultrasound, Miyagi et al(47) found a decline in eCrCl to be significantly correlated with a decline in fibrous tissue content and an increase in fat content of the atheromatous plaques; changes which indicate plaque vulnerability and herald plaque rupture and AMI.

Although PCI is an effective therapy for ACS, it remains associated with high complications rate and poor long-term outcomes in patients with advanced CKD(48). The burden of post- PCI morbidity and mortality was expressed in this study as the MACE the composite end point of death, MI and clinically driven target vessel or target lesion revascularization (TVR or TLR). This is the most commonly used composite end point in cardiovascular research(49). Kahn JK et al (50) used the more inclusive term, TVR, which encompasses, in addition to TLR, interventions outside the target lesion performed to treat other atherosclerotic plaques as well as interventions done within the target lesion to treat neo-intimal hyperplasia resulting in in-stent restenosis. Although TLR may better reflect the effectiveness of the initial intervention, TVR better reflects the increased burden of coronary atherosclerosis in patients with various grades of RI compared to patients without.

PCI in patients with ESRD is associated with a 60–81 % incidence of restenosis(51). In the present study, patients with severe RI had higher incidence of clinically driven TVR within 30 days of PCI compared with other RF groups (Table VII-A). Difficulties in technique due to arterial wall stiffness (42) compounded with bleeding complications(41) afflicting the atheromatous wall might explain this.

During long-term follow up, the increased TVR instances in severe RI patients was not statistically significant compared to other RF groups, probably due to the relatively small percentage of these patients (37/424 = 8.7 %). Similar to the results of Gitt et al(41) and Li et al,(31) the risk of in-hospital MI was not increased in patients with RI compared to patients without. However, these investigators found an increased risk of in-hospital mortality for patients with RI compared to patients without. Such an increased risk was not found in the present study.

We found a highly significant negative correlation between baseline eCrCl and number of late MACE (Table V). The particular events that occurred at a significantly higher rate in patients with more severe degrees of RI during long-term follow up were death and MI (Table VIIB), leading to a significantly higher incidence of total rate MACE and a significantly lower MACE free survival curve in patients with severe RI compared to the other groups (Figure 2). Na KY et al (52) reported survival curves in different CKD stages following PCI that were very close to our results. They found that the strongest predictors for mortality were CKD stage 5 and old age (P < 0.001 for both). Best et al (2) found a significantly increased risk of death and MI in patients with severe RI (eCrCl <30 ml/min) during one year interval following PCI. Similar to our results, the incidence of TVR was not increased in these patients. However, the actual incidence of restenosis in these patients is expected to be high(53) and so the significantly increased risk of death and MI during long term follow up found by Best et al and the present study may denote the presence of severe silent ischaemia.

RESEARCH LIMITATIONS

The effect of exposure to IV contrast used in PCI on RF was not specifically addressed in this study. However, occasional post-contrast injection rise in serum creatinine were only mild and recoverable with conservative measures like good hydration, pharmaco-vigilance for potentially nephrotoxic medications and occasional administration of acetylcysteine.(22)

Duration and etiology of CKD could not be precisely defined in some cases. Therefore, recent changes in RF at time of enrollment due to acute events could not be excluded and may make the baseline eCrCl not perfectly representing the basal level of CKD.

Creatinine based methods for estimation of glomerular filtration rate carry substantial degrees of inaccuracy(54). Finally, other outcome measures such as functional status and quality of life were not addressed.

CONCLUSION

Results of PCI in patients with severe RI remain suboptimal despite technological advances and increased use of coronary stents. These patients may be deprived the opportunity to receive GPIIb/IIIa inhibitors and other potentially beneficial medications. They have a significantly increased risk of TVR within one month of the index procedure and a significantly increased risk of MI, death and total MACE on the long term. Severe silent ischaemia may account for the

increased cardiac mortality in ESRD patients even after successful PCI. This underscores the need for vigilant regular follow up of these patients for early recognition and management of coronary insufficiency.

Recognition of the excess risk burden of various grades of RI in ACS patients treated with PCI is essential for risk stratification and may assist in development of management strategies tailored to improve outcome. Further investigations and targeted randomized clinical trial are needed to define the best medical and/or interventional approach for management of ACS in patients with various stages of CKD.

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