IHD & Renal Dysfunction

A Risky Combination

Ischemic heart disease is the world's leading cause of death. Acute coronary syndromes account for 45% of all-cause mortality in patients with any degree of renal impairment. This article is an update on the current management of ischemic heart disease in patients with renal disease.

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Ischemic heart disease is the leading cause of death worldwide associated with high patient morbidity and mortality.[1] Individuals with impaired renal function constitute a population highly afflicted with coronary heart disease. These patients are more likely to have traditional risk factors, including hypertension, diabetes, dyslipidemia and smoking, which may predispose them to an increased propensity for cardiovascular morbidity and mortality.[2] Acute coronary syndromes account for approximately 45% of all-cause mortality in patients with any degree of renal impairment.[3]

This article provides an update on the current management of ischemic heart disease in patients with renal disease, including:

- What is the role of medical therapy for acute coronary syndrome (ACS) patients with renal disease?
- What is the role of percutaneous coronary intervention (PCI)?
- What is the role of coronary artery bypass grafting (CABG)?

Medical therapy for patients with renal disease

Growing evidence shows renal impairment is an independent risk factor for increased patient morbidity and mortality in the ACS setting.

The term ACS encompasses patients afflicted with either unstable angina, non-ST elevation myocardial infarction (NonSTEMI) or ST elevation myocardial infarction (STEMI). Although the medical management of patients with ACS in the 21st century involves the use of acetylsalicylic acid, beta-blockers, nitrates, anticoagulation, statins, angiotensin-converting enzyme (ACE) inhibitors and thrombolysis, such is not the case with the renal population. Patients with renal impairment are less likely to receive appropriate medical care in an ACS setting with subsequent increased morbidity and mortality.

In the study by Al Suwaidi *et al.*, a metanalysis of four randomized control trials compared patients with and without any degree of renal impairment for both short-term and long-term clinical outcomes in an ACS setting.[4] The patient population was divided into two groups:

1. the NonSTEMI group: 11,152 (58%) patients with a normal creatinine value were compared to 8,152 (42%) patients with any degree of renal impairment and
2. the STEMI group: 10,951 (59%) patients with a normal creatinine were compared to 7,670 (41%) patients with renal disease.[4]

In both populations, patients with renal dysfunction were more likely to be older in age, diabetic, hypertensive and have concomitant cerebrovascular disease. These patients were less likely to receive appropriate

medical therapy or any form of invasive coronary revascularization—cardiac catheterization, PCI or CABG (Table 1).

Beneficial therapies are given less because patients are thought to be frail and more likely to experience side-effects. For example, the use of antiplatelet therapy has to be discontinued due to uremic effects on platelet function and subsequent increased bleeding risk. The tenuous use of ACE inhibitors, which raise creatinine, is also of major concern.

Finally, there are no randomized, controlled trials demonstrating the benefit of these agents in the renal population, as these patients are often excluded from the studies. This undertreatment may contribute to the very high mortality observed in this population. Clinicians who evaluate this risk-benefit trade off may, unfortunately, emphasize the tangible risk for short-term side-effects rather than the long-term benefits of reduced mortality.

Table 1

NonSTEMI & STEMI Trials

Characteristics	NonSTEMI Normal Cr	NonSTEMI RI	STEMI Normal Cr	STEMI RI
Patients (n)	11,152	8,152	10,951	7,670
Median age (n)	59	72	56	72
Female (%)	25	47	15	40
Smoker (%)	36	15	51	26
Diabetes (%)	18	26	15	18
Hypertension (%)	59	75	45	60
Cerebrovascular disease (%)	6	12	5	10
Cardiac catheterization (%)	55	32	48	32
PCI (%)	30	12	30	17
CABG (%)	20	6	10	3

NonSTEMI: Non-ST elevation myocardial infarction
STEMI: ST elevation myocardial infarction
Cr: Creatinine
RI: Renal impairment
n: Number
PCI: Percutaneous coronary intervention
CABG: Coronary artery bypass grafting

What is the role of PCI

Patients with varying degrees of renal impairment make up an increasing percentage of the population undergoing PCI. This is due to the prolonged lifespan of renal failure patients combined with an increased predisposition to accelerated atherosclerosis. The presence of even mild renal insufficiency appears to predict poor prognosis after PCI with or without stenting.

A number of trials have evaluated a variety of clinical settings, including elective PCI for stable angina syndromes and primary PCI in the setting of an acute MI (myocardial infarction).

The outcome of patients with mild renal insufficiency in the elective setting of PCI was evaluated by Best *el al.*[6] Using the Mayo PCI database, the baseline characteristics of 5,237 patients from 1994-1999 were identified and separated into four categories based on renal function (Table 2). For increasing degrees of renal impairment, the rates of stroke, MI and death (in hospital and during a one-year followup) were significantly higher.

The impact of renal dysfunction in patients undergoing primary PCI for acute MI was studied by

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Wright *et al.* study:

Reviews the Mayo CCU database, which includes 3,106 individuals from 1988-2000 and compares in-hospital and post-discharge outcomes in patients with varying degrees of renal impairment.[5] The incidence of cardiovascular risk factors were more common amongst patients with increasing creatinine values. Modern medical therapy, including the use of ASA, beta-blockers, anticoagulation, ACE inhibitors and thrombolysis were not used frequently in their renal patient population. There also appeared to be an increased rate of in-hospital death and out-of-hospital mortality (Table 3).

Sadeghi *et al.* in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study.[7]

CADILLAC patients were randomized to stenting versus balloon angioplasty and abciximab versus standard anticoagulation in a two-by-two factorial design. The frequency of single vessel disease, multivessel disease, use of stent and use of abciximab was similar between patients with preserved renal function and those with renal impairment (Table 4). Compared to individuals with a normal creatinine pre-procedure, patients undergoing PCI with a CrCl < 60 mM were three times more likely to develop acute renal failure and nine times more likely to die in hospital.

Extending the results to one year, the rates of stroke, reinfarction and death were significantly higher in patients with impaired renal function. Patients with renal dysfunction were more often older, had diffuse atherosclerosis, reduced ejection fraction, were undertreated with beta-blockers and statins and were more likely to develop restenosis and reocclusion.

A common perception that patients with any degree of renal impairment are poorer candidates for coronary revascularization because they have a higher risk for complications (bleeding, MI, stroke and death) from PCI, a higher prevalence of coronary anatomies unsuitable for revascularization (diffuse vessel disease) and have reported lower rates of long-term coronary patency.

Nonetheless, the indications for PCI are similar to the population of nonuremic subjects with CAD. Correction of coronary lesions in renal patients with PCI and stenting, especially in the current era of drug-eluting stents, will likely improve the poor cardiovascular morbidity and mortality observed in older studies when bare metal stents were used frequently.

Table 2

Effects of varying degrees of renal impairment

Characteristics	Cr < 130 mM	Cr 130-220 mM	Cr 220-345 mM	ESRD
In hospital				
Acute renal failure (%)	0.2	2.0	6.5	0.0
Stroke (%)	0.3	0.4	0.6	0.5
AMI (%)	0.7	2.0	2.0	1.5
Death (%)	0.6	2.3	7.1	6.0
One year followup				
AMI (%)	1.0	2.0	2.0	1.5
Death (%)	3.0	10.0	25.0	25.0

Cr: Creatinine
ESRD: End-stage renal disease
AMI: Acute myocardial infarction

Table 3

Wright study

Characteristics	Cr < 130 mM	Cr 130-220 mM	Cr 220-345 mM	ESRD
Median age (n)	57	72	83	73
Female (%)	20	39	66	48
Smoker (%)	22	28	30	57
Diabetes (%)	16	18	25	41
Hypertension (%)	35	48	68	61
Cerebrovascular disease (%)	5	9	27	30
ASA (%)	86	82	74	61
ACE inhibitor (%)	21	21	16	11
Beta-blocker (%)	44	45	32	20
Anticoagulation (%)	95	93	80	80
Thrombolysis (%)	76	60	30	10
In-hospital death (%)	2	6	21	30
Out-of-hospital mortality (%)	1.4	2.4	3.4	5.4

Cr: Creatinine
ESRD: End-stage renal disease
n: Number
ASA: Acetylsalicyclic acid
ACE: Angiotensin-converting enzyme

What is the role of CABG?

In the era of competing interests between PCI and CABG for revascularization in patients with multivessel coronary artery disease, a number of trials have demonstrated equivalence in long-term mortality. The two patient populations that benefit from CABG are patients afflicted with diabetes and patients with renal disease. If revascularization is warranted, it should be determined whether coronary revascularization with PCI or CABG improves morbidity and mortality.

Liu *et al.* evaluated 15,500 patients undergoing CABG in the New England states from 1992-1997. The prevalence of diabetes, peripheral vascular disease, cerebrovascular disease and hypertension were more common in the 279 patients with impaired renal function defined as a CrCl < 30 mM.[9] The risks of stroke, bleeding and death post-CABG were twofold, 1.5-fold and threefold increased in uremic patients, compared to patients with normal renal function.

The optimal method of coronary revascularization in the renal population remains controversial. A comparison of PCI, PCI and stent and CABG in dialysis patients was recently evaluated by Herzog *et al.*[10] Using the U.S. Renal Data System (USRDS), an analysis of 15,784 patients undergoing coronary revascularization with respect to long-term survival was performed.[10] The age, gender and etiology of renal dysfunction (diabetes and hypertension) were similar across all three groups. Despite a greater in-hospital death rate of 8.6% for CABG, 6.4% for PCI and 4.1% for stent, the two

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Gruberg *et al.* study:

The use of intracoronary radiation for the prevention of in-stent restenosis is a major issue for patients with renal impairment. The study examined the in-hospital and six-month clinical and angiographic outcome of 118 individuals with renal dysfunction and 481 individuals without renal impairment who were treated for intracoronary radiation for the prevention of in-stent restenosis in native coronaries and saphenous vein grafts.[8] The mortality rate at six months was higher in patients with renal disease compared to patients with preserved renal function (7.6% vs. 1.9%).

year all-cause survival was 56% in the CABG subgroup versus 48% in the PCI and stent groups.

As a group at particularly high risk for all-cause and cardiac mortality, the current evidence suggests patients with renal failure and multivessel coronary artery disease may benefit long term from complete revascularization with CABG. In particular, the use of grafting with an internal mammary artery may be the preferred revascularization procedure for increased survival. PCard

Table 4

Creatinine levels & renal failure

Characteristics	CrCl > 60	CrCl < 60
In hospital		
Patients (n)	1583	350
LAD (%)	38	37
Circumflex (%)	18	12
RCA (%)	45	50
3 Vessel CAD (%)	15	19
Stent (%)	57	56
Abciximab use (%)	53	54
Stroke (%)	0.1	0.3
Reinfarction (%)	0.8	0.9
Death (%)	0.8	7.5
One year followup		
Stroke (%)	0.4	0.9
Reinfarction (%)	2.2	2.8
Death (%)	2.4	12.7

CrCl: Creatinine clearance
n: Number
LAD: Left anterior descending
RCA: Right coronary artery
CAD: Coronary artery disease

Take-home message

- Patients with the highest mortality risk, (*i.e.*, those with renal insufficiency) should gain the greatest survival benefit from medications. Many pharmacologic agents used to manage patients with ACS (ASA, beta-blockers, nitroglycerin, anticoagulants) should be utilized in patients with renal disease, despite these patients being excluded from many of the large randomized, controlled trials. For renal patients requiring further coronary revascularization options, in the setting of single vessel disease, PCI with the use of drug-eluting stents should be explored.
- Caveat—Patients with renal impairment undergoing coronary revascularization (PCI or CABG) do have higher complication rates compared to patients with normal renal function.
- For patients with multivessel CAD and renal impairment, current evidence suggests CABG is superior to PCI.

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