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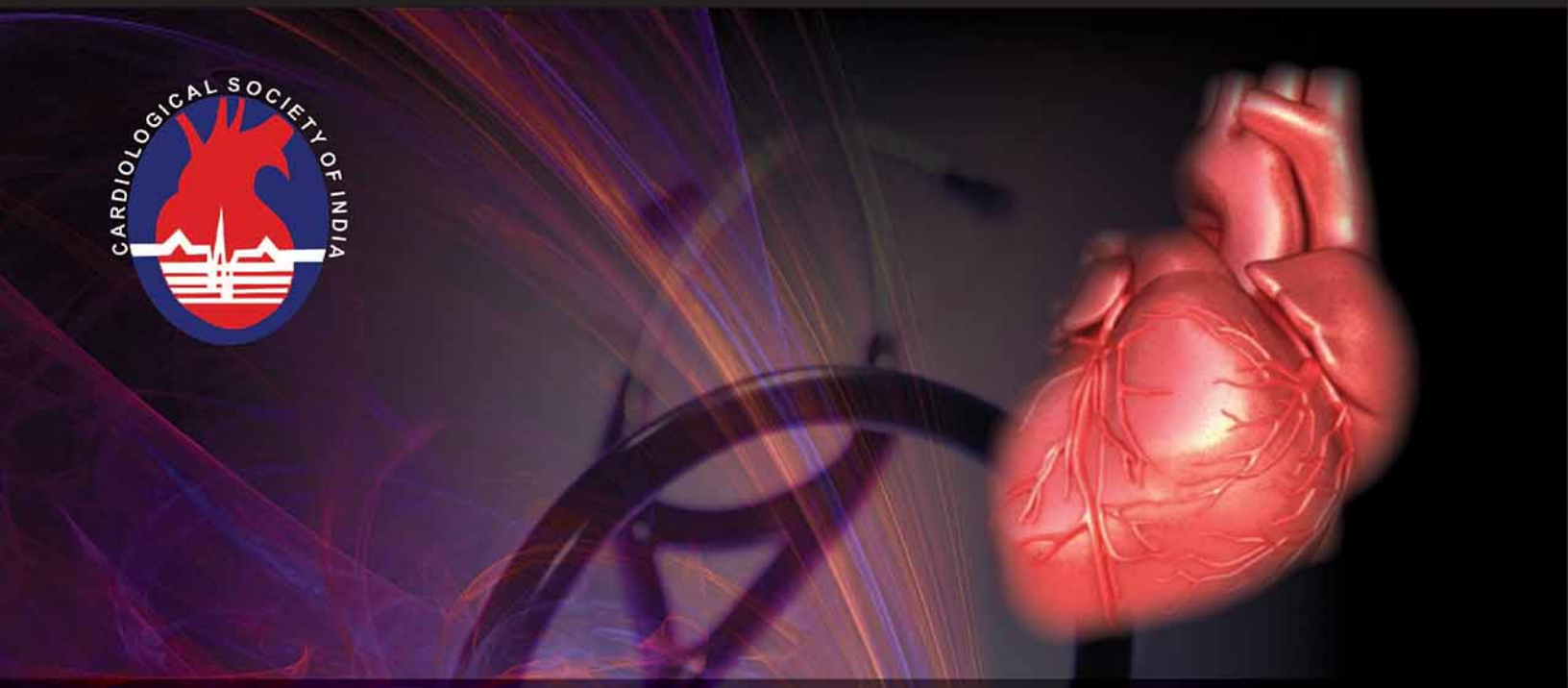

Cardiological Society of India

CARDIOLOGY UPDATE 2014

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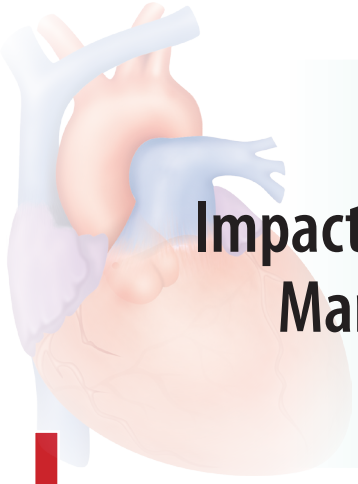

CHAPTER 3

Impact of Kidney Disease on the Outcome and Management of Acute Coronary Syndrome

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INTRODUCTION

Both, kidney disease including acute kidney injury (AKI) or chronic kidney disease (CKD) and acute coronary syndrome (ACS) are medical entities which are highly prevalent in the general population and in the daily clinical practice of a physician or cardiologist. The management of either alone and especially in combination presents challenges, often turning out to be double-edged swords in terms of treatment perspectives. Confounding these issues further, is the lack of evidence, in these subsets, due to the absence of prospective trials, as renal diseases often are exclusion criteria in most studies.

The impact of kidney disease on ACS can be discussed in the perspective of both AKI and CKD.

IMPACT OF ACUTE KIDNEY INJURY ON ACUTE CORONARY SYNDROME

The information available on the impact of acute renal failure (ARF) on the outcome of ACS is limited, especially due to the absence of standardization in the definitions or diagnosis of ARF. ARF is defined as a complex multicausal dysfunction with clinical features ranging from small changes in serum creatinine (SCr) to anuric renal failure. The diagnosis of ARF is often unrecognized, especially with mere small elevations in SCr. Hence, to standardize the diagnosis of ARF, and to establish the newer concept of AKI, two definitions, were introduced, as both these entities have subtle but important differences. Injury precedes failure and studies have proven that even small rises in SCr are associated with a worse prognosis.

The Acute Kidney Injury Network (AKIN)[1] developed a classification (Table 1), which uses the concept of small elevations of SCr over a short period of time with the purpose of allowing an early diagnosis and treatment of AKI.

TABLE 1: AKIN criteria for defining and staging AKI[a]

Stage	*Serum creatinine criteria*	*Urine output*
1[a]	Increase in SCr of ≥0.3 mg or increase of 150% to 200% (1.5 to 2x) above baseline.	<0.5 mL/kg/hour for >6 hours
2[b]	Increase in SCr of >200% to 300% (>2 to 3x)above baseline.	<0.5 mL/kg/hour for >12 hours
3[b]	Increase in SCr of >300% (>3x) above baseline or SCr of ≥4.0 mg/dL, with an acute increase of at least 0.5 mg/dL	<0.3 mL/kg/hour for 24 hours or anuria for hours

[a]Only one criterion (SCr or urine output) has to be fulfilled to qualify for a stage.
[b]200% to 300% increase = 2 to 3 × increase.
[c]Individuals who receive renal replacement therapy (RRT) are considered stage 3 regardless of the stage they exhibit at the time of RRT.

Abbreviations: AKIN, Acute Kidney Injury Network; AKI, acute kidney injury; SCr, serum creatinine

The Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE)[2] criteria (Table 2), also represent a system of diagnostic classification of AKI. The RIFLE criteria, defined the diagnosis of AKI as an increase in SCr of at least 1.5 times above the patient's baseline SCr value, which must be an abrupt one (within 1–7 days) and be sustained (> 24 hours). A documented reduction in urine output with an oliguria rate of less than 0.5 mL/kg/hr for more than 6 hours is also a criterion for diagnosis of AKI.

The RIFLE allows for a staged classification during hospitalization. AKI is associated with an increased risk of mortality in various clinical conditions, including ACS.

The increased rates of mortality and morbidity of ACS and AKI are because of the cardiorenal syndrome (CRS) and the association belongs to CRS type I, which is an acute worsening of heart function leading to kidney injury and/or dysfunction. In CRS type I, AKI occurs due to several complex mechanisms like hemodynamically mediated damage secondary to reduced

TABLE 2: RIFLE criteria for diagnosing AKI

Class	*GFR criteria*	*Urine output criteria*
Risk	SCr × 1.5 versus baseline	<0.5 mL/kg per hour × 6 hours
Injury	SCr × 2 versus baseline	<0.5 mL/kg per hour × 12 hours
Failure	SCr × 3 versus baseline or, when SCr ≥4 mg/dl, an acute increase of SCr > 0.5 mg/dL	<0.3 mL/kg per hour × 24 hours or anuria × 12 hours
Loss	Persistent ARF = complete loss of kidney function >4 weeks	
End-stage kidney disease	End-stage kidney disease >3 months	

RIFLE class is determined based on the worse of the two criteria (creatinine or urine output). Glomerular filtration criteria are calculated as an increase of SCr above the baseline SCr level. AKI should be abrupt (within 1 to 7 days) and sustained (24 hours). When the baseline SCr is elevated, an abrupt rise of at least 0.5 to 4 mg/dL is all that is required to achieve "Failure."

Abbreviations: RIFLE, Risk, Injury, Failure, Loss and End-stage kidney disease; AKI, acute kidney injury; GFR, glomerular filtration rate; SCr, serum creatinine; ARF, acute renal failure

cardiac output, humoral- and immune-mediated mechanisms, nephrotoxic effects of drugs or contrast-induced injury during percutaneous coronary interventions (PCI). These further worsen the glomerular filtration rate (GFR) with acute renal hypoperfusion, reduced oxygen delivery, increased resistance to atrial natriuretic peptide and B-type natriuretic peptide and increased cellular necrosis and apoptosis. Thus, AKI is not just a marker of the severity of the cardiac injury, but is also a cause for the acceleration of cardiovascular injury via various immunological, inflammatory and neurohumoral pathways.

But, the information on the prognostication of outcome on ACS and acute myocardial infarction (AMI) due to AKI are limited. Various studies, though with pitfalls, have shown the adverse outcomes of both transient and persistent AKI on ACS. In a study by Goldberg et al. of 1,038 patients with ST-segment elevation myocardial infarction (STEMI) in the presence or absence of worsening renal function, it was seen that 9.6% patients developed worsening renal function during hospitalization, which was associated with an adjusted odds risk (OR) of 11.4 for in-hospital mortality and 7.2 for 1-year mortality.[3]

In a retrospective cohort study by Newsome et al.[4] in 210,981 patients which included 87,094 elderly patients who were discharged after hospitalization for AMI, it was seen that absolute changes in the SCr values of 0.1 mg/dL, 0.2 mg/dL, 0.3–0.5 mg/dL and 0.6–3.0 mg/dL were all independent risk factors for late mortality after discharge. It was seen that the incidence of end-stage renal disease (ESRD) in patients without an elevation of SCr was 2.3 cases per 1,000 persons/year, and it was 20.0 cases per 1,000 persons/year for patients with a SCr elevation of 0.6–3 mg/dL while, the incidence of mortality was 139.1 cases per 1,000 persons/year and 274.9 cases per 1,000 persons/year, respectively. It is important to note this striking difference in mortality between these elderly patients who did not and did develop renal dysfunction, in contrast to only the smaller number differences of patients who developed ESRD.

Also, in a retrospective study by Parikh et al. of 234,769 patients, it was shown that AKI was an independent risk factor for long-term mortality in elderly patients with AMI.[5] The 10-year survival rate in the severe AKI group was 6.5% in contrast to the 31.7% patients without AKI ($p < 0.001$).

The effects of transient AKI (which showed SCr values which resolved during hospital stay) and persistent AKI (which showed SCr values which persisted at discharge from hospital), on the outcomes of STEMI patients were studied by Goldberg et al.[6] in 1,957 patients who were grouped into five, depending on their levels of SCr elevations including a control which did not have any increase in SCr. It was seen that patients with persistent moderate/severe AKI (SCr elevations more than 0.5 mg/dL) had the highest rates of mortality with an adjusted OR of 2.4 whereas the patients with transient mild AKI (SCr elevation of 0.3–0.49 mg/dL) had the lowest mortality with an adjusted OR of 1.2, when compared with patients without AKI. Interestingly, patients with transient moderate/severe AKI had mortality rates similar to those observed for persistent mild AKI, when compared with the control group. The limitations of this study, however, were that it was a retrospective one and that the RIFLE or AKIN classifications were not used.

In a study by Marenzi et al.[7] in 97 consecutive patients with STEMI and documented cardiogenic shock on admission and had received intra-aortic balloon pump support and primary PCI, in which AKI was arbitrarily defined as a 25% increase in baseline SCr, it was seen that 55% of the patients developed AKI during their hospitalization and AKI was associated independently with in-hospital mortality (OR: 12.3; $p < 0.001$).

Thus, available literature shows an association of poorer prognosis with worsening AKI and ACS.

Another important consideration is that probably many of these ACS patients developing AKI have an underlying more severe preexisting CKD, than those who do not develop AKI. Muntner et al. stated that underlying CKD increases the risk of developing AKI after an acute illness.[8] Thus, the information on AKI may be a confounding one because CKD is a definitive and known risk factor for mortality. So, it can be extrapolated that the underlying CKD and not AKI would be the actual reason for the observed higher rates of mortality with AKI in ACS, though an absolute increase in SCr during hospital stay is known to be associated with short-term and long-term mortality risks.

IMPACT OF CHRONIC KIDNEY DISEASE ON ACUTE CORONARY SYNDROME

Chronic kidney disease is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health, with or without decreased estimated GFR (eGFR <60 mL/min/1.73 m^2) or with evidence of kidney damage with one or more biomarkers as albuminuria greater than or equal to 30 mg/24 hours or spot urine albumin–creatinine ratio (ACR) greater than 30 mg/g, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplantation.[9]

The American Heart Association (AHA) and National Kidney Foundation recommend early detection of evidence of kidney disease in patients with or at risk of cardiovascular disease.[10] An

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eGFR of less than 60 mL/min/1.73 m^2 is regarded as abnormal and signifies increased cardiovascular risk.

Urine microalbuminuria is useful for detecting CKD in younger patients (age <46 years) whereas eGFR is more useful in older patients (age ≥46 years). However, when deciding overall risk of cardiovascular disease, both parameters are to be used in the same patient because the risk of cardiovascular events increases with decreasing eGFR and increasing microalbuminuria.

Assessment of eGFR is important and is recommended for the evaluation of renal function and can be done with equations as the Cockroft-Gault equation[11] or Modification of Diet in Renal Diet (MDRD) study equation.[12] But these equations can underestimate GFR at higher levels (>60 mL/min/1.73 m^2) and the equation proposed and validated by Levey et al.,[13] the Chronic Kidney Disease Epidemiology Collaboration Research Group (CKD-EPI) creatinine equation, is considered more accurate than MDRD, especially at higher GFRs. It is currently considered the preferred eGFR equation and a prognostic aid in assessing the future risk of cardiovascular risk and mortality.

Impact of Chronic Kidney Disease on the Outcome of Acute Coronary Syndrome

Renal dysfunction is a systemic inflammatory state associated with higher rates of plaque rupture and incident cardiovascular events. The uremia, resulting from CKD, is the notable cause for the multitude of cellular, humoral and systemic effects.

Uremia induces an altered hemostatic milieu. It causes decreased platelet aggregation due to decreases in dense granule content of adenosine triphosphate, serotonin and von Willebrand factor; reduced thromboxane A2 generation in response to thrombin and reduced availability and function of glycoprotein IIb/IIIa. It also results in increased plasminogen activation inhibitor, lower antithrombin III levels, excess thrombin generation and increased circulating thrombin–antithrombin complexes.

Accelerated atherosclerosis is another feature in CKD patients. It is induced in these patients by dyslipidemia resulting from reduced function of lipoprotein lipase and decreased high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) levels. When the eGFR level drops to less than 60 mL/min/1.73 m^2, the levels of homocysteine and other thiols increase, thereby enhancing the oxidation of LDL-C and the progression of atherosclerotic lesions.

Uremia also results in anemia (from impaired iron reutilization, erythropoietin deficiency), cardiomyocyte dysfunction, reduced myocardial capillary density, increased left ventricular mass, altering myocardial demand supply ratio, inducing myocardial ischemia. Further, it causes abnormal calcium-phosphate homeostasis resulting in phosphate retention and secondary hyperparathyroidism, hyperhomocysteinemia and hypervolemia, all of which contribute to myocardial dysfunction and fibrosis.

Chronic hyperactivation of the sympathetic nervous system and the imbalanced milieu caused between the powerful vasoconstrictor endothelin and nitric oxide, the local paracrine vasodilator, worsens hypertension and augments intravascular wall stress which can further accelerate the cardiovascular events.

This abnormal vascular biology is what places the patient with renal dysfunction at poor risk after an ACS. All these changes predispose a CKD patient with ACS to a higher risk of mortality from left ventricular dysfunction and arrhythmias. The higher cardiovascular mortality associated with CKD is either due to arrhythmias or cardiac pump failure. As kidney disease worsens, the patients are more likely to present with ACS and acute MI than with chronic stable angina. In patients with ESRD undergoing hemodialysis, the additional insult resulting from markedly increasing levels of cytokines, activation of tissue enzymes and transient ischemia adds to the increased morbidity and mortality.

Another reason other than uremia, for the poorer outcome of CKD on ACS patients is the underutilization of treatment. Therapeutic nihilism or the underuse of established therapies, like primary angioplasty, thrombolysis, or drugs as beta-blockers, antiplatelet or antithrombotic therapy by physicians, for the fear of complications or adverse sequelae also play a significant role in the poor outcomes of ACS in patients with CKD. This conservative approach by the physician is prompted by the usually late presentation of this subset of patients to the hospital; mostly with variegate complications and contraindications, urging the physicians to be overtly cautious with various medications and the timing of therapy. The increased propensity for bleeding with antiplatelet and other antithrombotic therapy is yet another reason for the poor outcome of ACS in CKD patients.

Though several advances have been made in the diagnosis and treatment of ACS in the general population, most of the information related to ACS in CKD population is retrospective. Such studies have shown that renal dysfunction is the most significant prognostic factor for long-term mortality when adjusted for other clinical factors like age, sex and other comorbidities.

Chronic kidney disease is considered a coronary risk equivalent and also a risk factor for the progression of cardiovascular disease. CKD is especially associated with a high risk for adverse outcomes in patients hospitalized for ACS. In contrast to the general population, the CKD patients undergoing dialysis have a 10–30 times greater mortality. In a study by McCullough et al., CKD patients who presented to the emergency department with chest pain, had an approximate 40% risk of MI, heart failure (HF) or mortality.[14]

As shown in the Global Registry of Acute Coronary Events (GRACE)[15] risk model for predicting in-hospital mortality in patients with unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) or STEMI, every 1 mg/dL rise in SCr was associated with a 1.2 fold increased risk of mortality.

In CKD, patients with ACS have more extensive coronary artery disease (CAD) and have higher risks for reinfarction, HF and mortality and are less likely to receive evidence-based therapy than are patients without CKD. The severity of kidney disease has an influence on short-term and long-term mortality after ACS. It was seen in studies that, older age, diabetes mellitus (DM) and HF were comorbidities associated with poor outcomes of ACS in CKD. Those with ESRD also had similar comorbidities including age (mean 64.9 years), DM (40.4%), and prior HF (31.7%). Also, patients with ESRD had the highest mortality after AMI when compared to any large chronic disease population.[16]

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Impact of Chronic Kidney Disease on the Management of Acute Coronary Syndrome

Management of CKD patients with ACS presents a double-edged sword scenario, with nontreatment, placing them at risk for atherothrombosis while treatment with anti-platelet or antithrombotic agents places them at risk for hemorrhagic complications. Added to the treatment dilemmas, there are also diagnostic issues pertaining to ACS in the CKD subset.

Diagnostic Issues

In patients with CKD or ESRD, troponin I is the biomarker of choice for the diagnosis of AMI as other biomarkers like myoglobin, creatinine kinase and troponin T assays may be elevated in these patients due to the associated skeletal muscle myopathy. However, to make a diagnosis of AMI, it is important to have other supportive evidence of AMI in the form of characteristic symptoms, electrocardiographic changes or angiographic findings of a culprit lesion.

However, when assessing a patient with ACS in the background of CKD the relevance of cardiac troponin is confounded. Though elevated levels of cardiac troponin are accurate for myocardial necrosis, it does not conclusively point to the etiology, as the levels may be elevated in both ACS as well as patients with renal impairment. The reasons for the higher incidence of elevated cardiac troponins in CKD is unclear, but may be due to myocardial damage or decreased renal clearance, skeletal muscle expression of cardiac-specific epitopes or other metabolic abnormalities. It is also possible that such troponin elevations in asymptomatic patients with renal insufficiency may be a manifestation of silent myocardial ischemia or accelerated myocyte apoptosis, as can be seen in asymptomatic patients undergoing dialysis. Higher troponin values are also seen in ESRD with increased left ventricular mass. Poor long-term survival has been shown in several studies of kidney patients having ST depression and release of troponin or other cardiac-biomarkers during dialysis. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IV trial, in the 7,800 patients with suspected ACS, troponin T was an independent predictor of the risk of death across the entire spectrum of renal function.[17]

In CKD patients on dialysis, the United States Food and Drug Administration (USFDA) has cleared the measurement of cardiac troponin T in the mid-week dialysis as a prognostic aid for assessing risk of mortality in these patients. Thus, in the diagnosis of MI, as a baseline elevation in troponin values above the 99% percentile is common in the normal population, in patients with CKD suspected to have ACS, it is important to look also for the characteristic rise and fall of troponin levels consistent with MI. Also, there has to be at least an additional one more supportive clinical criteria as, symptoms suggestive of myocardial ischemia, new or presumed new ST-T changes or new onset left bundle branch block, formation of pathologic Q-waves, or echocardiographic evidence of new loss of viable myocardium, new regional wall motion abnormalities or identification of thrombus on coronary angiography.

Thus, a typical serial cardiac troponin levels increase in the first 24 hours in patients suspected with ACS would support new onset cardiac injury, whereas chronically elevated levels would indicate either UA or a chronically diseased state.

Treatment Issues

Due to the high event rates in patients who have CKD with an eGFR less than 60 mL/min/1.73 m^2 or those with ESRD and on dialysis, who present with chest pain, admission to the hospital is mandatory. Though not much evidence from studies is available, generally, treatment that benefits ACS in the general population also benefits patients with CKD and ESRD.

Primary PCI with a door to balloon time of less than 90 minutes is the treatment of choice in patients with STEMI. In patients presenting outside this 90-minute window or those who would need a longer time to reach such centers offering PCI, thrombolytic reperfusion is the chosen initial strategy. In patients with CKD, however, there is an obvious delay in initiation of such therapy in patients with STEMI probably due to the ambiguity of symptoms or due to the delay in establishing the diagnosis. In a study of 109,169 patients with MI, by Newsome et al., it was found that fewer patients with renal disease received thrombolytic therapy and those with more severe renal disease with SCr greater than 1.6 mg/dL had the longest wait for treatment. It was probably due to concerns of thrombolysis induced bleeding.[18] In patients with CKD, there are no formal recommendations for dose adjustment in thrombolysis using streptokinase, alteplase, reteplase, or tenecteplase.

Observational studies in ACS patients with predialysis CKD suggest that they may benefit from revascularization with a reduction in 6-month mortality, though the chances of these patients being offered coronary angiography are low. The American College of Cardiology (ACC)/AHA guidelines for management of ACS give an insight into the management in the subset of CKD. In patients with UA or NSTEMI, mild-to-moderate CKD is a risk factor for the development of major complications and, hence, an early invasive strategy is preferred to conservative medical management. However, in patients with ESRD or patients undergoing dialysis, the guidelines are not supportive of catheterization as they may be harmful causing aggravation of HF, deterioration of renal function and even mortality.

In 23,262 consecutive patients with NSTEMI, in the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART), it was seen that with decreasing eGFR, the performance of coronary angiography and revascularization declined.[19] Only less than one-third of these patients with an eGFR less than 30 mL/min were taken up for an early invasive approach, probably due to risk factors as advanced age, risk of contrast-induced nephropathy, hemorrhage, and issues as questionable benefit or patient preference. In this study, the benefits in 1-year mortality with an early invasive strategy, seen in patients with mild and moderate CKD was not observed in patients with ESRD. With primary PCI strategy for AMI in patients with ESRD, probably the all-cause mortality from other causes as nonischemic arrhythmias, infections, thromboembolism and neurodegenerative disorders deferred any obvious benefit from the invasive strategy. In contrast, a study by Wong et al.[20] in patients with severe CKD, showed a benefit with a revascularization strategy. It showed that irrespective of the eGFR, there was an independent 1-year mortality benefit in these patients. A benefit with an early revascularization strategy in patients with CKD was also seen in a study by Charytan et al.[21] However, most of these trials are strongly influenced by selection

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bias and, hence, the actual benefit of a revascularization strategy in patients with ACS and CKD remains dubious.

Following reperfusion, the treatment of STEMI is as for NSTEMI. All CKD patients with UA or STEMI are to be treated with aspirin and beta-adrenergic receptor blockers unless contraindicated. However, dosage adjustments are needed on the basis of creatinine clearance for glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, low-molecular-weight heparins (LMWH) and bivalirudin. More effective use of these agents, despite the higher risk of complications, can help in decreasing the increased mortality that has been reported with ACS in the CKD and ESRD patients.

ANTIPLATELET AGENTS IN CHRONIC KIDNEY DISEASE PATIENTS WITH ACUTE CORONARY SYNDROME

Aspirin and thienopyridines can be used in CKD patients with ACS. But, the increased hemorrhagic propensity in these patients, has to be kept in mind. The recent ACC/AHA guidelines added prasugrel to the armamentarium of agents in ACS and is recommended (Class I) at the time of decision for PCI. The pharmacology and dosing in the patients with renal dysfunction for these agents are given in Table 3.

The ACC/AHA guidelines recommend the use of GP IIb/IIIa inhibitors in patients with elevated troponin levels and those at high risk of reinfarction or death with UA or NSTEMI, already taking aspirin and a thienopyridine and who are selected for urgent PCI. But, the upstream use of GP IIb/IIIa antagonists is not recommended in those with UA or NSTEMI who have a low risk for ischemic events, as those with a Thrombolysis in Myocardial Infarction (TIMI) Risk score less than 2 or those with a higher risk of bleeding already on treatment with aspirin and clopidogrel. Thus, most of the CKD patients, with an already increased hemorrhagic risk from dual antiplatelet therapy (DAPT), would not be candidates for therapy with GP IIb/IIIa inhibitors. Both abciximab and tirofiban have been shown to reduce mortality and fatal MI in patients with elevated troponin levels and should be considered as an adjunctive therapy for ACS, even in patients on dialysis. Abciximab is the agent of choice and its clearance is unaltered by dialysis, whereas tirofiban needs a 50% dose reduction in patients with an eGFR less than 30 mL/min. Eptifibatide undergoes renal clearance and also requires a 50% dosage reduction in patients with an eGFR less than 50 mL/min. However, eptifibatide is not recommended in patients on dialysis due to an increased bleeding risk. However, in spite of higher hemorrhagic risks, GP IIb/IIIa antagonists have been shown to have reduced in-hospital mortality in CKD patients who develop ACS.[22] The dose adjustments for GP IIb/IIIa antagonists are given in Table 4.

However, a meta-analysis by Palmer et al.,[26] of antiplatelet agents in patients with CKD showed low or very low quality evidence indicating little or no benefit of these agents during PCI with respect to all-cause mortality. [Relative Risk (RR): 0.86, 95% CI: 0.69–1.07].

ANTI-ISCHEMIC AGENTS AND STATINS IN CHRONIC KIDNEY DISEASE PATIENTS WITH ACUTE CORONARY SYNDROME

As with aspirin, a favorable risk to benefit ratio has been demonstrated for beta blockers (Table 5), nitrates (Table 6), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor II blockers (ARIIB), aldosterone receptor antagonists, calcium channel blockers (CCB) (Table 7) and statins (Table 8).

Among currently available statins, only high-dose atorvastatin has been shown to reduce death and ischemic events among patients with ACS.[30,31] Atorvastatin 10 mg in patients with CKD revealed a significantly lower risk of the primary end point (nonfatal MI or cardiac death) when compared with placebo.[32]

TABLE 3: Antiplatelet dosage adjustments for ACS in patients with CKD

Drug	*Pharmacology*	*Dose in normal population*	*Dose in renal dysfunction*
Aspirin	Metabolism: liver, microsomal enzyme system. Renal clearance: 80–100% 24–72 hours. Excretion: principally in urine (80–100%), sweat, saliva, feces.	AMI: 160-325 mg (per oral) PO as soon as possible. AMI prophylaxis: 81–162 mg PO, OD. PCI: 325 mg PO, 2-hour preprocedure, then 160–325 mg PO, maintenance. UA: 7–162 mg PO, OD	No specific dosing adjustments needed in patients with CKD
Clopidogrel	Metabolism: CYP3A4, CYP2C19 (predominantly), and others to generate active metabolite; also by esterase to an inactive metabolite Excretion: urine and feces	UA/NSTEMI: 300–600 mg initial loading dose, followed by 75 mg PO, OD with aspirin STEMI: 75 mg PO, OD, with aspirin 75–162 mg/day. Recent MI: 75 mg PO, OD	No specific dosing adjustments needed in patients with CKD
Prasugrel	Metabolism: liver; CYP450, CYP2B6, CYP2C9/CYP2C19 (minor), CYP3A4 substrate; CYP2B6 (weak) inhibitor. Excretion: urine (68%) and feces (27%).	ACS: Loading dose: 60 mg PO, once. Maintenance dose: 10 mg PO, OD with aspirin 81–325 mg/d; bleeding risk may increase if weight <60 kg; if so, consider 5 mg PO, OD (efficacy/safety not established)	No specific dose adjustments needed in patients with CKD
Ticagrelor	Metabolism: Hepatic CYP450. Excretion: Bile primarily, urine <1%.	ACS with PCI and stent: Starting dose: 180 mg PO once. Maintenance dose: 90 mg PO, twice daily To be given for 1 year with aspirin as an alternative option for dual antiplatelet therapy	No specific dose adjustements needed in patients with CKD

Abbreviations: AMI, acute myocardial infarction; PCI, percutaneous coronary interventions; UA, unstable angina; CKD, chronic kidney disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; ACS, acute coronary syndrome

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TABLE 4: GP IIb/IIIa inhibitors dose adjustments for ACS in patients with CKD

Drug	*Pharmacology*	*Dose in normal population*	*Dose in renal dysfunction**
Abciximab	Metabolism: Unknown, but likely to be the reticuloendothelial system Excretion: via urine	Adjunct to PCI: 0.25 mg/kg IV bolus over at least 1 min, 10–60 min before initiation of PCI, followed by 0.125 µg/kg/min (not to exceed 10 µg/min) continuous IV infusion for 12 hours UA with PCI planned within 24 hours: 0.25 mg/kg IV bolus over at least 1 min, followed by 0.125 µg/kg/min (not to exceed 10 µg/min) IV infusion for 18–24 hours, stopped 1 hour after PCI	No specific dose adjustments are needed for patients with CKD Abciximab should also be considered as adjunctive therapy in patients with ACS on dialysis In CKD, safety of abciximab has been shown for creatinine legels >2 mg/dL[23] although increased bleeding with abciximab in patients with CKD has been reported.[24] Other studies have shown no increase in bleeding for CKD vs no CKD for abciximab in PCI[25]
Eptifibatide	Metabolism: other, minimal CYP450: unknown involvement Excretion: 50% via urine	ACS: 180 µg/kg IV bolus, then 2 µg/kg/min IV for up to 72 hours PCI: 180 µg/kg IV, then a continuous infusion at 2 µg/kg IV bolus 10 min after the first bolus. Continue infusion for at least 12 hours	For creatinine clearance (Cr Cl) <50 mL/min and ACS: 180 µg/kg IV, then continuous infusion 1 µg/kg/min Safety and use during hemodialysis is not established
Tirofiban	Excretion: Via urine 65% (primarily unchanged), faeces 25% (primarily unchanged).	In patients undergoing PCI, tirofiban is not recommended as an alternative to abciximab ACS: 0.4 µg/kg/min IV for 30 min, then 0.1 µg/kg/min IV for 48–108 hours. PCI: continue 0.1 µg/kg/min IV through procedure and for 12–24 hours thereafter	For Cr Cl <30 mL/min and ACS: Reduce the dose to 50% of normal rate. Safety and use during hemodialysis is not established.

*When glycoprotein IIb/IIIa antagonists are used, abciximab and tirofiban should be considered as the preferred agents, as no dosing changes are required for abciximab, and dialysis-specific dosing recommendations are available for tirofiban. Increased bleeding but reduced in-hospital mortality in CKD patients with ACS treated with glycoprotein IIb/IIIa antigonists has also been shown.[22]

Abbreviations: GP, glycoprotein; ACS, acute coronary syndrome; CKD, chronic kidney disease; PCI, percutaneous coronary interventions; UA, unstable angina

TABLE 5: Beta-blocker dose adjustments for ACS is patients with CKD

Drug	*Pharmacology*	*Dose in normal population*	*Dose in renal dysfunction*
Metoprolol	Dialyzable. Metabolism: Hepatic CYP2D6 Metabolities: Inactive Excretion: 95% via urine	Acute MI: Metoprolol tartrate: 2.5–5 mg rapid IV every 2–5 min, up to 15 mg over 10–15 min, then 15 min after last IV and receiving 15 mg IV or 50 mg PO every 6 hours for 48 hours, then 50–100 mg PO twice daily Angina: Metoprolol tartrate: initially 50 mg PO twice daily, then titrated to 200 mg PO twice daily. Metoprolol tartrate: Initially 50 mg PO twice daily, then titrated to 200 mg PO twice daily Metoprolol succinate: 100 mg POOD. No more then 400 mg/day	No specific dose adjustments required for patients with CKD Recommend close monitoring for adverse effects
Esmolol	Metabolism: Extensively metabolized by esterase in cytosol of red blood cells Metabolites: Major acid metabolite (ASL-8123), methanol (inactive) Excretion: via urine <1–2%	Immediate control for intraoperative treatment: Give an 80 mg (approximately 1 mg/kg) bolus dose over 30 sec followed by a 150 µg/kg/min infusion, if needed Maximum infusion rate: 300 µg/kg/min Gradual control For postoperative treatment, give loading dosage infusion of 500 µg/kg/min over 1 min followed by a 4 min infusion of 50 µg/kg/min. If no effect within 5 mins, repeat loading dose and follow with infusion increased to 100 µg/kg/min	No specific dose adjustments reqired for patients with CKD.
Carvedilol	Elimination: Is mainly biliary Excretion: Primarily through feces	Hypertension and post-MI protection: 6.25–25 mg PO twice daily. Start at 6.25 mg PO twice daily, then increase every 3–14 days to 12.5 mg PO daily, then 25 mg PO twice daily	No specific dose adjustments required for patients with CKD. In a small study of patients on dailysis with dilated cardiomyopathies, Carvedilol improved left ventricular function and decreased hospitalization, cardiovascular deaths, and total mortality[27]

Abbreviations: ACS, acute coronary syndrome; CKD, chronic kidney disease; MI, myocardial infarction

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TABLE 6: Antianginal adjustments for ACS in patients with CKD

Drug	*Pharmacology*	*Dose in normal population*	*Dose in renal dysfunction*
Nitrates: Nitroglycerin	Metabolism: Mainly in liver and extrahepatic sites, such as vascular wall, red blood cells Excretion: Via urine	2% ointment: Angina: 0.5–2 inches applied in morning and 6 hrs later to truncal skin Heart failure: 1.5 inches, increase by 0.5–1 inch up to 4 inches, every 4 hours Sublingual: 0.4 mg for relief of chest pain in ACS Sublingual: 0.3–0.6 mg every 5 min Maximum: 3 doses within 15 min	No specific dose adjustments required for patients with CKD. Care must be taken to avoid hypotension in low-volume states, as in dialysis sessions
Antianginal: Ranolazine	Excretion: 73–75% via urine; 25% via feces	500–1000 mg PO, twice daily. Max dose: 2000 mg/d	No specific dose adjustments required for patients with CKD. Prolongs QT interval (QTc). Recommend close monitoring

Abbreviations: ACS, acute coronary syndrome; CKD, chronic kidney disease

TABLE 7: ACEI, ARIIB and CCB dose adjustments for ACS in patients with CKD

Drug	*Pharmacology*	*Dose in normal population*	*Dose in renal dysfunction*
ACEIs, e.g. captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, fosinopril	Elimination: mainly renal with an elimination half-life of 12.6 hours in healthy individuals. In patients with impaired renal function (CrCl ≤30 mL/min), a longer half-life and accumulation have been observed without clinical consequences	Indicated for the treatment of hypertension, prevention of cardiovascular events, including heart failure in those at risk, reduction in the provression of type I diabetic nephropathy, and reduction in cardiovascular events in patients post-MI with left ventricular dysfunction or heart failure. Also indicated for the treatment of heart failure	The dosing schedules may need to be individualized for each dialysis session to avoid intradialytic hypotension
ARIIBs, e.g. losartan, irbesartan, olmesartan, candesartan, valsartan, telmisartan	Losartan has 88% hepatic and 12% renal clearance.	Indicated for treatment of hypertension, to reduce the progression of type 2 diabetic nephropathy, and reduce cardiovascular events in patients post-MI with left ventricular dysfunction or heart failure Indicated for heart failure in those intolerant to ACE inhibitors	As first-line treatment in most patients with CKD it is recommended to use ACE inhibitors or ARIIBs as both have been shown to reduce LVH in patients on hemodialysis[28,29] Levels of ARBs do not change significantly during hemodialysis
CCBs: Dihydropyridines, e.g. amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nitrendipine Non-dihyrdropyridines, e.g. diltiazem, verapamil.	Amlodipine has renal elimination as the major route of excretion, with about 60% cleared in the urine. Diltiazem undergoes primary liver metabolism	In UA/NSTEMI, if β-blockers are contraindicated, a non-dihydropyridine CCB should be chosen in the absence of clinically significant left ventricular dysfunction or other contraindications	No specific dose adjustments for patients with CKD The management of chronic CAD in patients on dialysis should follow that of the general population and use of CCBs as indicated

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARIIBs, angiotensin receptor II blockers; CCBs, calcium channel blockers; ACS, acute coronary syndrome; CKD, chronic kidney disease; LVH, left ventricular hypertrophy; CAD, coronary artery disease; MI, myocardial infarction; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction

TABLE 8: Stain dose adjustments for ACS in patients with CKD

Drug	*Pharmacology*	*Dose in normal population*	*Dose in renal dysfunction*
Simvastatin	Metabolism: Liver, CYP450 Excretion: primarily via bile and < 2% via urine	Cardiovascular event protection: 20 mg PO Maximum dose: 40 mg PO, given at hour of sleep	Consider starting dose at 5 mg in the evening in patients with CKD
Atorvastatin	Metabolism: liver, CYP450 Excretion: bile primarily, urine <2%	STEMI: High dose (80 mg) PO OD.	No specific dose adjustments are required for patients with CKD
Fluvastatin	Excretion: feces 90%, urine 5%	Cardiovascular event protection: 40 mg by mouth twice daily Extended-release: 80 mg by mouth once daily	No specific dose adjustments for patients for patients with CKD. Caution to be observed for increased risk of rhabdomyolysis
Pravastatin	Excretion: feces 70%, urine 20%	Cardiovascular event protection: Start: 40 mg by mouth once daily, may adjust dose every 4 weeks Maximum dose: 80 mg by mouth once daily	Start at 10 mg by mouth once daily in patients with CKD

Contd...

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Drug	Pharmacology	Dose in normal population	Dose in renal dysfunction
Rosuvastatin	Rosuvastatin is not extensively metabolized. Approximately only 10% of radio-labeled dose is recovered as a metabolite formed by CP450 2C9. More than 90% of the active plasma HMG-CoA reductase inhibitory activity is accounted by the parent compound itself. Excretion: 90% is via feces. The elimination half life is approximately 19 hours. After an intravenous dose, 72% of clearance was hepatic and 28% via renal route	Cardiovascular event protection: Recommended starting dose is 10–20 mg/d, administered at any time of the day, with or without food. After initiation, assess lipid levels in 2–4 weeks and adjust dosage accordingly. 40 mg should be used only for those who do not achieve LDL goals with 20 mg	In patients with severe renal impairment (GFR < 30 mL/min/1.73 m^2) and not on hemodialiysis, rosuvastatin should be started at 5 mg OD and should not exceed 10 mg OD. In patients on hemodialysis, plasma concentrations were approximately 50% greater compared with healthy volunteers. Dose reduction should be considered in patients on rosuvastatin with unexplained proteinuria or hematuria

Abbreviations: ACS, acute coronary syndrome; CKD, chronic kidney disease; STEMI, ST-segment elevation myocardial infarction; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; LDL, low-density lipoprotein; GFR, glomerular filtration rate

In the Treating to New Targets (TNT) study, atorvastatin showed improvement in renal function in patients with CKD.[33]

ANTITHROMBOTIC THERAPY IN CHRONIC KIDNEY DISEASE PATIENTS WITH ACUTE CORONARY SYNDROME

Untreated CKD patients have higher thrombotic tendencies, as a result of excessive generation of thrombin and decreased levels of protein C, due to either reduced production or increased losses in urine, especially in those with proteinuria. However, on the opposite pole, these patients with CKD have a higher incidence of minor and major hemorrhagic events when treated with all forms of indirect thrombin and factor Xa inhibitors [Unfractionated heparin (UFH), LMWH and fondaparinux] due to a greater anticoagulation effect resulting from larger number of circulating thrombin–antithrombin complexes in them. However, in CKD patients, in comparison to heparin, the intravenous direct thrombin inhibitor bivalirudin has been associated with a lower hemorrhagic risk and better cardiovascular outcomes.[34]

Unfractionated heparin has partial dependence on renal function for metabolism but can be used in patients with CKD and those on dialysis. LMWH has been shown in clinical trials to be superior to UFH in patients with increased troponin levels in the UA and NSTEMI settings.[35,36] However, enoxaparin is a renally cleared LMWH and hence should be used with caution in the renally impaired patients due to a higher risk of hemorrhagic complications. Also, enoxaparin is not advised in patients undergoing dialysis.

The direct thrombin inhibitor, bivalirudin, in patients selected for an invasive strategy has been shown to be associated with favorable outcomes in CKD, when compared with UFH, provided renal dose adjustments have been made. It is also important to be aware that, bivalirudin is dialyzable. The dose adjustments for anti-thrombotic agents in renal dysfunction are given in Table 9.

Fondaparinux, an indirect factor Xa inhibitor is also cleared renally and is hence contraindicated in patients with a CrCl less than 30 mL/min.

After an ACS, the patients still remain at high risk for cardiovascular events. The Fifth Organization to Assess Strategies in Ischemic Syndromes (OASIS-5)[37] and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI)[38] trials showed that continued therapy with fondaparinux or bivalirudin resulted in a reduction of ischemic events, reinfarction and mortality. Therefore, the role of apixaban for secondary prevention after ACS was studied in Apixaban for Prevention of Acute Ischemic Events-2 (APPRAISE-2) trial[39] which showed an increase in major bleeds in combination with DAPT in ACS and the trial was terminated early. Similar experience was seen with the oral direct thrombin inhibitor ximelagatran in the Efficacy and Safety of the oral Thrombin inhibitor ximelagatran in combination with aspirin in patients with recent myocardial damage (ESTEEM) trial[40] and dabigatran in the Dose Finding study for Dabigatran Etexilate in Patients with Acute Coronary Syndrome (REDEEM) trial[41] and both agents were not studied beyond phase II trials. However, dabigatran has been approved for use by USFDA for anticoagulation in patients with nonvalvular atrial fibrillation (AF), which is rather common in the ACS substrate in CKD patients.

Rivaroxaban is a factor Xa inhibitor which has been approved by USFDA, for stroke prevention in nonvalvular AF, replacing warfarin. The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with ACS (ATLAS ACS 2-TIMI 51) trial[42] showed decreased cardiovascular events and death but was associated with an increase in bleeding and intracranial hemorrhage. Further studies would be required for guiding optimal dose in ACS in CKD, especially along with DAPT. Regular reassessment of renal function is recommended for all patients on novel anticoagulants, which would warrant appropriate dosage adjustments.

Contrast-induced nephropathy (CIN) is another important issue in the management of ACS in CKD. The ACC/AHA guidelines for PCI place less emphasis on specific types of contrast agents and stress rather on limiting the volume of contrast being used, in addition to proper hydration with intravenous isotonic crystalloids prior to angiography or angioplasty to decrease the risk of CIN.

Thus, kidney disease in its acute and chronic forms exerts a significant impact on the outcome and management of ACS. However, a comprehensive knowledge on the pathophysiology of renal dysfunction and how it variably interacts with ACS and an understanding of the various drugs and their altered pharmacokinetics and pharmacodynamics, hand in hand with a timely intervention by the treating physician would help in the optimal and effective management of this diverse subset of CKD patients with ACS.

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TABLE 9: Antithrombotic agent dosage adjustments for ACS in patients with CKD

Drug	*Pharmacology*	*Dose in normal population*	*Dose in renal dysfunction*
Indirect factor Xa Inhibitors: UFH	Metabolism: liver (partial) Metabolites: none Excretion: urine	Recommended dosage and desired aPTT values are as per institutional protocol PCI: 60–100 units/kg intravenous (IV) given once to target ACT 250-350 sec. In patients receiving GP IIb/IIIa inhibitor, give 50-70 units/kg IV to target ACT 200 sec STEMI: adjunct treatment Streptokinase use: 800 units/hours when <80 kg body weight or 1000 U/hours when > 80 kg body weight Start: 5000 units IV, adjust dose to target aPTT 50–75 seconds NSTEMI: 12-15 units/kg/hour IV Start: 60-70 units bolus, max rate 1000 U/hour. Adjust dose to target aPTT 50-75 seconds.	In patients with CKD, suggested starting dose of heparin is 50 IU/kg bolus, then 18 IU/kg/hour Monitor aPTT level and adjust dose as per institutional protocol
LMWH (e.g. enoxaparin)	Excretion: urine 40%	UA, non-Q-wave, AMI: 1 mg/kg subcutaneously twice (s/c) daily STEMI, aged < 75 years: 30 mg IV bolus plus 1 mg IV bolus plus 1 mg/kg, s/c, then 1 mg/kg, s/c every 12 hours. PCI additional 0.3 mg/kg IV bolus if last s/c administration given > 8 hours before balloon inflation. STEMI, aged > 75 years: 0.75 mg/kg s/c every 12 hours (no IV bolus)	In CrCl < 30 mL/min STEMI, aged < 75 years: 30 mg IV bolus plus 1 mg/kg s/c, then 1 mg/kg s/c OD STEMI, aged >75 years: 1 mg/kg s/c OD
Direct factor Xa inhibitor Foundaparinux	Excretion: Via urine (primarily unchanged)	UA/NSTEMI Conservative strategy: 2.5 mg s/c OD During PCI: add UFH, 50–60 units/kg IV bolus for prophylaxis of catheter induced thrombosis	CrCl 30–50 mL/min: use with caution CrCl < mL/min: not indicated
Direct thrombin inhibitors: Bivalirudin	Dialyzable: with 25% reduction in levels. Excretion: urine	Intended for use with aspirin 300–325 mg/day 0.75 mg/kg IV bolus initially, followed by continuous infusion at rate of 1.75 mg/kg/h for duration of procedure. Perform ACT 5 min after bolus dose Administer additional 0.3 mg/kg bolus, if Necessary May continue infusion after PCI beyond 4 hours, (Optional post-PCI, at discretion of the treating psysician) initiated at a rate of 0.2 mg/kg/hour for up to 20 hours, as needed	If CrCl 10–29 mL/min: usual bolus dose and then initial infusion of 1 mg/kg/h IV up to 4 hours. If on hemodialysis: usual bolus dose, and then initial infusion of 0.25 mg/kg/h IV up to 4 hours. Bivalirudin requires specific dosing adjustments for patients on dialysis and should be preferentially considered
Dabigatran	Excretion: 7% via urine and 86% via feces	Indicated for the prevention of stroke and thromboembolism associated with nonvalvular atrial fibrillation If CrCl > 30 mL/min: 150 mg PO twice daily	If CrCl 15–30 mL/min: 75 mg PO, twice daily If CrCl < 15 mL/min or hemodialysis: Not indicated For patients currently taking dabigatran, wait for 12 hours (CrCl ≥ 30 mL/min) or 24 hours (CrCl < 30 mL/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant. If possible, discontinue dabigatran, 1–2 days (CrCl ≥ 50 mL/min) or 3–5 days (CrCl < 50 mL/min) before invasive or surgical procedures because of increased risk of bleeding
Rivaroxaban	Metabolism: liver CYP450. Excretion: 66% via urine and 28% via feces. Half-life: 5–9 hours or 11–13 hours in elderly.	Indicated for prevention of stroke and thromboembolism associated with nonvalvular atrial fibrillation CrCl > 50 mL/min: 20 mg PO at hour of sleep	CrCl 15–50 mL/min 15 mg PO at hour of sleep CrCl <15 mL/min: not indicated

Abbreviations: ACS, acute coronary syndrome; CKD, chronic kidney disease; UFH, unfractionated heparin; aPTT, activated partial thromboplastin time; PCI, percutaneous coronary interventions; ACT, activated clotting time; GP, glycoprotein; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LMWH, low-molecular-weight heparin; UA, unstable angina

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