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Revascularization Strategies in Patients with Chronic Kidney Disease and Acute Coronary Syndromes

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Abstract

Purpose of Review Chronic kidney disease (CKD) is a highly prevalent condition that increases the incidence and complexity of acute coronary syndrome (ACS). The purpose of this review is to summarize current evidence, uncertainties, and opportunities in the management of patients with CKD and ACS, with a focus on revascularization.

Recent Findings Patients with CKD have been systematically under-represented or excluded from clinical trials in ACS. Available data, however, demonstrates that although patients with CKD and ACS benefit from revascularization, they are also less likely to receive recommended medical and revascularization therapies when compared to patients with normal kidney function.

Summary Despite the increased short-term risk of major morbidity and mortality, patients with CKD and ACS should be considered for an early invasive strategy while also trying to mitigate the risks of procedural related complications. Until evidence emerges from randomized clinical trials, the decision about revascularization strategy should involve multi-disciplinary collaboration, heart team consensus, and patient shared decision-making.

Keywords Acute coronary syndrome · Chronic kidney disease · Coronary revascularization · Percutaneous coronary intervention · Coronary artery bypass surgery

Introduction

Chronic kidney disease (CKD) affects approximately 15% of Americans or an estimated 37 million people in the United States (US) [1]. Among patients with CKD, cardiovascular disease (CVD) is the leading cause of death, and patients with CKD have a 15- to 30-fold higher age-adjusted CVD mortality compared with the general population [2, 3]. According to the National Cardiovascular Registry-Acute Coronary Treatment and Interventions Outcome Network (NCDR-ACTION), approximately 30% of all patients with ST elevation myocardial infarction (STEMI) and 40% of patients with non-ST elevation myocardial infarction (NSTEMI) have CKD [4]. Among patients with an acute coronary syndrome (ACS), the presence of CKD is a strong independent predictor of mortality and major adverse cardiovascular and cerebrovascular events (MACCE), and the relationship between severity of CKD and likelihood of MACCE is graded with patients on hemodialysis experiencing particularly poor outcomes [5, 6]. Unfortunately, patients with CKD, especially those with end-stage renal disease (ESRD) and those on dialysis, have largely been excluded from major cardiovascular clinical trial participation, and the efficacy of medical and revascularization therapies in patients with CKD remains somewhat uncertain [7]. While limited data exists for percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) in the management of stable ischemic heart disease (SIHD) in CKD, there are no randomized clinical trials comparing the two revascularization strategies in patients with CKD and ACS [8•, 9–11]. As a result, the management of ACS in patients with CKD is not

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strictly evidence-based and relies heavily on expert opinion and weighing the anticipated balance between potential benefits and harms of available treatment options. In this review, we will discuss the background importance of CKD in the management of CVD with a particular focus on ACS and the options for revascularization.

Epidemiology

Approximately 600,000 to 700,000 Americans experience an ACS every year, and the incidence rate among patients with CKD is disproportionately high. Several studies have indicated that CKD confers a similar, if not greater, risk of ACS compared to diabetes [1]. In a cohort of more than 1.3 million patients, the incidence of acute myocardial infarction (AMI) was significantly higher in patients with CKD compared with those with diabetes and normal renal function (6.9 per 1000 person-years (95% confidence interval (CI), 6.6–7.2) vs. 5.4 per 1000 person-years (95% CI, 5.2–5.7)) [12]. Similarly, using data from the Taiwan National Health Insurance program, Chang and colleagues demonstrated that adults greater than 64 years of age with CKD had a similar risk of ACS compared with patients with normal renal function and diabetes [13]. Patients with non-dialysis-requiring CKD have a higher likelihood of MACE than developing ESRD and requirement for renal replacement [14]. Once renal replacement therapy is initiated, however, the rate of CAD progression becomes accelerated and the incidence of ACS becomes particularly high. In the 2018 United States Renal Data System (USRDS) report on ESRD, the annual incidence of AMI was 12% and 14% for patients on peritoneal and hemodialysis, respectively [15]. These and other studies strongly support the argument that CKD should be considered a CVD risk equivalent. In addition to ACS, patients with advanced CKD and ESRD have higher rates of valvular heart disease, heart failure, arrhythmia, and sudden cardiac death compared with the general population [15]. While CVD accounts for approximately 30–40% of deaths in ESRD, only 11% is attributable to AMI with a much larger proportion (70–80%) explained by arrhythmia and cardiac arrest [15].

ACS Risk Factors

Traditional CVD risk factors including tobacco, dyslipidemia, diabetes, family history, and advanced age are highly prevalent in patients with CKD. These risk factors play an important role in the development of coronary artery disease (CAD) in all patient populations, but the strength of correlation to ACS among patients with CKD is not as strong as those with normal renal function [16]. For example, while LDL levels are positively correlated with increasing risk of AMI, the strength of correlation becomes weaker as creatinine clearance (CrCl) declines [17]. Given the weaker association between LDL and AMI, the use of statin therapy in CKD has been questioned. Patients with moderate to severe CKD were randomized in the SHARP trial to either simvastatin and ezetimibe or placebo. There was a significant reduction in MACCE in the treatment group among patients with moderate and severe but not dialysis-dependent CKD [18]. Similarly, studies of atorvastatin and rosuvastatin in ESRD have demonstrated no benefit in MACCE reduction despite significant reduction in LDL [19, 20]. One potential explanation for these observations is that as renal function declines, a unique group of “uremia-specific” risk factors emerge to affect the development and progression of CAD, and the incidence of ACS. These factors include endothelial dysfunction, anemia, chronic inflammation, albuminuria, homocysteinuria, impaired calcium and phosphorus metabolism due to secondary hyperparathyroidism, and oxidative stress [21].

Impact of CKD on ACS Prognosis

In addition to having higher ACS incidence than the general population, patients with CKD also have worse ACS-related outcomes. Multiple analyses have demonstrated a strong, independent, and graded association between CKD- and ACS-related MACCE [1, 5, 6, 22–24]. In the GRACE study, admission CrCl was independently associated with increased odds of death. Hospital mortality for ACS patients was 1.4% in minimal/no CKD (CrCl > 60 mL/min/1.73 m^2), 5.5% in moderate CKD (CrCl 30–60 mL/min/1.73 m^2), and 12.2% in the presence of severe CKD (CrCl < 30 mL/min/1.73 m^2). The adjusted odds ratio (OR) for mortality was 2.09 (95% CI, 1.55–2.81) and 3.71 (95% CI, 2.57–5.37) in moderate and severe CKD, respectively. In patients with STEMI, CKD was a significant predictor of mortality across all ranges of estimated glomerular filtration rate (eGFR) [23]. In an analysis of over 14,000 patients with AMI in the Valsartan in Acute Myocardial Infarction Trial, every decline of 10 mL/min in eGFR was associated with a 10% increase in the hazard of death or nonfatal adverse cardiovascular outcome (95% CI, 1.08–1.12) [5]. In patients with ESRD, the likelihood of survival after STEMI is particularly poor with in-hospital, 1-year, and 2-year mortality rates between 20 and 40%, 30–50%, and 60–80%, respectively [6, 22, 24]. The presence of CKD in patients with ACS is also associated with an increased likelihood of cardiogenic shock, congestive heart failure, stroke, major bleeding and vascular complications, acute kidney injury (AKI), and prolonged length of stay [24–27].

Management of ACS in CKD

Why Is the Management of ACS in CKD Different?

Pathophysiology

Patients with CKD have an altered intravascular physiology that leads to a higher prevalence of both atherosclerosis and arteriosclerosis [25, 28]. On a histopathological level, atherosclerotic plaque composition changes as the burden of kidney dysfunction increases, with increased lipid, necrotic core, and dense calcium content [29–31]. Additionally, renal dysfunction is associated with increased neovascularization and decreased fibrous content of atherosclerotic plaques, which is thought to increase susceptibility to intraplaque hemorrhage and rupture [29, 30, 32]. Optical coherence tomography (OCT) studies of culprit lesion characteristics in ACS have demonstrated that calcific nodules account for approximately 2–8% of culprit lesions and that this lesion type is 3–4-fold more common among patients with ESRD compared with the general population [33–35].

Diagnosis

The diagnosis of ACS in patients with CKD can often be masked by atypical or silent symptoms, inadequate risk-stratification by standard risk factors, and reduced sensitivity and specificity of cardiac biomarkers and non-invasive imaging studies (Table 1) [36–40]. As a result, there is an increased rate of missed and delayed ACS diagnosis in patients with CKD. In a large cohort of hospitalized patients diagnosed with ACS, only 31.5% of dialysis patients were admitted under the diagnosis of ACS, compared with 65% of non-dialysis patients [38]. While elevated troponin measurements are a marker of increased mortality risk in all patients, the specificity for ACS is reduced in patients with CKD [41, 42]. At baseline, troponin T and I levels are above the 99th percentile in 82% and 6% of ESRD patients, respectively [41]. Using high-sensitivity assays, troponin T and I levels exceed the 99th percentile at baseline in approximately 68% and 38% of patients with CKD (defined as eGFR < 60 Cl < 30 mL/min/1.73 m^2), and high-sensitivity troponin T levels exceed the 99th percentile in greater than 95% of asymptomatic patients on renal replacement [43, 44]. Chronic troponin elevation in CKD is thought to reflect both cardiac release from factors such as elevated filling pressure, small vessel obstruction, hypotension, anemia, and direct cardiotoxicity from uremia as well as reduced renal clearance [45]. As a result, and in accordance with the 4th universal definition of myocardial infarction, the diagnosis of type 1 myocardial infarction in patients with CKD requires the rise and fall of troponin values coupled with signs or symptoms of myocardial ischemia or documentation of imaging evidence of loss of viable myocardium, new wall motion abnormality, or coronary thrombus [46•]. In the absence of plaque rupture, patients with CKD are also at high risk for developing oxygen supply: demand mismatch and type 2 myocardial infarction [46•]. Together, these challenges in diagnosis and risk-stratification contribute to treatment delays and reduced revascularization rates in patients with CKD and ACS.

Pharmacology

Altered pharmacodynamics and inadequate renal dose adjustment may contribute to increased risk of both ischemic- and thrombotic-related complications in patients with CKD and ACS. Current guidelines and statements suggest that patients with moderate to severe CKD who present with ACS should be treated similar to the general population, with dose adjustments as needed based on the degree of renal dysfunction [42, 47, 48]. Specific elements worth addressing include the following:

- 30-day mortality is reduced with aspirin, beta-blocker, and ACE-inhibitor therapies in patients with ESRD and AMI [48, 49].
- Statins are effective in lowering primary and secondary CVD event rates in patients with mild to moderate CKD and should be considered in all patients with ACS [18, 48, 50]. Although patients with advanced CKD and ESRD

Table 1 Presenting symptoms of ACS in patients with CKD [34]

Symptom or presentation	Prevalence according to renal function		
	eGFR > 90 mL/min/1.72 m^2	eGFR < 60 mL/min/1.72 m^2	eGFR < 15 mL/min/1.72 m^2 and ESRD
Chest pain/pressure	90%	65–76%	67%
Heart failure (Killip class ≥ II)	10%	31–46%	38%
STEMI	41%	22–29%	22%
NSTEMI	56%	60–66%	66%

ACS acute coronary syndrome, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, (*ESRD* end-stage renal disease, *STEMI* ST segment elevation myocardial infarction, *NSTEMI* non-ST segment elevation myocardial infarction have been excluded from randomized clinical trials of statin therapy in ACS, primary prevention trials in advanced CKD and ESRD have failed to demonstrate a benefit of statins in lowering CVD event rates [50]. Whether statins are harmful from a CVD perspective through the promotion of vascular calcification or beneficial from an all-cause mortality standpoint by lowering sepsis-related death adds to the controversy and uncertainty of statin utilization in ESRD [51, 52].

- Caution is advised with the use of ACE-inhibitor, angiotensin receptor blockers, and aldosterone antagonists in patients with moderate to severe CKD, and their use may be contraindicated depending on the CrCl and potassium level.
- Patients with advanced CKD have higher residual platelet activity with clopidogrel compared to ticagrelor, and the latter has been associated with improved CVD outcomes in ACS without significant difference in major bleeding [47, 53–55].
- Enoxaparin requires dose adjustment in CKD; the optimal dose in advanced CKD (eGFR < 30 mL/min/1.73 m^2) is uncertain, and clinical trials that included patients with CrCl < 30 mL/min/1.73 m^2 demonstrated an increased risk of major bleeding according to the degree of renal dysfunction [48, 56].
- The benefit with respect to MACE and bleeding event reduction of bivalirudin compared with unfractionated heparin (UFH) with or without glycoprotein protein IIb/IIIa inhibitor therapy in patients with CKD and ACS is in large part uncertain. A randomized clinical trial of antithrombotic strategies in patients with moderate to severe CKD and ACS undergoing PCI is needed to better guide clinical practice [48, 57].

Revascularization Strategies for ACS in CKD

Patients with moderate to severe CKD are under-represented in most randomized clinical trials comparing revascularization strategies in patients with ACS, and patients on hemodialysis have been excluded from these studies [7]. Observational studies have consistently demonstrated that patients with CKD are less likely to receive guideline-recommended medical and revascularization therapy, and that this is true for both NSTEMI and STEMI [4, 37, 58].

Although CKD patients with ACS have elevated baseline risk, revascularization is associated with a net improvement in outcomes (Table 2) [59–66]. Observational studies have demonstrated that compared to medical therapy, early revascularization with either PCI or CABG in patients with mild to moderate CKD and ACS is associated with improved survival. Several studies and meta-analysis have demonstrated that routine invasive therapy is superior to an ischemia-guided strategy in ACS [67–69]. The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluate According to Recommended Therapies Trial (SWEDEHEART) demonstrated that propensity-adjusted 1-year mortality was lower with invasive therapy compared with medical therapy in patients with mild (HR 0.64, 95% CI 0.52–0.80) and moderate (HR 0.68, 95% CI 0.54–0.86) CKD [70]. In this cohort, there was no significant 1-year mortality benefit of revascularization among those with severe CKD (HR 0.91, 95% CI 0.51–0.61) or on hemodialysis (HR 1.61, 95% CI 0.84–3.09). A more recent meta-analysis of observational studies, however, demonstrated a benefit in 1- and 3-year mortality with revascularization across all categories of CKD, including those on hemodialysis [71].

The 2014 ACC/AHA guidelines for the management of patients with NSTEMI-ACS state that an invasive strategy is reasonable for patients with ACS and stage 2 or 3 CKD (class IIa, LOE B) [47]. An early invasive strategy is not, however, recommended in patients with ESRD (class III, LOE C) with concern that risks of revascularization may outweigh the benefits [47]. Regardless of CKD status, current ACC/AHA guidelines indicate that all patients with STEMI should be considered for primary PCI (Fig. 1) [72].

Percutaneous Coronary Intervention

Effect of CKD on PCI-Related Outcomes

Patients with CKD have a high prevalence of diabetes and an increased likelihood of three-vessel CAD, left main disease, and coronary calcification [73]. As the severity of CKD progresses, so does the extent and severity of CAD and the calculated SYNTAX score [74]. As a result, it is not surprising that PCI in patients with CKD is associated with increased risk compared to patients with normal renal function and that these risks are amplified in ACS. Increased coronary calcification is associated with stent malapposition, under-expansion, and fracture, and these factors may in turn predispose patients to stent thrombosis (ST) [75]. Among patients with CKD, the risk of ST is approximately 6–7-fold higher compared to patients with normal GFR [76]. Additionally, in an analysis of data from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization project between 2007 and 2011, CKD was demonstrated to increase the risk of PCI-related in-hospital mortality (no CKD 1.4%, CKD 2.7%, ESRD 4.4%), post-procedural bleeding (no CKD 3.5%, CKD 5.4%, ESRD 6.0%), average length of stay (no CKD 2.9 days, CKD 5.0 days, ESRD 6.4 days), and average cost (no CKD $60,526, CKD $77,324, ESRD $97,102) [26].

Table 2 Impact of coronary revascularization and medical therapy on survival in patients with chronic kidney disease

Outcome	Population/study	Management strategy		
		CABG	PCI (POBA and/or stenting)	Medical therapy
	ESRD	8–13%	3–5%	
In-hospital mortality	[61] Herzog CA, et al. Kid Intl, 1999 (*N* = 14,306)	13%, 930/7419	5%, 371/6887	
	[62] Herzog CA, et al. Circ, 2002 (*N* = 15,784)	9%, 573/6668	5%, 485/9116	
	[64] Shroff GR, et al. Circ 2013 (*N* = 18,022)	8%, 506/6178	3%, 565/16855 • DES 2.7%, 320/11844 • BMS 4.9%, 245/5011	
	CKD, non-dialysis			
30-day mortality	[59] Bangalore S, et al. JACC 2014 (*N* = 5920)	2%, 51/2960	DES 1%, 29/2960	
	ESRD	3–11%	DES 4–6%	
	[64] Shroff GR, et al. Circ 2013 (*N* = 18,022)	11%, 667/6178	6%, 710/11844	
	[65] Sunagawa G, et al. Ann Thorac Surg 2010 (*N* = 104)	3%, 1/29	4%, 3/75	
	ESRD	18–30%	24–34%	
1-year mortality	[62] Herzog CA, et al. Circ, 2002 (*N* = 15,784)	29%, 1900/6668	34%, 3063/9116	
	[66] Szczech LA, et al. Kidney Int 2001 (*N* = 182)	18%, 20/111	24%, 17/71	
	[64] Shroff GR, et al. Circ 2013 (*N* = 18,022)	30%, 1853/6178	31%, 5288/16855 • DES 29%, 3434/11844 • BMS 37%, 1854/5011	
	ESRD	16–44%	32–52%	
2-year mortality	[61] Herzog CA, et al. Kidney Int 1999 (*N* = 14,306)	43%, 3197/7419	47%, 3243/6887	
	[62] Herzog CA, et al. Circ 2002 (*N* = 15,784)	44%, 2907/6668	52%, 4174/9116	
	[64] Shroff GR, et al. Circ 2013 (*N* = 18,022)	43%, 2643/6178	49%, 8171/16855	
	[65] Sunagawa G, et al. Ann Thorac Surg 2010 (*N* = 104)	16%, 5/29	• DES 47%, 5566/11844	
	[66] Szczech LA, et al. Kidney Int 2001 (*N* = 182)	25%, 28/111	• BMS 52%, 2605/5011 32%, 24/75 (DES) 41%, 29/71	
3-year mortality	CKD, non-dialysis			
	[59] Bangalore S, et al. JACC 2015 (*N* = 2936)	21%, 469/2287	23%, 458/2018	
	ESRD	28–54%	40–62%	
	[59] Bangalore S, et al. JACC 2015 (*N* = 5920)	28%, 69/243	40%, 98/243 (DES)	
	[66] Szczech LA, et al. Kidney Int 2001 (*N* = 182)	38%, 42/111	47%, 33/71	
	[64] Shroff GR, et al. Circ 2013 (*N* = 18,022)	54%, 3336/6178	62%, 10363/16855 • DES 60%, 7106/11844 • BMS 65%, 3257/5011	
	ESRD			
5-year mortality	[64] Shroff GR, et al. Circ 2013 (*N* = 18,022)	72%, 4448/6178	78%, 13059/16855 • DES 76%, 9001/11844 • BMS 81%, 4058/5011	
	General population			
8-year mortality	[60] Hemmelgarn BR, et al. Circ 2004 (*N* = 40,374)	17%, 1781/10728	14%, 2084/14887	25%, 3631/14759
	CKD, non-dialysis			
	(*N* = 750)	63%, 139/219	68%, 148/216	60%, 189/315
	ESRD			
	(*N* = 662)	61%, 93/153	52%, 76/147	57%, 206/362

ESRD end-stage renal disease, *CABG* coronary artery bypass surgery, *PCI* percutaneous coronary intervention, *POBA* plain old balloon angioplasty, *CKD* chronic kidney disease, *DES* drug-eluting stent, *BMS* bare-metal stent

Bare Metal Versus Drug-Eluting Stents

The recommendation regarding the use of bare metal (BMS) versus drug-eluting stents (DES) in patients with CKD has evolved recently [77, 78]. A recent review, meta-analysis, and network meta-analysis of clinical outcomes of DES versus BMS in CKD demonstrated that use of DES was associated with a significantly lower incidence of all-cause mortality (RR 0.82, 95% CI 0.71–0.94) [66]. The composite of death or MI (RR 0.78, 95% CI 0.67–0.91), ST (RR 0.57, 95% CI 0.34–0.95), and target vessel/lesion revascularization (TVR/

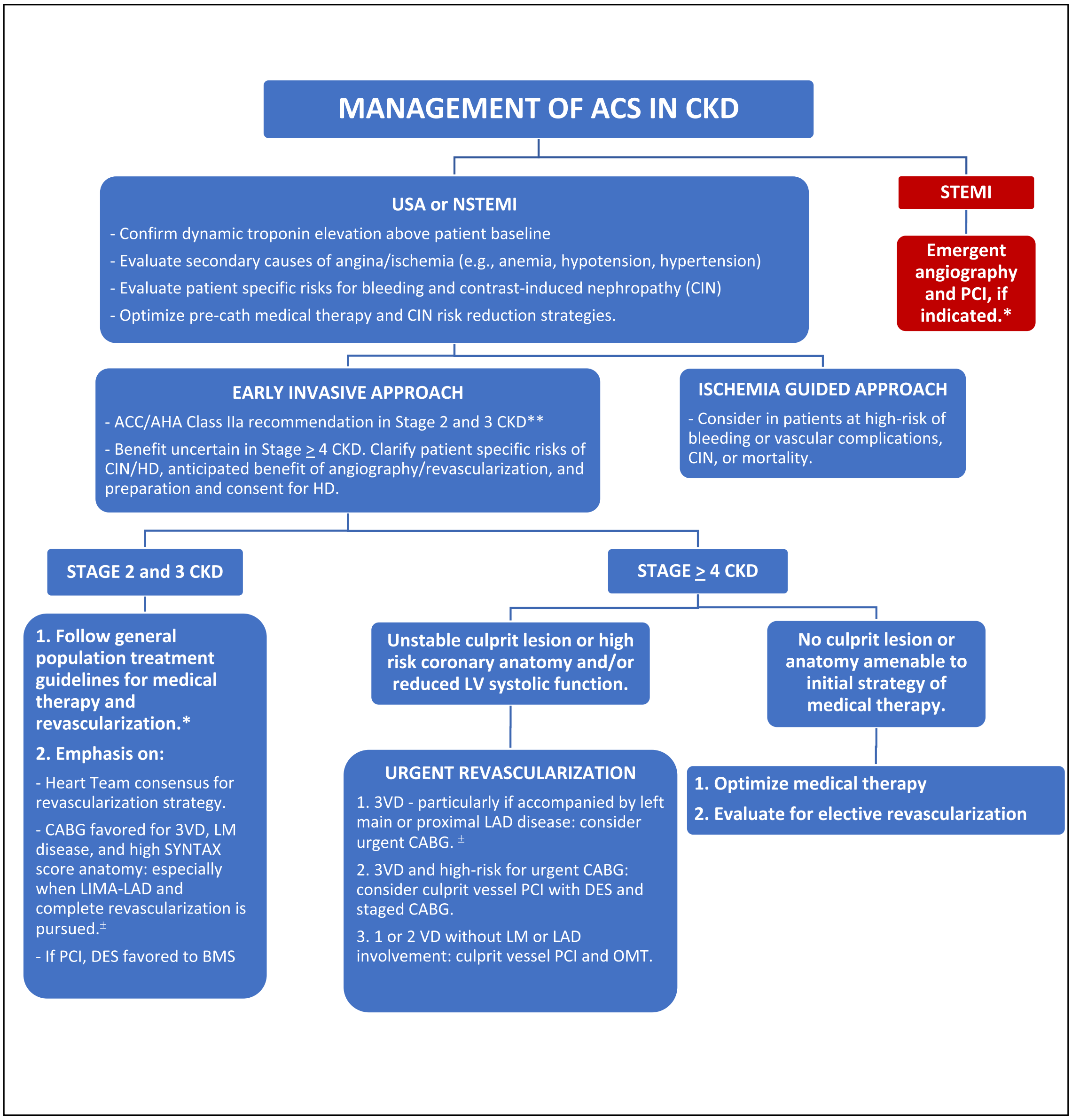

Fig. 1 Management strategies and considerations in patients with ACS and CKD. *Amsterdam, EA, et al., Circulation, 2014. 130: pp. 2354–94 [40]; **O'Gara PT, et al., Circulation, 2013. 127:e362-e425 [63]; ±Hillis, LD, et al., Circulation, 2011: 124: e652–735 [91]. Acute coronary syndrome (ACS), chronic kidney disease (CKD), unstable angina (USA), non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), contrast-induced nephropathy (CIN), American College of Cardiology (ACC), American Heart Association (AHA), hemodialysis (HD), coronary artery bypass surgery (CABG), vessel coronary artery disease (VD), left main (LM), left internal mammary to left anterior descending bypass graft (LIMA-LAD), percutaneous coronary intervention (PCI), coronary artery disease (CAD), optimal medical therapy (OMT), left ventricle (LV), drug-eluting syndrome (DES), bare-metal stent (BMS)

TLR) (RR 0.69, 95% CI 0.57–0.84) were also significantly reduced with DES compared with BMS. Compared to first-generation DES, the use of second-generation DES was associated with further relative RR: 18% reduction in all-cause death, 39% reduction in stent thrombosis, and 27% reduction in TVR/TLR [75]. Although not addressed in the current US guidelines, European Society guidelines state that if PCI is indicated in patients with CKD, DES is preferred to BMS [77, 79].

Specific PCI-Related Complications

Bleeding

CKD is strongly associated with an increased risk of bleeding in patients undergoing PCI, but the true estimate of risk is not well-understood secondary to exclusion of CKD patients from randomized clinical trials and underuse of guideline-recommended treatment. Non-randomized studies, however, consistently demonstrate at least a 4-fold increase in bleeding rates in patients with CKD, compared with those with normal renal function [57, 71–73]. In a recent analysis of patients with ESRD participating in the NCDR registry, the incidence of major in-hospital bleeding after PCI was 8.2% [57]. In an earlier analysis, Latif and colleagues reported a 14.3% incidence of any bleeding, vascular access complication, or blood transfusion after PCI in patients with CKD, compared with 3.3% in patients with normal renal function [80]. In a pooled analysis of patients with CKD participating in seven different Intracoronary Stenting and Antithrombotic Regimen (ISAR) trials, the incidence of major bleeding was 16.5%, and these events were independently associated with 1-year mortality (HR 1.9, 95% CI 1.3–2.7) [81]. The increased risk of access and non-access site–related bleeding is likely mediated by decreased clearance of antithrombotic agents, inappropriate renal dose adjustment, higher prevalence of peripheral arterial disease (PAD), more frequent femoral artery access, decreased arterial compliance, and increased vascular calcification [82]. A recent analysis of the NCDR Cath-PCI Registry between 2009 and 2015 demonstrated that in patients with ESRD undergoing PCI, bivalirudin was associated with lower rates of hospital bleeding (7% vs. 9.5%, adjusted odds 0.82, 95% CI, 0.76–0.87) and mortality (2.6% vs. 4.2%, adjusted odds ratio, 0.87, 95% CI, 0.78–0.97) compared with UFH [57]. However, the observational nature of the study and the fact that patients were more likely to receive UFH if they had an ACS presentation (37.8% vs. 27.4%) or were in cardiogenic shock (3.74% vs. 1.98) highlight the need for a randomized clinical trial. Reflecting the lack of clinical equipoise, and perhaps concerns about cost and safety, US physicians demonstrated a strong preference for UFH (> 60%) compared with bivalirudin (< 40%) in the last several quarters of time analysis (January 2014–July 2015) [57].

Vascular Complications and Choice of Access

CKD is a strong independent predictor of procedural related vascular access site complications, including vascular closure device failure (OR 1.032; 95% CI 1.019–1.046; $p < 0.0001$) [83]. Compared with femoral artery access, transradial access (TRA) is associated with significant reductions in bleeding and vascular complications, and in patients with STEMI, TRA has a demonstrated mortality benefit [84–88]. In patients with CKD, however, there is reduced utilization of TRA due to concern and controversy that TRA may limit future options for dialysis access. In the absence of randomized clinical trial data, however, TRA should remain an important strategy for improving PCI-related outcomes in patients with CKD and ACS. Unlike the general population where a “radial first” approach is appropriate, the choice of arterial access site in patients with CKD and ACS requires an individualized risk assessment that considers not only the risk and implications of bleeding and vascular complications but also the implications on renal care.

Acute Kidney Injury

Contrast-induced nephropathy (CIN) is associated with significantly increased short- and long-term mortality with an observed incidence of 7% in the NCDR Cath-PCI Registry [89]. Despite the inherent risk association between PCI and CIN, studies have demonstrated a higher risk of AKI with CABG [90, 91]. In a retrospective analysis of Permanente Northern California and Medicare beneficiaries, CABG was associated with a 2- to 3-fold increase in AKI risk compared with PCI [91]. Similar findings were observed in a propensity score–matched analysis of patients across all ranges for renal function in National Inpatient Sample database where the overall incidence of AKI after PCI and CABG was 4.5% and 8.9%, respectively (OR 2.05, 95% CI 1.99–2.12, $p < 0.001$) [90]. Among patients with advanced CKD, the relative advantage of PCI compared with CABG was persistent (31% vs. 67%, $p < 0.001$) [92]. Specific strategies to reduce the risk of PCI-related CIN include the following:

- Adequate hydration with isotonic saline (1–1.5 mL/kg/h for 3–12 h before the procedure and 3–6 h after the procedure) to prevent hypovolemia and minimization of contrast volume are the only proven interventions in preventing CIN [93–95].
- Evidence for use of fenoldopam, ascorbic acid, N-acetylcysteine, or sodium bicarbonate infusion is either non-supportive or inconclusive [95, 96]. The PRESERVE trial was a large ($N = 5177$) randomized clinical trial that used a 2-by-2 factorial design to evaluate the role of sodium bicarbonate and oral acetylcysteine in preventing CIN in patients at high risk for renal complications [96]. The trial was stopped prematurely due to the lack of efficacy of either treatment.
- Risk equations should be used to calculate the patient-specific risk of CIN and to estimate renal risk limits for contrast volume [97, 98].
- Staged revascularization with avoidance of excess contrast volume during any one procedure is recommended.
- Low-osmolar contrast media, compared with iso-osmolar agents, and statin therapy may help prevent CIN [95].
- TRA utilization has been associated with reduced contrast utilization and reduced incidence of AKI [88].

Coronary Artery Bypass Surgery

Effect of CKD and ACS on CABG-Related Outcomes

The presence and severity of CKD significantly modify the risk of CABG operative mortality. In a review of the Society of Thoracic Surgeons National Adult Cardiac Database between 2000 and 2003, preoperative renal dysfunction demonstrated a graded relationship with operative mortality. Compared with patients with normal renal function (GFR ≥ 90), patients with mild CKD (60–90 mL/min per 1.73 m^2), moderate CKD (GFR 30–59 mL/min per 1.73 m^2), severe dysfunction (<30 mL/min per 1.73 m^2), or on dialysis had risk-adjusted odds of operative mortality of 1.02 (0.96–1.9), 1.55 (1.45–1.65), 2.87 (2.61–3.16), and 3.82 (3.45–4.25), respectively. Dialysis dependence was also associated with > 2-fold increase in the risk of stroke, prolonged ventilation, deep sternal wound infection, prolonged hospitalization, and reoperation. Finally, GFR was a strong predictor of postoperative renal failure requiring dialysis: with a 70% increase among patients with mild CKD (95% CI, 1.42–2.04), > 4-fold increase in patients with moderate CKD (95% CI, 3.87–5.6), and > 20-fold increase in patients with severe CKD (95% CI, 16.68–24.87) [99]. Similarly, Hillis et al. demonstrated in a single-center study of non-dialysis patients undergoing CABG that for every 10 mL/min increase in GFR, the likelihood of 30-day survival increased by 32%, and the likelihood of survival at a median follow-up of 2.3 years increased by 20% [100]. In a subgroup analysis of the SYNTAX trial, patients with stage 3 CKD or greater had significantly worse 5-year mortality compared with patients with normal renal function (21.2% vs. 10.6%, $p = 0.005$) [9].

The presence of ACS also significantly modifies the short- and long-term outcomes after CABG. In an analysis of 23,033 ESRD patients undergoing CABG, all-cause mortality at short- and long-term intervals were consistently higher among patients with ACS as compared with patients without ACS [101].

Specific Challenges Related to CABG in CKD and ACS

Patients with CKD, with and without ACS, represent a particularly high-risk and challenging subset of patients for CABG. In addition to increased prevalence of comorbid conditions such as diabetes, prior stroke, and PAD, the presence of upper extremity arterial-venous fistulae, prior vein harvesting, and aortic calcification may limit coronary artery bypass conduit and surgical options in patients with CKD. The presence of CKD has been associated with an increased risk of saphenous vein graft occlusion, and CABG in ESRD has been associated with increased risk of postoperative infection, mesenteric ischemia, and heart failure [102–105].

CABG Outcomes in Patients with CKD and ACS

Despite the increase in short-term risk of surgery in CKD, observational studies have consistently demonstrated that CABG confers a long-term survival benefit compared with medical therapy and PCI. In a retrospective analysis of patients with ESRD undergoing multivessel coronary revascularization between 1997 and 2009, CABG was associated with an increased short-term hazard but significant reduction in 5-year mortality (HR 0.87, 0.84–0.9) compared with PCI, and the presence of MI on presentation did not modify this effect [106]. In patients with CKD enrolled in the SYNTAX trial, CABG compared with PCI was associated with a significant reduction in repeat revascularization (21.9% vs. 8.9%, $p = 0.004$) but an insignificant reduction in all-cause death at 5 years (26.7% vs. 21.2%, $p = 0.14$). In patients with diabetes and CKD, however, CABG conferred a significant reduction in death, stroke, or MI (47.9% vs. 24.4%, $p = 0.005$) and all-cause death (40.9% vs. 17.7%, p = 0.004) compared with PCI [9].

ISCHEMIA-CKD is an ongoing randomized clinical trial of approximately 800 patients that compares an initial invasive strategy with revascularization (PCI or CABG), if appropriate, and optimal medical therapy (OMT) versus a conservative strategy of OMT alone in patients with advanced CKD (eGFR < 30 mL/min/1.73 m^2 or on dialysis) and SIHD [107••]. It is not, however, a study of patients with ACS and it does not involve a randomized comparison of PCI versus CABG. The estimated study completion date is December 2019.

Current guideline recommendations for CABG in patients with CKD and ACS are limited, and the restricted statements in these guidelines are largely based on observational data [77, 79, 108, 109]. The 2014 ESC/EACTS guidelines on myocardial revascularization recommend a preference for CABG over PCI in patients with CKD with at least a 1-year life expectancy, and the updated 2018 ESC/EACTS guidelines did not identify any evidence to support modification of this recommendation [77, 79]. The 2011 ACCF/AHA guidelines for CABG recommend CABG to improve survival in patients with ESRD and left main disease (IIb, level of evidence C), and to improve angina in patients with ESRD and significant three-vessel CAD or significant two-vessel CAD with proximal LAD involvement (IIb, level of evidence B) [108].

Given the paucity of randomized clinical trial data in patients with CKD and ACS, patient-centered strategies for revascularization with an emphasis on multi-disciplinary collaboration may be especially important (Fig. 1). This may be particularly true in select patients with moderate to severe CKD and NSTEMI-ACS where the increased complexity and risk associated with urgent revascularization and apparent long-term benefit of CABG compared with PCI may favor consideration of a hybrid revascularization strategy or a period of medical optimization followed by elective CABG. It should be emphasized that Heart Team engagement and consensus, multi-disciplinary collaboration, and patient education and shared decision-making are also critical in choosing appropriate revascularization strategies.

Unanswered Questions, Challenges, and Future Developments

The underrepresentation of patients with CKD, especially those with advanced CKD, in randomized clinical trials in CVD is well established [7]. The reliance on expert opinion, subgroup analyses, and observational studies provides a stark contrast to the strong evidence-base that guides CVD management in patients without CKD.

There are a number of challenges to increasing representation of patients with CKD in randomized clinical trials [7, 110]. The higher risk and comorbidity profile of patients with CKD may lead to a preference toward more conservative medical therapies, compared with revascularization. These same factors may influence investigators, clinicians, and patients to think that investigative treatments will be poorly tolerated. Investigators may fear that inclusion of patients with CKD will threaten funding sources, increase costs, and weaken statistical power due to the variance of treatment effect on patients with and without CKD. All of these problems are compounded in patients with ESRD and those awaiting renal transplantation as competing interests and priorities of various treatment teams may not always be aligned, and the realities of managing patients with ESRD before and after renal replacement initiation are complicated and not always conducive to the rigidity of the clinical trial design.

Despite the obstacles, it is imperative that we strive to improve our knowledge gaps in the management of CVD in patients with CKD. Key to this objective is collaboration across specialties and specialty societies, and between departments at funding sources such as the National Institutes of Health (NIH). The NIH-funded ISCHEMIA-CKD clinical trial serves as an excellent example of this type of effort, and we hope it will significantly improve our understanding of the optimal revascularization strategy of SIHD in patients with advanced CKD [107••]. What remains critically absent are studies of both medical and revascularization therapies in patients with CKD and ACS.

Conclusion

CKD is a highly prevalent condition, and a substantial proportion of patients with ACS have CKD. The presence of CKD in patients with ACS is a strong independent risk factor for short-term MACE compared with patients with normal renal function. Despite the short-term risk, revascularization appears to confer a long-term benefit compared with medical therapy in patients with CKD and ACS. While CABG has been proven benefits compared with PCI and medical therapy in the management of SIHD, the comparative effectiveness in patients with CKD and ACS is very much unproven. Until randomized clinical trial data is available, we are forced to extrapolate from general population data, interpret observational data, and rely on expert opinion. In order to provide CKD patients with optimal care, promotion of a cross-discipline collaboration, patient education and shared decision-making, and Heart Team engagement is suggested.

Compliance with Ethical Standards

Conflict of Interest Evan C. Klein, Ridhima Kapoor, David Lewandowski, and Peter J. Mason each declare that he/she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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