



Review

Coronary Revascularization in Patients With Advanced Chronic Kidney Disease

Pierluigi Costanzo, MD, MSc, MRCP, FESC, and
Vladimír Džavík, MD, FRCPC, FACC, FAHA, FSCAI

Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada

ABSTRACT

Patients with chronic kidney disease (CKD) have an increased risk of obstructive coronary artery disease (CAD), whereas patients with end stage renal disease who are receiving hemodialysis represent a population at particularly high risk of developing cardiac ischemic events. Patients with CKD and acute coronary syndromes should be treated the same way as acute coronary syndromes patients without kidney dysfunction. The benefit of revascularization in patients with advanced kidney failure and CAD is unknown. Observational studies suggest that revascularization might confer a survival benefit compared with medical therapy alone. Little evidence from randomized trials exists regarding the effectiveness of revascularization of patients with CAD with either coronary artery bypass grafting or percutaneous coronary intervention vs medical therapy alone in patients with CKD. The risk of contrast-induced nephropathy is a major concern when percutaneous coronary intervention is performed in patients with CKD. Strict rehydration protocols and techniques to minimize contrast use are paramount to reduce this risk. Finally, in CKD patients who are awaiting kidney transplantation, a noninvasive or invasive CAD screening approach according to the cardiovascular risk profile should be used. Revascularization should be performed in candidates with critical lesions.

RÉSUMÉ

Les patients atteints de néphropathie chronique (NC) présentent un risque accru de coronaropathie obstructive, tandis que les patients atteints de néphropathie terminale sous hémodialyse présentent un risque particulièrement élevé d'ischémie cardiaque. Les patients atteints de NC et d'un syndrome coronarien aigu doivent recevoir le même traitement que les patients atteints d'un syndrome coronarien aigu sans insuffisance rénale. Les bienfaits de la revascularisation chez les patients atteints d'insuffisance rénale à un stade avancé et de coronaropathie ne sont pas connus. Des études d'observation indiquent que la revascularisation pourrait améliorer la survie comparativement à un traitement médical administré seul. Il existe peu de données probantes provenant d'essais avec répartition aléatoire concernant l'efficacité de la revascularisation chez les patients atteints de coronaropathie qui ont subi un pontage aortocoronarien ou une intervention coronarienne percutanée comparativement aux patients atteints de NC ayant reçu un traitement médical seulement. Le risque de néphropathie induite par un agent de contraste est élevé chez les patients atteints de NC subissant une intervention coronarienne percutanée. Des protocoles et des techniques de réhydratation rigoureux visant à minimiser l'emploi d'agents de contraste sont essentiels pour réduire ce risque. Enfin, chez les patients atteints de NC qui sont en attente d'une greffe de rein, le dépistage de la coronaropathie par une méthode invasive ou non invasive, en fonction du profil de risque cardiovasculaire, est recommandé. Une revascularisation s'impose chez les patients présentant des lésions critiques.

Patients with chronic kidney disease (CKD) have an increased risk of obstructive coronary artery disease (CAD), a risk that increases as kidney function deteriorates.¹ Kidney dysfunction is categorized according to the estimated glomerular filtration rate (eGFR).² Normal kidney function is defined as an eGFR > 90 mL/min/1.73 m², mild CKD (stage 2) between 89 and

60 mL/min/1.73 m², moderate CKD (stage 3) between 59 and 30 mL/min/1.73 m², severe CKD (stage 4) between 29 and 15 mL/min/1.73 m², and end stage renal disease (ESRD; stage 5) < 15 mL/min/1.73 m².² The worse the CKD stage, the higher is the prevalence of at least 1 coronary artery with > 70% atherosclerotic stenosis.¹

Received for publication November 6, 2018. Accepted February 25, 2019.

Corresponding author: Dr Vladimír Džavík, Peter Munk Cardiac Centre, 6-246A EN Toronto General Hospital, 200 Elizabeth St, Toronto, Ontario M5G 2C4, Canada. Tel.: +1-416-340-4800; fax: +1-416-340-3390.

E-mail: vlad.dzavik@uhn.ca

See page 1010 for disclosure information.

Epidemiology and Prognosis of CAD in CKD

Worsening eGFR is associated with increasing cardiovascular morbidity and mortality.³ In a large cohort of more than a million subjects from California with kidney function ranging from normal to severe dysfunction (excluding dialysis), eGFR was independently and gradually associated with

the risk of death and cardiovascular events. These risks were already evident with mild CKD.³ This was confirmed in a large Canadian cohort from the Alberta Kidney Disease Network database, in which the risk of cardiovascular death was inversely related to eGFR.⁴ In particular, the risk of cardiovascular death due to ischemic heart disease in patients with CKD but not receiving hemodialysis was > 50%.⁴ Furthermore, the risk of sudden cardiac death in CAD patients has been shown to increase by 11% for every 10 mL/min decline in eGFR (Fig. 1).⁵

Finally, albuminuria has more recently emerged as an additional tool for prediction of cardiovascular events in patients with CKD.⁶ A large individual patient data meta-analysis showed that the additional use of albuminuria-creatinine ratio to the eGFR outperforms the eGFR on its own in predicting cardiovascular events.⁶ The Kidney Disease Improving Global Outcomes most recent clinical management guidelines recommend considering the level of albuminuria to stage the severity of CKD.⁷

CAD is the most frequent cause of death in patients with ESRD who are receiving dialysis, with up to 20% of deaths being due to acute myocardial infarction (MI).⁸ There is an early hazard of MI related to the initiation of dialysis, with 52% within 2 years after its initiation.⁵ One of the largest ESRD cohorts examined, the US Renal Database System, specifically examined patients with ST-elevation MI (STEMI) and non-STEMI (NSTEMI). With almost 43,000 dialysis patients, the study showed that in-hospital mortality with STEMI was high but decreased from 38% in 1993 to 26% in 2008.⁹ Compared with the current average in-hospital mortality for all-comers with STEMI of between 6% and 7%,¹⁰ these very high mortality rates are likely related to the increased complexity of CAD in CKD patients, which renders revascularization more challenging, which leads to suboptimal results, and higher thrombotic as well as bleeding risk.¹¹⁻¹⁵

The effect of CKD on developing CAD is large and it correlates with the degree of severity of the kidney function deterioration. The prognostic implications are of particular relevance in determining the best therapeutic approach.

Coronary Revascularization in CKD

The benefit of revascularization in patients with advanced kidney failure and CAD is poorly delineated. Observational studies have suggested that revascularization procedures might convey a survival benefit compared with medical therapy alone.¹⁶⁻²⁴ In a meta-analysis of nonrandomized studies of patients with CKD, revascularization, compared with medical therapy alone, might have similar short-term mortality but lower long-term mortality (Fig. 2).²⁵ However, these studies are affected by the bias of selection of the “less healthy” patients for more conservative treatment alternatives, therefore the signal of advantage of revascularization over medical therapy might be spurious. An ongoing multicentre trial, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches—Chronic Kidney Disease (ISCHEMIA-CKD) study, was designed to address the uncertainties regarding on optimal long-term revascularization strategies (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG] where suitable vs optimal medical therapy) in patients with moderate to

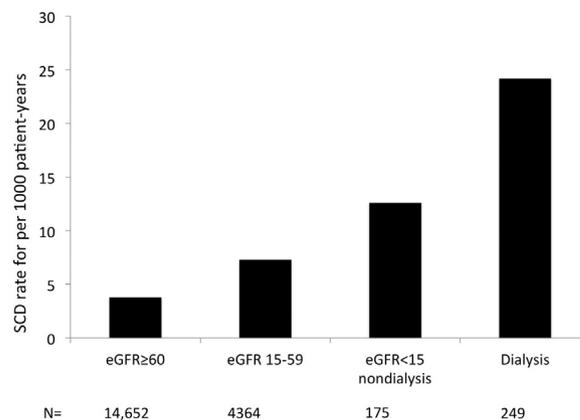


Figure 1. Rates of sudden cardiac death according to the baseline estimated glomerular filtration rate (eGFR) category. Rates shown as events per 1000 patient-years. SCD, sudden cardiac death. Modified from Pun et al.⁵ with permission from Elsevier.

severe stress-induced ischemia and severe CKD (eGFR < 30 mL/min/1.73 m²).²⁶ The trial has enrolled 777 patients and is currently in the follow-up phase.²⁶

PCI in CKD

Patients with CKD who undergo PCI have more cardiovascular risk factors at baseline, with kidney failure being an independent predictor of cardiovascular events and mortality.^{27,28} The risk gradually increases with worsening stages of CKD as shown by the Mayo Clinic group during an era of predominant balloon angioplasty and subsequently confirmed in the stent era in a large Canadian cohort from the Peter Munk Cardiac Centre (Fig. 3).^{27,28}

In the setting of acute coronary syndromes (ACS), large registry studies have shown that in the presence of mild to moderate CKD stages early revascularization compared with medical therapy leads to better short- and long-term survival.^{29,30} However, in CKD stages 4 and 5, the association between revascularization and better outcome is less clear, as shown by a large Swedish registry.³¹ In terms of kidney outcomes in the setting of ACS, despite being associated with a small increase in risk of acute kidney injury in the short term, an early invasive strategy was not associated with long-term progression to ESRD compared with medical management in a propensity score-matched cohort from Alberta.³² This is reflected in the 2014 American College of Cardiology and American Heart Association guidelines for managing NSTEMI, in which an invasive strategy is considered reasonable with a class IIa indication only in patients with mild stage 2 and stage 3 CKD.³³

Coronary revascularization is performed with deployment of either drug-eluting stents (DES) or bare metal stents (BMS).³⁴ The latter were developed to decrease neointimal proliferation, which contributes to the development of restenosis.³⁴ However, implantation of DES necessitates more prolonged dual antiplatelet therapy compared with implantation of BMS. This can be an issue in patients with CKD, who have an increased risk of bleeding, proportional to the CKD stage.¹⁴ No randomized trial is available in the kidney failure population not receiving dialysis, with a comparison of outcomes after deployment of DES and BMS. In general,

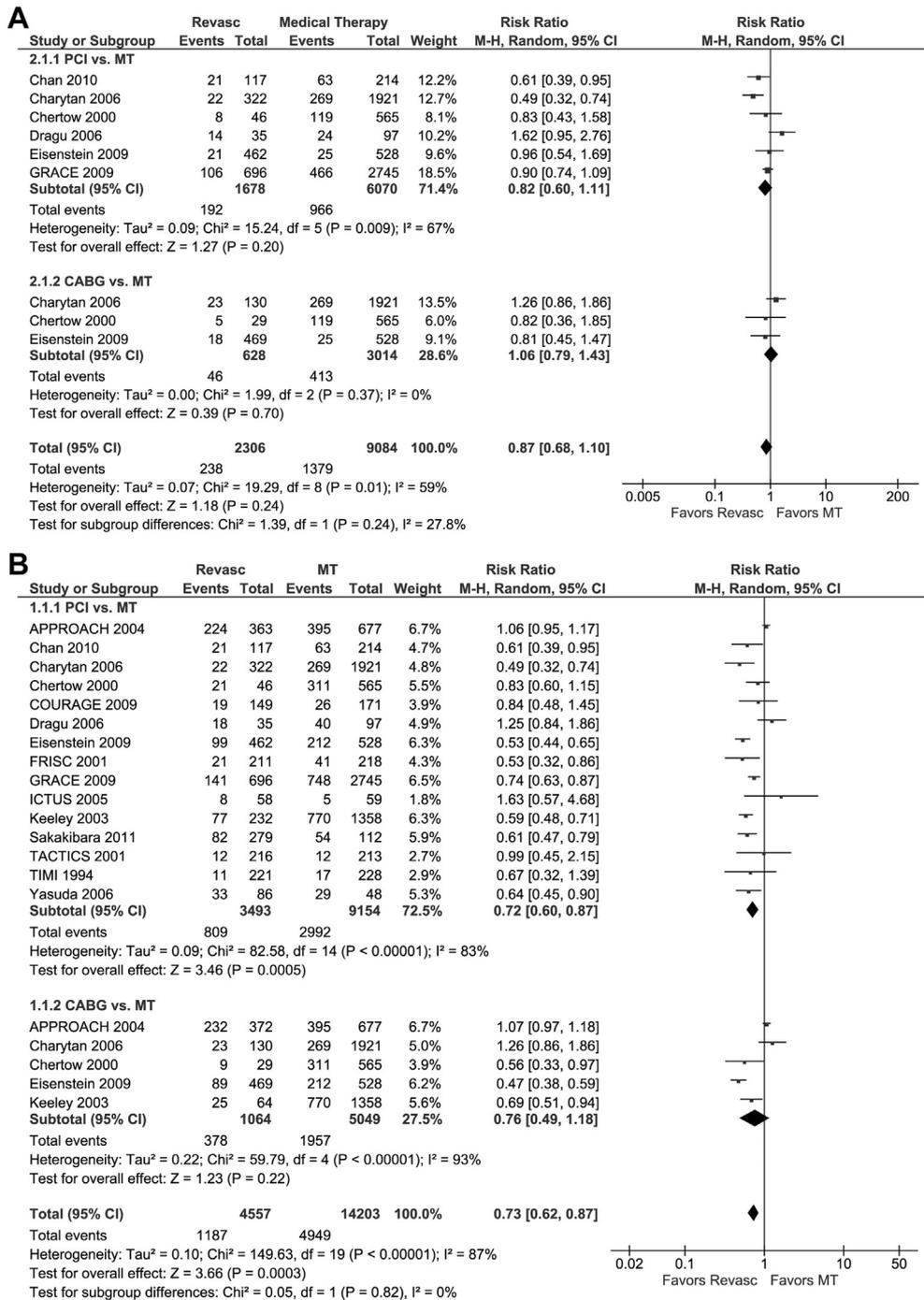


Figure 2. Revascularization vs medical therapy (MT): **(A)** short-term mortality; **(B)** long-term mortality. CABG, coronary artery bypass surgery; CI, confidence interval; PCI, percutaneous coronary intervention. Reproduced from Volodarskiy et al.²⁵ with permission from Elsevier.

observational studies have yielded mixed results, some reporting a lower mortality with DES,^{35,36} and others not.^{37,38} In a recent meta-analysis that examined all of these observational data, it was suggested that DES might reduce mortality, risk of MI, and target vessel revascularization in patients with advanced CKD not receiving dialysis, and in those receiving dialysis.³⁹ Nevertheless, in the absence of randomized data, the superiority of DES over BMS in patients with advanced CKD cannot be ascertained.

Coronary plaques in patients with ESRD usually have increased media thickness and marked calcification compared with nonuremic patients.¹¹ Plaque complexity also increases progressively with decreasing kidney function with a lower eGFR being a strong predictor of a higher Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score.¹² Therefore, PCI is technically more challenging in these patients, and CKD has been shown to be independently associated with decreased procedural

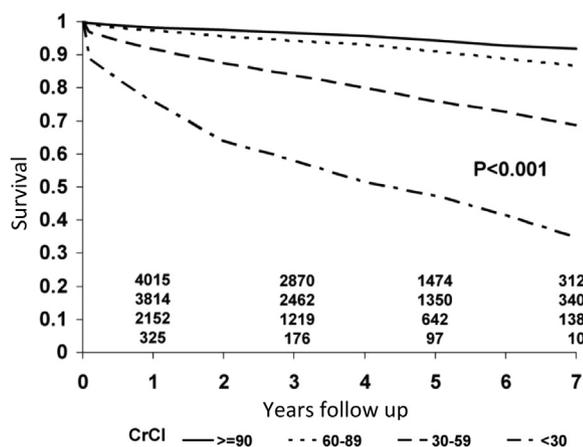


Figure 3. Kaplan–Meier survival curves as a function of renal function. (Normal renal function (creatinine clearance [CrCl] 90 mL/min), mild chronic kidney disease (CKD) (CrCl 60–89 mL/min), moderate CKD (CrCl 30–59 mL/min), or severe CKD (CrCl < 30 mL/min). Modified from Appleby et al.²⁸ with permission from Wolters Kluwer Health, Inc.

success.^{13,40,41} Contributing to their poor prognosis is also the fact that patients with CKD are also less likely than those with normal kidney function to undergo PCI or to receive evidence-based care.^{23,42–44} Several reasons account for this, including a perceived paucity of evidence in this population, a perception of a higher risk-benefit ratio, and a risk-adverse attitude of physicians.⁴⁴

In recognition of this, it has been recommended in the 2018 European Society of Cardiology guidelines that patients with CKD who develop non-ST-elevation ACS should be treated in the same manner as patients with normal kidney function.⁴⁵ The recommendation is made recognizing that CKD patients are often under-represented in clinical trials. The 2014 American Heart Association and American College of Cardiology non-ST-elevation ACS management guidelines state that it is reasonable to adopt an invasive strategy in patients with stage 2 and stage 3 CKD, whereas there are insufficient data regarding the benefit-risk profile of an invasive strategy in patients with advanced CKD (stages 4 and 5) who present with NSTEMI.³³ The Canadian perspective on invasive management of ACS/NSTEMI does not mention specific stages of kidney failure at which revascularization should be performed, instead advocating assessment of benefits and risks in individual patients.⁴⁶

Completeness of revascularization in ACS is a subject of ongoing debate. It is of particular relevance to patients with CKD because complete revascularization might result in a greater likelihood of acute kidney injury and thus possibly worse outcome. Meta-analyses of smaller studies that evaluated stenting strategies in patients with STEMI have suggested better outcome with complete revascularization.⁴⁷ There are, however, no data in the CKD population. A large Canadian-led international trial of staged complete vs culprit-only revascularization in patients with STEMI is currently in the follow-up phase and will be reporting soon. Data specifically in STEMI complicated by cardiogenic shock might provide important clues. The **Culprit** Lesion Only PCI vs Multivessel

PCI in Cardiogenic **Shock** (CULPRIT-SHOCK) showed that culprit lesion only vs multivessel PCI resulted in a lower risk of death or severe renal failure leading to renal replacement therapy at 30 days. Although the trial was not conducted specifically in patients with CKD, the median eGFR of the patients enrolled in this trial was just > 60 mL/kg/min. Thus, the findings of this trial favouring culprit PCI could be applied to CKD patients with acute myocardial infarction and cardiogenic shock.⁴⁸

PCI appears to be a reasonable coronary revascularization option in patients with CAD and reduced kidney function, particularly in those with a mild to moderate degree of CKD either in the setting of ACS or stable CAD.

Contrast-Induced Acute Kidney Injury

Contrast-induced acute kidney injury (CI-AKI) is a complication of radiological procedures, including PCI, in which contrast media are used. After contrast exposure, serum creatinine levels tend to peak between 2 and 5 days, usually returning to normal within 14 days.⁴⁹ CI-AKI is defined as kidney function deterioration, measured as either a 25% rise in serum creatinine level from baseline or alternatively a 0.5 mg/dL (44 μmol/L) increase in absolute serum creatinine level, within 48–72 hours after intravenous and/or intra-arterial contrast administration.⁵⁰ A combination of oxidative stress, vasoconstriction, ischemia of the outer medulla, and osmotic tubular nephrosis are the leading mechanisms considered to cause CI-AKI.⁵¹ For kidney failure to be considered secondary to contrast administration, it should usually occur within 2–3 days and up to 7 days after the procedure. Other identifiable causes of kidney failure should also be excluded.

The contribution of contrast media to the development of kidney failure in patients who undergo PCI is on the rise, especially because of the increasing number of patients with more complex coronary anatomy who undergo PCI, and require more contrast.⁵² However, the temporal trend of kidney failure post coronary angiography in patients admitted with MI is declining.⁵³ It could be speculated that acute kidney injury prevention strategies might play a role in this.⁵³ CI-AKI has a direct consequence on patient outcome, with persistent postprocedural kidney dysfunction having been shown to be associated with up to a threefold increase in mortality.⁵⁴ Whether or not transient CI-AKI is also associated with increased long-term mortality remains unresolved.^{54,55}

The risk of CI-AKI depends on several patient-related factors, such as pre-existence of CKD, diabetes mellitus, congestive heart failure, advanced age, female sex, hemodynamic instability, reduced plasma volume, periprocedural bleeding, anemia, and type and volume of contrast administered.^{56–62} A well validated CI-AKI risk score on the basis of 8 variables (patient related: age > 75 years, chronic congestive heart failure or admission with acute pulmonary edema, diabetes mellitus, hypotension, anemia, CKD; and procedure-related: increasing volumes of contrast media or the use of elective intra-aortic balloon pump) can be calculated to determine an individual patient's risk of developing the complication. An increasing score confers an exponentially increased CI-AKI risk (Fig. 4).⁵⁶ A limitation of this risk score

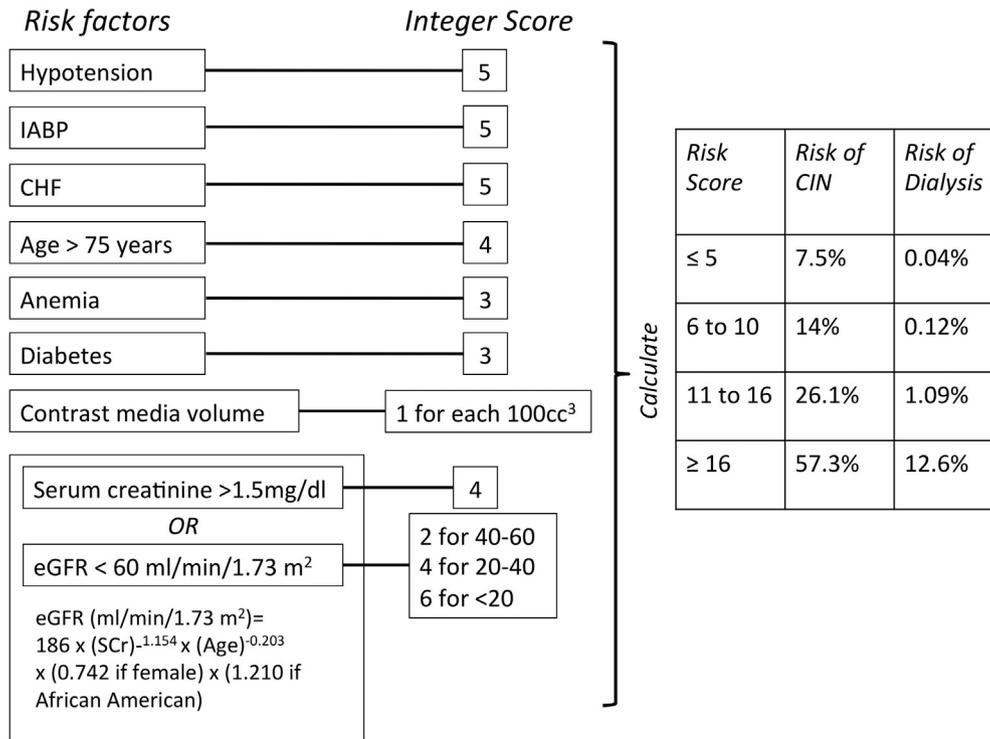


Figure 4. Scheme to define contrast-induced nephropathy (CIN) risk score. Anemia was determined as baseline hematocrit value < 39% for men and < 36% for women. Congestive heart failure (CHF) was determined according to New York Heart Association classification III/IV and/or history of pulmonary edema. Hypotension was determined according to systolic blood pressure < 80 mm Hg for at least 1 hour requiring inotropic support with medications or intra-aortic balloon pump (IABP) within 24 hours periprocedurally. Other risk scores are also available, independent of contrast volume and externally validated.⁶³⁻⁶⁵ eGFR, estimated glomerular filtration rate. Modified from Mehran et al.⁵⁶ with permission from Elsevier.

for preprocedural risk assessment is that it includes the contrast volume, which can only be estimated before the procedure. More recently, risk scores for CI-AKI prediction, independent of contrast volume have been developed and externally validated.⁶³⁻⁶⁵

The mainstays of CI-AKI prevention are adequate hydration⁶⁶⁻⁷⁰ and minimization of contrast volume. The hydration protocol with the best evidence derives from the Prevention of Contrast Renal Injury With Different Hydration Strategies (POSEIDON) trial.⁷¹ In this study, CKD patients were to undergo PCI were enrolled and randomized to either routine hydration with normal saline at 1.5 mL/kg/h or left ventricular end diastolic pressure (LVEDP)-guided hydration (5 mL/kg/h for LVEDP < 13 mm Hg, 3 mL/kg/h for LVEDP 13-18 mm Hg, and > 1.5 mL/kg/h for LVEDP > 18 mm Hg). Either of the two was preceded by normal

saline at 3 mL/kg 1 hour before the procedure. The randomized hydration regimen was continued for 4 hours (Table 1). In the LVEDP-based hydration strategy group, a 25% or 44 μmol/L increase in serum creatinine was observed in 6.7% and in 16.3% of the standard hydration group (P = 0.005). The relative risk for LVEDP-based hydration compared with standard hydration was 0.41 (95% confidence interval, 0.22-0.79). However, the need for dialysis at 6 months was similar in the 2 groups (0.5% vs 2.0%; P = not significant), although the trial was underpowered to detect a difference in this outcome.⁷¹

Although indicated for secondary prevention irrespective of the risk of CI-AKI, high-dose statins are also beneficial.⁷² Their protective effects are likely multifactorial, and include reduction of the reabsorption of contrast agents in kidney tubules and modulation of kidney hypoperfusion by down-regulation of angiotensin receptors.⁷³ The best evidence available is for atorvastatin and rosuvastatin, with 62% and 57%, respectively, reduction in the incidence of CI-AKI in a meta-analysis of randomized clinical trials.⁷⁴ N-acetylcysteine and sodium bicarbonate, previously recommended for CI-AKI reduction, have not been shown to reduce its risk.^{70,72}

Strategies to minimize procedural contrast volume might include intravascular ultrasound (IVUS), because of its ability to precisely measure lumen, plaque, and vessel dimensions, at least in many steps during the PCI procedure.⁷⁵ In a retrospective study from Columbia University 31 patients with eGFR 16 ± 8 mL/min/1.73 m² underwent PCI with no

Table 1. Hydration protocol from the POSEIDON trial⁷¹

Preprocedure	LVEDP-guided hydration	
	3 mL/kg/h	
During procedure	LVEDP mm Hg	Rate mL/kg/h
	< 13	5
	13-18	3
	> 18	1
Postprocedure	Continue intraprocedural rate for 4 hours	

LVEDP, left ventricular end diastolic pressure; POSEIDON, Prevention of Contrast Renal Injury With Different Hydration Strategies.

contrast use, with IVUS guidance only, and with fractional flow reserve and coronary flow reserve guidance to confirm physiological improvement. All patients had a successful PCI with no major adverse cardiovascular events, and all had preservation of kidney function.⁷⁶ Importantly though, complications such as coronary perforation cannot be clearly diagnosed with IVUS. It is unclear how this technique would perform in complex procedures that are the mainstay of many labs, in particular in patients with CKD.

It is more likely that intravascular imaging can be used to substantively reduce contrast volume rather than not using contrast at all. The **Minimizing Contrast Utilization With IVUS Guidance in Coronary Angioplasty (MOZART)** study, which evaluated the role of IVUS in patients at risk of developing CI-AKI but without severe CKD, 83 patients were randomized to IVUS-guided or angiography-guided PCI. The primary end point was the total volume of contrast agent used during PCI. The approach was shown to be effective, safe, and with no excessive use of additional stents or increase in the incidence of clinical adverse events. The median total volume of contrast was 64.5 mL in the angiography-guided group vs 20.0 in the IVUS-guided group ($P < 0.001$). In-hospital and 4-month outcomes were similar in the 2 groups.⁷⁷

Another strategy to reduce contrast volume during PCI is the use of rapid-exchange “mother and child” guide extension that permit deep and subselective intubation of the target vessel, providing back-up support in addition to that provided by the guiding catheter. Additionally, because the design of the device is on the basis of a monorail-based rapid-exchange platform, contrast injections through the guiding catheter enter the proximal portion of the extension catheter and exit it distally (selectively in the target vessel). Because there is little loss of contrast into more proximal side branches, the volume of dye necessary for target vessel opacification is typically lower than if contrast were injected through the guiding catheter alone.⁷⁸

A similar technique has been shown in a series 150 patients by Mamas et al. using a 5F Terumo guide catheter (Heartrail II, Terumo Corp, Tokyo, Japan) into a standard 6-French (Fr) guide catheter with the tip protruding beyond the 6-Fr guide. The Heartrail II is an extra-length soft-tipped 5-Fr catheter able to fit in a standard 6-Fr catheter. It can extend up to 16 cm distal to the tip, allowing contrast to be injected selectively into the target coronary segment.⁷⁹

The use of automated contrast injection systems can reduce the volume of procedural contrast. A recent meta-analysis showed a reduced contrast volume delivery by 45 mL per case compared with manual injection ($P < 0.001$) with CI-AKI incidence significantly reduced by 15%.⁸⁰

Optical coherence tomography guidance during PCI using dextran, as a strategy to reduce the risk of CI-AKI occurrence in patients with CKD has been proposed.⁸¹ Further studies will be needed in light of the potential occasional reported nephrotoxicity of dextran.^{82,83}

Finally, the use of hemodynamic support with the Impella (Abiomed, Danvers, MA) device has been proposed as a way to reduce the risk of CI-AKI in patients who undergo high-risk PCI.⁸⁴ Theoretically, the continuous blood flow during a PCI supported by Impella (Abiomed), significantly decreases renal hypoperfusion and avoids contrast stagnation in the renal tubules.⁸⁴ However, the evidence is only on the basis of

retrospective data, which might not be free of confounding factors.

The occurrence of CI-AKI is a detrimental prognostic factor to consider when planning PCI revascularization of patients with CAD, particularly those with pre-existent CKD. Protocols to minimize the risk, although complex, are well defined, and should be followed. In particular, strategies to minimize this risk include appropriateness of the revascularization option such as consideration of an alternative management option (medical or CABG), using a peri- and postprocedural hydration regimen, minimizing contrast volume, including use of noncontrast-based imaging technology (IVUS), and staging in multivessel PCI.

CABG in Patients With CKD

Studies on patients with moderate CKD and not receiving hemodialysis who undergo CABG have consistently shown serum creatinine and eGFR as a predictor of postoperative adverse outcome, predominantly acute kidney failure, but also death and stroke.⁸⁵⁻⁸⁸ Nevertheless, it is important to consider that these studies are not uniform because of arbitrary definitions of moderate and severe kidney dysfunction and of varying threshold creatinine concentrations, rather than the more discriminating calculated eGFR. In a study of more than 400,000 CKD patients not receiving hemodialysis who received isolated CABG from 2000 to 2003 using data from the Society of Thoracic Surgeons National Adult Cardiac Database (United States), Cooper et al. showed perioperative mortality to be inversely associated with declining kidney function, ranging from 9.3% in patients with severe CKD to 1.3% in those with normal kidney function.⁸⁷ In patients with an eGFR < 30 mL/min/1.73 m² the use of internal mammary artery grafts was significantly protective against operative death compared with the use of venous grafts.⁸⁷

Patients receiving dialysis who undergo CABG are particularly at risk of peri- and postoperative morbidity and mortality.⁸⁹ The perioperative risks involved in cardiac surgery are higher in patients with ESRD who receive hemodialysis than in the general cardiac patient population or in CKD patients not receiving hemodialysis.⁸⁷ According to the American College of Cardiology and American Heart Association guidelines, CABG can be performed in select dialysis patients, with an increased but acceptable risk of perioperative morbidity and mortality.⁹⁰ Use of the mammary artery from the same side as the arteriovenous fistula, is associated with an increased risk of coronary steal during dialysis causing angina.⁹¹ Use of the contralateral mammary artery for use as the critical conduit to the left anterior descending coronary artery might be thus preferable.⁹¹

Off-Pump vs On-Pump CABG Surgery in Patients With CKD

In patients with CKD not receiving hemodialysis who undergo CABG, the risk of postoperative kidney failure requiring dialysis varies from 1% to 5%.⁹² Off-pump CABG might offer theoretical advantages compared with on-pump. These include less dynamic perioperative fluid shifts, fewer bleeding complications, and shorter periods of postoperative mechanical ventilation.⁹³ Studies that have compared

off-pump with on-pump CABG have reported contradictory results with respect to short- and long-term outcomes.⁹⁴ A propensity-matched study failed to show a difference in risk of end stage kidney failure requiring dialysis, stroke, and mortality of off-pump vs on-pump CABG.⁹⁵ The only randomized study was a small study of 116 patients that showed a higher risk of developing ESRD requiring hemodialysis in patients who undergo on-pump CABG.⁹⁶ Finally, a recent meta-analysis of nearly all retrospective studies suggested no difference in the risk of mortality and MI with the 2 approaches but a reduced risk of stroke and hospital stay with the off-pump technique.⁹⁴ Overall, there is no strong evidence favouring either approach. However, off-pump might be beneficial if in-house surgical skills allow and coronary anatomy permits reliable placement of distal anastomoses to provide complete revascularization. Therefore, whenever possible off-pump CABG might be a reasonable option in patients with CKD who require coronary revascularization.

CABG, either on- or off-pump can be performed in patients with CAD and CKD with the risk of short- and long-term adverse outcomes being associated with the degree of kidney dysfunction. This includes selected hemodialysis-dependent patients who are considered to have an acceptable perioperative risk of morbidity and mortality.

CABG vs PCI in Patients With CKD

There is a paucity of data from randomized trials on the effectiveness of revascularization with PCI compared with CABG of patients with CAD and kidney failure. An Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry report from the balloon angioplasty and bare-metal stent era that included 1412 patients with CKD, showed that among patients with CKD who were not dialysis-dependent, CABG but not PCI was associated with improved survival compared with medical therapy.¹⁷ Similarly, in a propensity-matched cohort of 1786 CKD patients with multivessel CAD in Ontario who underwent a first revascularization procedure, CABG was shown to be associated with a lower risk of events, including all-cause death out to 3 years (Fig. 5) compared with PCI.⁹⁷ Although this study was propensity score-adjusted, the presence of unmeasured confounders cannot be excluded.

In contrast, a propensity score-adjusted study of 5920 subjects with CKD and multivessel CAD who underwent either PCI with everolimus-eluting stents or CABG conducted in New York State, showed PCI to be associated with a lower short-term risk of death, stroke, and repeat revascularization, a similar long-term risk of death, an increased risk of MI (mainly in those with incomplete revascularization), a higher risk of repeat revascularization, and a lower risk of stroke compared with CABG.⁹⁸ Similar results were reported in a study of 1069 patients with CKD who underwent revascularization for multivessel CAD conducted in China, in which CABG compared with PCI with DES, was associated with a similar incidence of death, MI, or cerebrovascular events, but with a decreased risk of repeat revascularization in the 3-vessel cohort.⁹⁹

Randomized data are also lacking for revascularization in CKD patients who are hemodialysis-dependent. A large registry of 21,981 patients receiving maintenance dialysis who

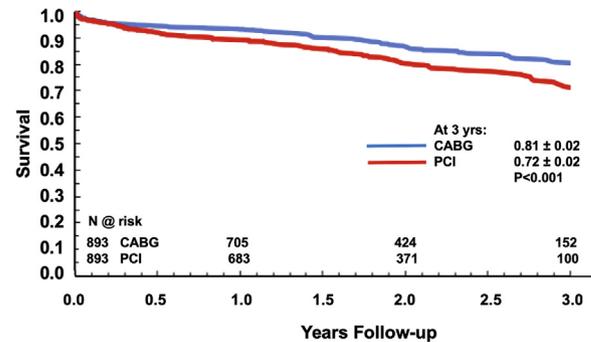


Figure 5. Kaplan–Meier survival analysis in propensity-matched patients with chronic kidney disease who underwent percutaneous coronary intervention (PCI) vs coronary artery bypass graft surgery (CABG). From Chan et al.⁹⁷ with permission from Wolters Kluwer Health, Inc.

received CABG or PCI between 1997 and 2009 in the United States Renal Data System, showed consistently poor survival, with unadjusted 5-year survival rates of 22%–25%, regardless of the revascularization strategy.¹⁰⁰ In adjusted analyses, CABG was reported to be associated with a significantly lower risk of death, as well as the composite of death or MI compared with PCI.¹⁰⁰

Subgroup analyses of patients with CKD from 2 of the main randomized trials (Evaluation of XIENCE vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization [EXCEL] and SYNTAX), which compared PCI vs CABG for left main and multivessel CAD, have recently been published.^{101,102} In the SYNTAX trial, the subgroup of patients with CKD (309 patients) who underwent PCI had an increased risk of major adverse events and repeat revascularization at 5 years. The diabetic population of this subgroup analysis had higher mortality with PCI.¹⁰¹ In the EXCEL CKD subgroup of 361 patients, acute kidney failure occurred less frequently post PCI than post CABG whereas no significant differences between PCI and CABG were observed in the rates of death, stroke, or MI at 3 years.¹⁰²

Predictive tools for identifying CKD patients who are more likely to derive benefit from one particular revascularization strategy have been proposed, but not yet systematically validated externally.¹⁰³ Thus, in the absence of randomized data, these results indicate that CABG might be more beneficial over PCI in appropriately selected patients with CKD and multivessel CAD. Whether or not this happens in the real world is unclear. The perception is that patients with multivessel CAD and severe CKD are often turned down for surgical revascularization because of a high comorbidity burden associated with CKD, and hence undergo the less invasive PCI strategy. This could have contributed to the more favourable results observed with CABG vs PCI in CKD patients, in published observational studies.

CABG is associated with higher in-hospital mortality than PCI, but better long-term cardiovascular outcomes. Nevertheless, evidence for this is derived from nonrandomized and observational studies, in which selection bias might have played a significant role. When considering a revascularization approach in CKD patients, therapeutic options must be weighed, and take into account the severity of both conditions

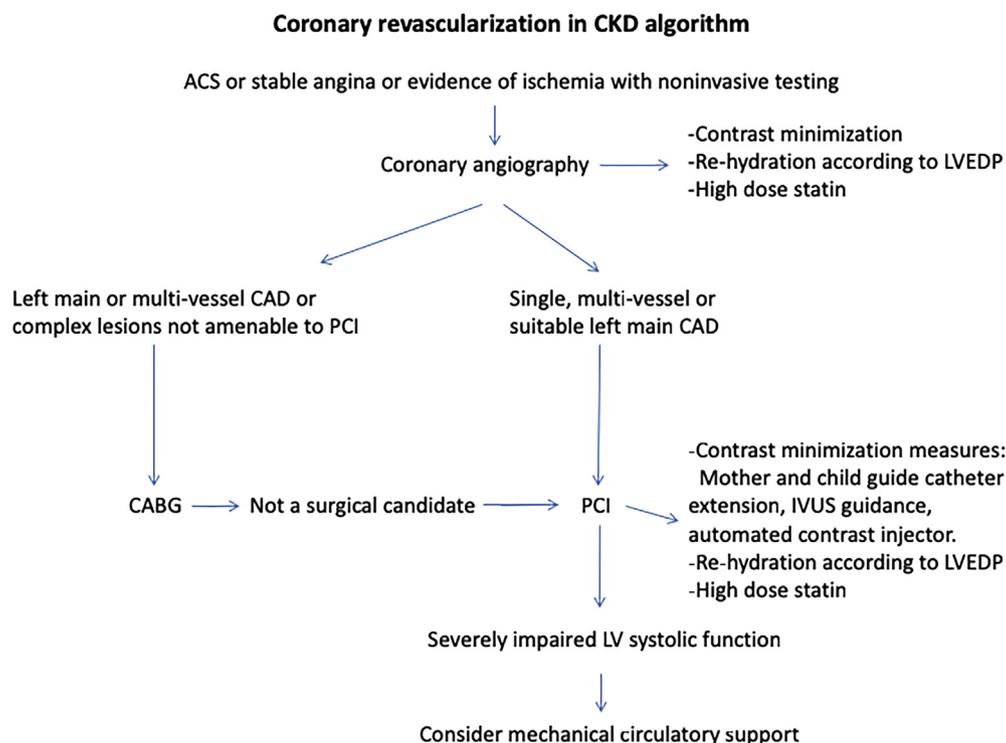


Figure 6. Algorithm for coronary revascularization in chronic kidney disease (CKD). ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; IVUS, intravascular ultrasound; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; PCI, percutaneous coronary intervention. Data from Neumann et al.⁴⁵ and Fihn et al.¹¹⁹

(CAD and CKD), and should be individualized and guided by symptoms as well as long-term prognosis.

Platelet Inhibition in CKD Patients Who Undergo PCI

In patients with CKD who undergo PCI, it is important to take into account the role of the efficacy and safety of the antiplatelet therapy that might be affected by reduced kidney clearance. As are all patients who undergo PCI, CKD patients are treated with peri- and postprocedural dual antiplatelet therapy. Aspirin is used universally, along with 1 of 3 currently available P2Y12 inhibitors, the choice of which might be affected by kidney function.

Clopidogrel, the most commonly utilized P2Y12 inhibitor, is a second-generation thienopyridine that inhibits adenosine diphosphate-related platelet activation. No dose adjustment is required in CKD patients who receive it.¹⁰⁴ Prasugrel is a third-generation oral thienopyridine P2Y12 receptor antagonist that reaches peak effect more rapidly than clopidogrel.¹⁰⁵ Although in ESRD its active metabolite levels are reduced by 40%, the degree of platelet inhibition is similar to that in patients with normal kidney function, therefore no dose adjustment is required.¹⁰⁵ Like prasugrel, ticagrelor, a reversible P2Y12 receptor antagonist, produces a greater antiplatelet effect than clopidogrel.¹⁰⁶ In the CKD subgroup analysis of the **Platelet Inhibition and Patient Outcomes (PLATO)** trial, in which ticagrelor was compared with clopidogrel in patients who presented with ACS, in those with an eGFR < 60 mL/min, the primary cardiovascular end point

was significantly reduced by ticagrelor compared with clopidogrel (17.3% vs 22.0%; hazard ratio, 0.77; 95% confidence interval, 0.65-0.90).¹⁰⁷ Because this finding was from a subgroup analysis and therefore underpowered, adequately powered randomized studies are needed. In the setting of hemodialysis, in addition to aspirin, clopidogrel is currently the most widely used antiplatelet agent although no information derived from clinical trials are available for this patient group for any of the P2Y12 inhibitors. In routine clinical practice, because of the large experience acquired, the awareness of safety is higher for clopidogrel than for the newer antiplatelet agents.¹⁰⁸

Peri- and postprocedural dual antiplatelet therapy is the mainstay of PCI. Along with the universal use of aspirin, 3 different P2Y12 inhibitors are used (clopidogrel, prasugrel, and ticagrelor). No adequately powered randomized data in the CKD population are available to recommend one over the other. Awareness of safety is higher with clopidogrel because of its longer use, although subgroup analyses suggest that ticagrelor might be more efficacious and provide similar safety.

Revascularization in Kidney Transplantation Candidates and Transplant Recipients

Cardiac disease is the leading cause of death after kidney transplantation, with cardiovascular events ranging from 35% to 50% of all deaths after transplantation. Ischemic heart disease is responsible for approximately 50% of kidney transplantation perioperative deaths.¹⁰⁹

All CKD patients are at increased risk for cardiac disease because of their exposure to numerous risk factors including uremia itself.¹¹⁰ Thus, all patients being considered for transplantation should be screened for the presence of CAD and cardiac dysfunction.¹¹¹ Asymptomatic patients with diabetes or multiple CAD risk factors should undergo noninvasive testing. Coronary angiography is recommended, if the stress test is abnormal. Transplantation candidates with angina, or those with diabetes with noninvasive evidence of ischemia, should undergo coronary angiography directly.¹¹² There is no consensus regarding the optimal noninvasive test modality. This should be determined according to the expertise at the individual centre. In kidney transplantation candidates with an initial normal stress echocardiogram, the cardiac event rate doubles within 2 years while on the transplant waiting list.¹¹² Therefore, as waiting times remain prolonged, it is recommended that noninvasive testing be repeated every year.¹¹¹

Little evidence is available regarding the benefits of revascularization of significant CAD in kidney transplant candidates. In a small, randomized controlled trial of 26 diabetic candidates for kidney transplantation with asymptomatic CAD, the outcome for those who were revascularized was superior to that of patients managed medically, with only 2 of 13 randomized to revascularization, reaching a cardiovascular end point (ACS and cardiac death) in 8.4 months of follow-up compared with 10 of 13 of the patients randomized to medical management.¹¹³ However, this study was obviously limited by the small sample size. The American Society of Transplantation guidelines recommend revascularization before kidney transplantation in asymptomatic ESRD patients with critical lesions only.¹⁰⁹ Guidelines do not specify the amount of ischemic myocardium that would be appropriate to revascularize in this setting. Common practice is to revascularize major vessels as well as side branches large enough to accommodate the minimum stent size available (≥ 2.0 mm in diameter).¹¹⁴

In patients who have already received a kidney transplant, cardiovascular disease remains a leading cause of death, almost equaling deaths resulting from malignancies and infections combined.¹¹⁵ This is attributed not only to traditional risk factors, but also to nontraditional risk factors such as adverse effects of immunosuppression therapy, allograft dysfunction, and systemic inflammation.¹¹⁶

Scant data are available regarding the preferred modality of coronary revascularization in kidney transplantation patients. In a 2013 United States Renal Data System (USRDS) study that evaluated 2272 kidney transplant recipients who received either PCI or CABG during the years 1997-2009 for multivessel CAD, no significant differences in death, or the composite of death or MI were observed between the 2 revascularization modalities with 5-year survival of 55% in both groups,¹¹⁵ a rate that remains low compared with a 90% 5-year survival in patients with normal kidney function post multivessel revascularization.¹¹⁷ However, this compares favourably with the 22%-25% survival rates at 5 years reported in dialysis-dependent patients with ESRD who received multivessel revascularization.¹⁰⁰

The Canadian Australasian Randomized Trial of Screening Kidney Transplant Recipients (CARSK) is an ongoing trial that is investigating selective vs routine screening for CAD.¹¹⁸

Results of CARSK will provide insight into the risk-benefit balance of routine CAD screening in asymptomatic patients awaiting kidney transplantation.¹¹⁸

In patients awaiting kidney transplantation, a noninvasive or invasive screening for coronary atherosclerosis, an approach depending on the overall CAD risk profile, should be used. Revascularization is considered a reasonable option in case of critical disease.

Conclusions

Morbidity from CAD is highly prevalent among patients with CKD, particularly those who are hemodialysis-dependent. Therapeutic options that are effective in the general population are often less so in patients with advanced CKD. The benefit of revascularization in patients with advanced kidney failure and CAD is unknown. Observational studies suggest that revascularization might confer a survival benefit compared with medical therapy alone. The ongoing randomized ISCHEMIA-CKD study will further clarify this issue.²⁶ In terms of the revascularization approach, CABG is associated with higher in-hospital mortality than PCI, but better long-term cardiovascular outcomes. However, this evidence is mainly derived from observational studies in which selection bias might have played a significant role. The decision regarding therapeutic options in CKD patients must be weighed considering the severity of both conditions, and should be individualized and guided by symptoms as well as long-term prognosis (Fig. 6). In CKD patients awaiting kidney transplantation, depending on the overall CAD risk profile, a noninvasive or invasive CAD screening approach should be used and revascularization should be performed in case of critical disease. Adequately powered randomized trials are needed to determine optimal revascularization strategies in these high-risk populations.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Chonchol M, Whittle J, Desbien A, et al. Chronic kidney disease is associated with angiographic coronary artery disease. *Am J Nephrol* 2008;28:354-60.
2. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl* (2011) 2013;3:19-62.
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
4. Thompson S, James M, Wiebe N, et al. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol* 2015;26:2504-11.
5. Pun PH, Smarz TR, Honeycutt EF, et al. Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney Int* 2009;76:652-8.
6. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2015;3:514-25.

7. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;3:1.
8. Collins AJ, Foley RN, Chavers B, et al. US renal data system 2013 annual data report: preface. *Am J Kidney Dis* 2014;63:A7.
9. Shroff GR, Li S, Herzog CA. Trends in mortality following acute myocardial infarction among dialysis patients in the United States over 15 years. *J Am Heart Assoc* 2015;4:e002460.
10. 30-Day Acute Myocardial Infarction in-Hospital Mortality. The Risk-Adjusted Rate of All-Cause in-Hospital Death Occurring Within 30 Days of First Discharge From an Acute Care Hospital With a Diagnosis of Acute Myocardial Infarction (AMI). Canadian Institute for Health Information, 2015. Available at: <https://www.cihi.ca>. Accessed July 13, 2019.
11. Schwarz U, Buzello M, Ritz E, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant* 2000;15:218-23.
12. Coskun U, Orta Kilickesmez K, Abaci O, et al. The relationship between chronic kidney disease and SYNTAX score. *Angiology* 2011;62:504-8.
13. Osten MD, Ivanov J, Eichhofer J, et al. Impact of renal insufficiency on angiographic, procedural, and in-hospital outcomes following percutaneous coronary intervention. *Am J Cardiol* 2008;101:780-5.
14. Attallah N, Yassine L, Fisher K, Yee J. Risk of bleeding and restenosis among chronic kidney disease patients undergoing percutaneous coronary intervention. *Clin Nephrol* 2005;64:412-8.
15. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. *Semin Thromb Hemost* 2010;36:34-40.
16. Sedlis SP, Jurkowitz CT, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention for patients with stable coronary artery disease and chronic kidney disease. *Am J Cardiol* 2009;104:1647-53.
17. Hemmelgarn BR, Southern D, Culleton BF, et al. Survival after coronary revascularization among patients with kidney disease. *Circulation* 2004;110:1890-5.
18. Chan MY, Becker RC, Sim LL, et al. Reperfusion strategy and mortality in ST-elevation myocardial infarction among patients with and without impaired renal function. *Ann Acad Med Singapore* 2010;39:179-84.
19. Charytan DM, Wallentin L, Lagerqvist B, et al. Early angiography in patients with chronic kidney disease: a collaborative systematic review. *Clin J Am Soc Nephrol* 2009;4:1032-43.
20. Chertow GM, Normand SL, Silva LR, McNeil BJ. Survival after acute myocardial infarction in patients with end-stage renal disease: results from the cooperative cardiovascular project. *Am J Kidney Dis* 2000;35:1044-51.
21. Dragu R, Behar S, Sandach A, et al. Should primary percutaneous coronary intervention be the preferred method of reperfusion therapy for patients with renal failure and ST-elevation acute myocardial infarction? *Am J Cardiol* 2006;97:1142-5.
22. Eisenstein EL, Sun JL, Anstrom KJ, et al. Assessing the economic attractiveness of coronary artery revascularization in chronic kidney disease patients. *J Med Syst* 2009;33:287-97.
23. Keeley EC, Kadakia R, Soman S, Borzak S, McCullough PA. Analysis of long-term survival after revascularization in patients with chronic kidney disease presenting with acute coronary syndromes. *Am J Cardiol* 2003;92:509-14.
24. Yasuda K. Comparison of percutaneous coronary intervention with medication in the treatment of coronary artery disease in hemodialysis patients. *J Am Soc Nephrol* 2006;17:2322-32.
25. Volodarskiy A, Kumar S, Amin S, Bangalore S. Optimal treatment strategies in patients with chronic kidney disease and coronary artery disease. *Am J Med* 2016;129:1288-98.
26. Bangalore S, Maron DJ, Fleg JL, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches—Chronic Kidney Disease (ISCHEMIA-CKD): rationale and design. *Am Heart J* 2018;205:42-52.
27. Best PJM, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 2002;39:1113-9.
28. Appleby CE, Ivanov J, Lavi S, et al. The adverse long-term impact of renal impairment in patients undergoing percutaneous coronary intervention in the drug-eluting stent era. *Circ Cardiovasc Interv* 2009;2:309-16.
29. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* 2002;137:563.
30. Charytan D, Mauri L, Agarwal A, et al. The use of invasive cardiac procedures after acute myocardial infarction in long-term dialysis patients. *Am Heart J* 2006;152:558-64.
31. Szummer K, Lundman P, Jacobson SH, et al. Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Circulation* 2009;120:851-8.
32. James MT, Tonelli M, Ghali WA, et al. Renal outcomes associated with invasive vs conservative management of acute coronary syndrome: propensity matched cohort study. *BMJ* 2013;347:f4151.
33. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:e139-228.
34. Colleran R, Kastrati A. Percutaneous coronary intervention: balloons, stents and scaffolds. *Clin Res Cardiol* 2018;107:55-63.
35. Bae EH, Lim SY, Choi YH, et al. Drug-eluting vs. bare-metal stents for treatment of acute myocardial infarction with renal insufficiency. Results from Korea Acute Myocardial Infarction Registry. *Circ J* 2011;75:2798-804.
36. Tsai TT, Messenger JC, Brennan JM, et al. Safety and efficacy of drug-eluting stents in older patients with chronic kidney disease: a report from the linked CathPCI Registry/CMS claims database. *J Am Coll Cardiol* 2011;58:1859-69.
37. Green SM, Selzer F, Mulukutla SR, et al. Comparison of bare-metal and drug-eluting stents in patients with chronic kidney disease (from the NHLBI Dynamic Registry). *Am J Cardiol* 2011;108:1658-64.
38. Saltzman AJ, Stone GW, Claessen BE, et al. Long-term impact of chronic kidney disease in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv* 2011;4:1011-9.
39. Volodarskiy A, Kumar S, Pracon R, et al. Drug-eluting vs bare-metal stents in patients with chronic kidney disease and coronary artery

- disease: insights from a systematic review and meta-analysis. *J Inv Cardiol* 2018;30:10-7.
40. Azzalini L, Ojeda S, Demir OM, et al. Recanalization of chronic total occlusions in patients with vs. without chronic kidney disease: the impact of contrast-induced acute kidney injury. *Can J Cardiol* 2018;34:1275-82.
 41. Har BJ, James MT. Assessing benefit vs risk of complex percutaneous coronary intervention in people with chronic kidney disease. *Can J Cardiol* 2018;34:1244-6.
 42. Medi C, Montalescot G, Budaj A, et al. Reperfusion in patients with renal dysfunction after presentation with ST-segment elevation or left bundle branch block. GRACE (Global Registry of Acute Coronary Events). *JACC Cardiovasc Interv* 2009;2:26-33.
 43. Medi C, Chew DPB, Amerena J, et al. An invasive management strategy is associated with improved outcomes in high-risk acute coronary syndromes in patients with chronic kidney disease. *Intern Med J* 2011;41:743-50.
 44. Lau JK, Anastasius MO, Hyun KK, et al. Evidence-based care in a population with chronic kidney disease and acute coronary syndrome. Findings from the Australian Cooperative National Registry of Acute Coronary Care, Guideline Adherence and Clinical Events (CONCORDANCE). *Am Heart J* 2015;170:566-72.e561.
 45. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87-165.
 46. Fitchett DH, Theroux P, Brophy JM, et al. Assessment and management of acute coronary syndromes (ACS): a Canadian perspective on current guideline-recommended treatment - part 1: non-ST-segment elevation. *ACS. Can J Cardiol* 2011;27:S387-401.
 47. Pasceri V, Patti G, Pelliccia F, et al. Complete revascularization during primary percutaneous coronary intervention reduces death and myocardial infarction in patients with multivessel disease: meta-analysis and meta-regression of randomized trials. *JACC Cardiovasc Interv* 2018;11:833-43.
 48. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017;377:2419-32.
 49. Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. *J Am Soc Nephrol* 2000;11:177-82.
 50. Kellum JA, Lameire N, Aspelin P, et al. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* (2011) 2012;2:1-138.
 51. Azzalini L, Spagnoli V, Ly HQ. Contrast-induced nephropathy: from pathophysiology to preventive strategies. *Can J Cardiol* 2016;32:247-55.
 52. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl* 2006:S11-5.
 53. Amin AP, Salisburry AC, McCullough PA, et al. Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. *Arch Intern Med* 2012;172:246-53.
 54. Brown JR, Malenka DJ, DeVries JT, et al. Transient and persistent renal dysfunction are predictors of survival after percutaneous coronary intervention: insights from the Dartmouth Dynamic Registry. *Catheter Cardiovasc Interv* 2008;72:347-54.
 55. Abe M, Morimoto T, Nakagawa Y, et al. Impact of transient or persistent contrast-induced nephropathy on long-term mortality after elective percutaneous coronary intervention. *Am J Cardiol* 2017;120:2146-53.
 56. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;44:1393-9.
 57. Ohno Y, Maekawa Y, Miyata H, et al. Impact of periprocedural bleeding on incidence of contrast-induced acute kidney injury in patients treated with percutaneous coronary intervention. *J Am Coll Cardiol* 2013;62:1260-6.
 58. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003;348:491-9.
 59. Solomon RJ, Natarajan MK, Doucet S, et al. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation* 2007;115:3189-96.
 60. Jo SH, Youn TJ, Koo BK, et al. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. *J Am Coll Cardiol* 2006;48:924-30.
 61. Marenzi G, Assanelli E, Campodonico J, et al. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med* 2009;150:170-7.
 62. Azzalini L, Candilio L, McCullough PA, Colombo A. Current risk of contrast-induced acute kidney injury after coronary angiography and intervention: a reappraisal of the literature. *Can J Cardiol* 2017;33:1225-8.
 63. Brown JR, MacKenzie TA, Maddox TM, et al. Acute kidney injury risk prediction in patients undergoing coronary angiography in a national Veterans Health Administration cohort with external validation. *J Am Heart Assoc* 2015;4:e002136.
 64. Tsai TT, Patel UD, Chang TI, et al. Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *J Am Heart Assoc* 2014;3:e001380.
 65. Allen DW, Ma B, Leung KC, et al. Risk prediction models for contrast-induced acute kidney injury accompanying cardiac catheterization: systematic review and meta-analysis. *Can J Cardiol* 2017;33:724-36.
 66. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002;162:329-36.
 67. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004;291:2328-34.
 68. Brar SS, Shen AYJ, Jorgensen MB, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA* 2008;300:1038-46.
 69. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet* 2017;389:1312-22.
 70. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med* 2018;378:603-14.

71. Brar SS, Aharonian V, Mansukhani P, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet* 2014;383:1814-23.
72. Giacoppo D, Gargiulo G, Buccheri S, et al. Preventive strategies for contrast-induced acute kidney injury in patients undergoing percutaneous coronary procedures: evidence from a hierarchical bayesian network meta-analysis of 124 trials and 28 240 patients. *Circ Cardiovasc Interv* 2017;10:e004383.
73. Verhulst A, D'Haese PC, De Broe ME. Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in human kidney proximal tubular cells. *J Am Soc Nephrol* 2004;15:2249-57.
74. Singh N, Lee JZ, Huang JJ, et al. Benefit of statin pretreatment in prevention of contrast-induced nephropathy in different adult patient population: systematic review and meta-analysis. *Open Heart* 2014;1:e000127.
75. Karimi Galoughi K, Mintz GS, Karpaliotis D, Ali ZA. Zero-contrast percutaneous coronary intervention on calcified lesions facilitated by rotational atherectomy. *Catheter Cardiovasc Interv* 2017;90:E85-9.
76. Ali ZA, Karimi Galoughi K, Nazif T, et al. Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study. *Eur Heart J* 2016;37:3090-5.
77. Mariani J, Guedes C, Soares P, et al. Intravascular ultrasound guidance to minimize the use of iodine contrast in percutaneous coronary intervention: the MOZART (Minimizing cOntrast utiliZation With IVUS Guidance in coRonary angioplasTy) randomized controlled trial. *JACC Cardiovasc Interv* 2014;7:1287-93.
78. Tunuguntla A, Daneault B, Kirtane AJ. Novel use of the GuideLiner catheter to minimize contrast use during PCI in a patient with chronic kidney disease. *Catheter Cardiovasc Interv* 2012;80:453-5.
79. Mamas MA, Fath-Ordoubadi F, Fraser DG. Telescoping catheter technique: looking towards the kidneys. *Cardiovasc Revasc Med* 2011;12:123-8.
80. Call J, Sacrinty M, Applegate R, et al. Automated contrast injection in contemporary practice during cardiac catheterization and PCI: effects on contrast-induced nephropathy. *J Invasive Cardiol* 2006;18:469-74.
81. Azzalini L, Mitomo S, Hachinohe D, Regazzoli D, Colombo A. Zero-contrast percutaneous coronary intervention guided by dextran-based optical coherence tomography. *Can J Cardiol* 2018;34. 342.e341-3.
82. Mailloux L, Swartz CD, Capizzi R, et al. Acute renal failure after administration of low-molecular weight dextran. *N Engl J Med* 1967;277:1113-8.
83. Ferraboli R, Malheiro PS, Abdulkader RC, et al. Anuric acute renal failure caused by dextran 40 administration. *Ren Fail* 1997;19:303-6.
84. Flaherty MP, Pant S, Patel SV, et al. Hemodynamic support with a microaxial percutaneous left ventricular assist device (Impella) protects against acute kidney injury in patients undergoing high-risk percutaneous coronary intervention. *Circ Res* 2017;120:692-700.
85. Holzmann MJ, Hammar N, Ahnve S, et al. Renal insufficiency and long-term mortality and incidence of myocardial infarction in patients undergoing coronary artery bypass grafting. *Eur Heart J* 2007;28:865-71.
86. Noyez L, Plesiewicz I, Verheugt FWA. Estimated creatinine clearance instead of plasma creatinine level as prognostic test for postoperative renal function in patients undergoing coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2006;29:461-5.
87. Cooper WA, O'Brien SM, Thourani VH, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation* 2006;113:1063-70.
88. Lok CE, Austin PC, Wang H, Tu JV. Impact of renal insufficiency on short- and long-term outcomes after cardiac surgery. *Am Heart J* 2004;148:430-8.
89. United States Renal Data System (USR) group. Cardiovascular special studies. *Am J Kidney Dis* 2003;41:S165-76.
90. Patel MR, Calhoun JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease. *J Am Coll Cardiol* 2017;69:2212-41.
91. Gaudino M, Serricchio M, Luciani N, et al. Risks of using internal thoracic artery grafts in patients in chronic hemodialysis via upper extremity arteriovenous fistula. *Circulation* 2003;107:2653-5.
92. Hu J, Chen R, Liu S, et al. Global incidence and outcomes of adult patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth* 2016;30:82-9.
93. Sellke FW, DiMaio JM, Caplan LR, et al. Comparing on-pump and off-pump coronary artery bypass grafting: numerous studies but few conclusions: a scientific statement from the American Heart Association council on cardiovascular surgery and anesthesia in collaboration with the interdisciplinary working group on quality of care and outcomes research. *Circulation* 2005;111:2858-64.
94. Wang Y, Zhu S, Gao P, Zhou J, Zhang Q. Off-pump vs on-pump coronary surgery in patients with chronic kidney disease: a meta-analysis. *Clin Exp Nephrol* 2018;22:99-109.
95. Chukwuemeka A, Weisel A, Maganti M, et al. Renal dysfunction in high-risk patients after on-pump and off-pump coronary artery bypass surgery: a propensity score analysis. *Ann Thorac Surg* 2005;80:2148-53.
96. Sajja LR, Mannam G, Chakravarthi RM, et al. Coronary artery bypass grafting with or without cardiopulmonary bypass in patients with preoperative non-dialysis dependent renal insufficiency: a randomized study. *J Thorac Cardiovasc Surg* 2007;133:378-88.
97. Chan W, Ivanov J, Ko D, et al. Clinical outcomes of treatment by percutaneous coronary intervention vs coronary artery bypass graft surgery in patients with chronic kidney disease undergoing index revascularization in Ontario. *Circ Cardiovasc Interv* 2015;8:1-10.
98. Bangalore S, Guo Y, Samadashvili Z, et al. Revascularization in patients with multivessel coronary artery disease and chronic kidney disease everolimus-eluting stents vs coronary artery bypass graft surgery. *J Am Coll Cardiol* 2015;66:1209-20.
99. Wang ZJ, Zhou YJ, Liu YY, et al. Comparison of drug-eluting stents and coronary artery bypass grafting for the treatment of multivessel coronary artery disease in patients with chronic kidney disease. *Circ J* 2009;73:1228-34.
100. Chang TI, Shilane D, Kazi DS, et al. Multivessel coronary artery bypass grafting vs percutaneous coronary intervention in ESRD. *J Am Soc Nephrol* 2012;23:2042-9.
101. Milojevic M, Head SJ, Mack MJ, et al. The impact of chronic kidney disease on outcomes following percutaneous coronary intervention vs coronary artery bypass grafting in patients with complex coronary artery disease: five-year follow-up of the SYNTAX trial. *EuroIntervention* 2018;14:102-11.
102. Giustino G, Mehran R, Serruys PW, et al. Left main revascularization with PCI or CABG in patients with chronic kidney disease: EXCEL trial. *J Am Coll Cardiol* 2018;72:754-65.

103. Charytan DM, Yang SS, McGurk S, Rawn J. Long- and short-term outcomes following coronary artery bypass grafting in patients with and without chronic kidney disease. *Nephrol Dial Transplant* 2010;25:3654-63.
104. Savi P, Pereillo JM, Uzabiaga MF, et al. Identification and biological activity of the active metabolite of clopidogrel. *Thromb Haemost* 2000;84:891-6.
105. Small DS, Wrishko RE, Ernest CS, et al. Prasugrel pharmacokinetics and pharmacodynamics in subjects with moderate renal impairment and end-stage renal disease. *J Clin Pharm Ther* 2009;34:585-94.
106. Anderson SD, Shah NK, Yim J, Epstein BJ. Efficacy and safety of ticagrelor: a reversible P2Y12 receptor antagonist. *Ann Pharmacother* 2010;44:524-37.
107. James S, Budaj A, Aylward P, et al. Ticagrelor vs clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2010;122:1056-67.
108. Summaria F, Giannico MB, Talarico GP, Patrizi R. Antiplatelet therapy in hemodialysis patients undergoing percutaneous coronary interventions. *Nephrourol Mon* 2015;7:e28099.
109. Kasiske BL, Cangro CB, Hariharan S, et al. The evaluation of renal transplant candidates: clinical practice guidelines. *Am J Transplant* 2001;2:5-95.
110. Tonelli M, Karumanchi SA, Thadhani R. Epidemiology and mechanisms of uremia-related cardiovascular disease. *Circulation* 2016;133:518-36.
111. Knoll G, Cockfield S, Blydt-Hansen T, et al. Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation. *CMAJ* 2005;173:S1-25.
112. Gill JS, Ma I, Landsberg D, Johnson N, Levin A. Cardiovascular events and investigation in patients who are awaiting cadaveric kidney transplantation. *J Am Soc Nephrol* 2005;16:808-16.
113. Manske CL, Wang Y, Rector T, Wilson RF, White CW. Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. *Lancet* 1992;340:998-1002.
114. Rathore S. Small coronary vessel angioplasty: outcomes and technical considerations. *Vasc Health Risk Manag* 2010;6:915-22.
115. Lenihan CR, Montez-Rath ME, Winkelmayer WC, Chang TI. Multivessel coronary revascularization and outcomes in kidney transplant recipients. *Transplant Int* 2013;26:1080-7.
116. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. *Transplantation* 2006;82:603-11.
117. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009;373:1190-7.
118. Ramsdale DR, Bellamy CM. Management of atrial exit block during physiological pacing for cardiogenic shock post myocardial infarction. *Pacing Clin Electrophysiol* 1990;13:821-2.
119. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2014;130:1749-67.