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Coronary Angiography Before and After Renal Transplantation

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1. Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality in both dialysis dependent patients and those either waiting for or following up after renal transplantation. Concerns about the risk of contrast-induced acute kidney injury (CI-AKI) associated with coronary angiography in patients with stage 4 or 5 chronic kidney disease (CKD) have sometimes resulted in coronary angiography being delayed until after transplantation. Pretransplant cardiovascular disease is a well established risk factor for post transplant cardiovascular disease and cardiovascular mortality. In addition, post transplant dyslipidemia,¹⁻³ hypertension,⁴⁻⁷ allograft dysfunction, delayed or slow graft function⁸ and post transplant erythrocytosis^{9, 10} are some of the more specific factors that increase cardiovascular risk in renal transplant recipients as compared to the general population. Prompt diagnosis and treatment of cardiovascular disease in CKD and end stage renal disease population prior to transplant is aimed to reduce cardiovascular morbidity and mortality in the perioperative period and beyond. Several studies have demonstrated that left ventricular function and hypertrophy improve after renal transplantation. Ferreira et al prospectively studied 24 patients with end stage renal disease and demonstrated a significant decrease in hypertension, reduction in left ventricular hypertrophy and dilation, and improvement in systolic function after successful renal transplantation.¹¹ Wali et al followed up 103 renal patients with left ventricular ejection fraction less than 40% with radionuclide ventriculography and renal transplantation and found the mean left ventricular ejection fraction increased from 31.6% to 52.2% at 12 months after transplantation. A longer pre-transplantation interval decreased the likelihood of normalization of ejection fraction. New York Heart Association functional status improved significantly concordant with an improvement of ejection fraction. These studies indicate that renal transplantation should not be withheld for patients with severe cardiac dysfunction as both left ventricular function and survival are expected to improve with renal transplantation.¹²

This chapter will describe the approach to patients with CKD who are being considered for renal transplantation. Careful consideration to the background history, risk of cardiovascular disease, and risk of atherosclerotic events with the transplant operation will be discussed. The risks and benefits of coronary revascularization will be outlined in the

context of a patient with very little renal function remaining at the time of evaluation. Finally, we will summarize the major caveats for coronary angiography in patients who have received a kidney transplant and are being evaluated for new symptoms.

2. Preoperative cardiovascular evaluation prior to renal transplantation

Cardiovascular screening is recommended in certain groups of high risk CKD patients prior to transplantation.¹³ These include persons with diabetes, men over age 45 years, women over 55 years, previous history of ischemic heart disease, an abnormal electrocardiogram, left ventricular dysfunction, smoking history and duration of dialysis more than 2 years.¹⁴ Controversies exist regarding the ideal screening test for coronary artery disease among exercise stress test, dobutamine stress echocardiogram, and myocardial perfusion studies. Lentine et al in 2008 analyzed the United States Renal Data System on 27,786 eligible patients for renal transplantation and concluded that 46.3% of patients underwent cardiac evaluation prior to transplantation, of whom 9.5% required coronary revascularization. Among patients transplanted without cardiovascular evaluation, the three-year incidence of post transplant acute myocardial infarction was 3% in lower risk group and 10% in higher risk group.¹⁵

All patients should be assessed for ischemic heart disease before renal transplantation. The minimum workup required includes a history, physical examination, electrocardiogram, and a chest radiograph.¹³ Assessment of functional status is critical. In general, if a patient can sustain a moderate or high work rate (> 5 metabolic equivalents of work) without symptoms, then there is a low risk of perioperative myocardial infarction or cardiovascular death. The pretest probability of coronary artery disease plays a major role in determination of cardiac testing. The Canadian society of transplantation recommends noninvasive testing for symptomatic patients or patients with prior history of coronary artery disease, as well as asymptomatic patients with diabetes mellitus or multiple risk factors for coronary artery disease.¹⁷ The choice of noninvasive testing has been a matter of debate with nuclear scintigraphy showing a high negative predictive value and performing well in diabetic patients.¹⁸⁻²¹ Marwick et al has shown that the sensitivity of dipyridamole thallium scintigraphy in patients with CKD is lower than that of controls.²² The speculated reasons for this observation are reduced coronary flow reserve, left ventricular hypertrophy and interstitial cardiac fibrosis. Results with stress echocardiography have been found to be comparable to nuclear imaging,^{23, 24} and the expertise of technical and physician personnel often plays the major role in determining which test will be done at each institution. The Society further recommends coronary angiography be performed in patients with a positive noninvasive test or in very high risk patients irrespective of a noninvasive test. De Lima and colleagues have shown that coronary angiography is the best predictor of cardiac events in renal transplant candidates when compared to clinical risk stratification and non invasive testing.¹⁶ Some centers advocate angiography in most transplant candidates with diabetes, while others pursue cardiac catheterization only in candidates with positive screening examination.²⁵ Low risk patients, asymptomatic patients with a negative noninvasive test result or noncritical disease on angiography on appropriate medical therapy, or who have undergone successful intervention can be considered eligible for transplantation without any further evaluation. Coronary angiography remains the gold standard for evaluation of coronary arteries among patients with positive screening tests or high risk of cardiovascular events. It is complicated by its invasive nature and the risk of contrast nephropathy and

cholesterol embolism which will be discussed below.¹⁴ The yield of coronary angiography in this population is high. De Lima et al in 2003 found that about 42% of patients in this group had significant coronary artery stenosis (more than 70% by visual estimation). Significant coronary artery stenosis was also the most significant predictor of cardiac events at 48 months.¹⁶ A suggested approach to preoperative cardiovascular assessment and non invasive stress testing in CKD patients prior to renal transplantation is proposed by Karthikeyan et al in Figure 1.³⁹ Abnormal results on non invasive stress tests such as coronary CT angiography and myocardial perfusion imaging often need invasive coronary angiography for diagnosis and possible intervention. This will lead to unnecessary delay, contrast and radiation exposure. So initial invasive coronary angiography is preferable in patients with multiple co-morbidities and risk factors and those with intermediate to high pre-test probability for non-invasive stress testing.

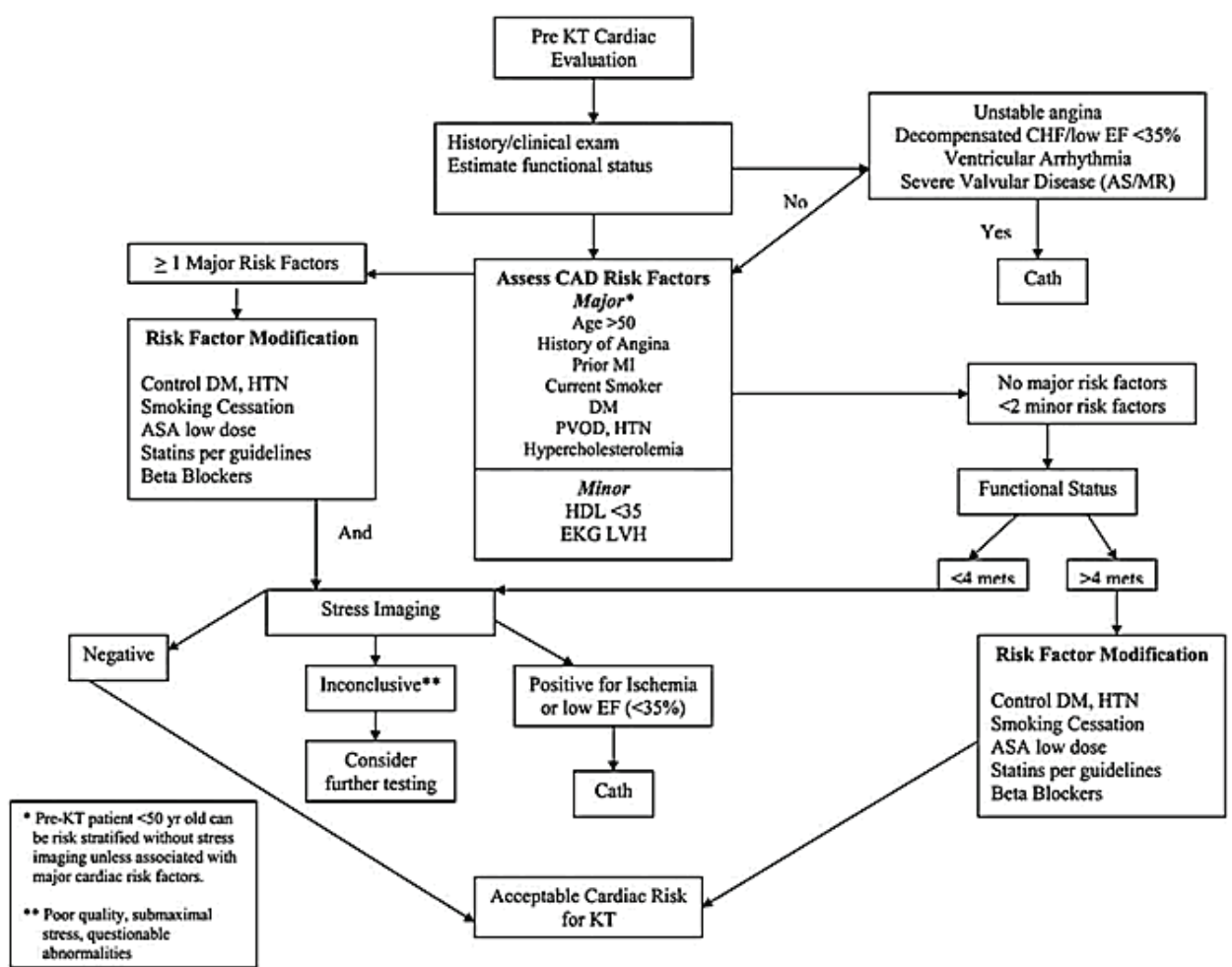


Fig. 1.
Adapted from Cardiology Review (2009); 5: page 183

3. Risk and benefits of coronary angiography in transplant recipients

The major risks of coronary angiography in renal transplant candidates are CI-AKI and cholesterol embolism which may hasten the progression to dialysis. In the general population, the risk of CI-AKI is 3.3 – 14.5%.²⁶ Risk factors include reduced renal filtration

function, older age, diabetes, congestive heart failure and preprocedure myocardial infarction.²⁷ Acute kidney injury requiring dialysis is rare but may occur in 0.44 to 0.77% of patients. This development is associated with a significant in hospital mortality rate of 35.7 to 39%. The risk of CI-AKI is higher among pretransplant candidates because of their underlying advanced chronic kidney disease and is estimated to be 4-50% with 8-26% eventually requiring dialysis at some point prior to transplantation.²⁸ Gruberg et al reported that 4.9% of patients with baseline creatinine more than 1.8mg/dl required temporary dialysis after coronary angiography.²⁹ Cholesterol embolism occurs from disruption of vascular endothelial plaques resulting in release of cholesterol crystals into the blood stream. In severe forms, it may lead to localized inflammation and fibrosis most commonly seen in the skin, digits, kidney and eye. The reported incidence after coronary angiography is as high as 2% and manifests as persistent elevation of creatinine up to 3 weeks after the procedure.³⁰ The relative contribution of subtle degrees of cholesterol embolism without peripheral signs to AKI is unknown. Further studies are warranted to assess the exact impact of this entity on pretransplant candidates undergoing coronary angiography and evaluate potential measures to reduce their incidence.

4. Safety of coronary angiography in pretransplant candidates

Contrast-induced AKI remains an important and potentially avoidable complication after coronary angiography and coronary and vascular interventions.⁴⁰ A direct inverse relationship exists between a patient's estimated glomerular filtration rate (eGFR) and their risk of contrast-induced AKI.⁴¹ In the setting of severely reduced renal filtration, the risk of sustained intrarenal vasoconstriction, tubular and peritubular stasis of contrast agents, cellular toxicity and permanent loss of functioning nephrons are greatly increased.⁴² Because coronary events are a major cause of perioperative risk and postoperative morbidity in patients considered for renal transplantation, coronary angiography is frequently performed prior to transplantation, particularly in patients with a history of angina or provokable myocardial ischemia on stress testing.⁴³ If coronary disease becomes a concern after renal transplantation, the intravascular administration of a contrast agent is associated with a high risk (>15%) of contrast-induced AKI in the transplanted kidney.⁴⁴ Thus it is reasonable to consider upfront contrast-induced AKI in the native kidneys before transplantation. Kumar and co-workers reported on the intermediate-term outcomes of 76 predialysis patients with CKD undergoing coronary angiography prior to renal transplantation.⁴⁵ The mean eGFR before contrast exposure was 12.5 ± 3.4 ml/min/1.73 m² and the mean iodinated contrast load administered was 55.7 ± 50.2 ml. In total, 25 of the 76 patients (32.9%) who had coronary angiography subsequently underwent transplantation; 22 of the patients who underwent transplantation had not received any form of dialysis beforehand. Exposure to contrast media did not seem to hasten progression to end-stage renal disease. The cumulative dialysis-free survival among all 76 patients who had coronary angiography was 89.1% at 6 months post coronary angiography. A number of factors probably worked together to produce these excellent results and a 'safe landing' after coronary angiography. Patients were stable and relatively young (mean age 56.3 years). Other factors that contributed to favorable outcome include discontinuation of all potentially nephrotoxic drugs 24 hours before the angiogram, use of statins, generous hydration prior to procedure, use of N-acetylcysteine and iso-osmolar contrast and the use of biplane angiography.

Statins have pleiotropic effects and their anti-oxidant properties may play a role against the oxidative stress involved in the pathogenesis of contrast induced AKI.^{46,47} Hydration prior to administration of contrast may have multiple theoretical benefits for the kidney which include decreased activity of renin angiotensin system, downregulation of tubuloglomerular feedback, augmentation of diuresis and sodium excretion, dilution of contrast media, prevention of renal cortical vasospasm, reduced pre-constriction of vessels, avoidance of tubular obstruction and reduction of endothelin and other renal vasoconstrictors.⁴⁸ Reactive oxygen species generated by radiocontrast in the renal tubules and peritubular space are believed to be central in the pathogenesis of CI-AKI. The potential benefit of N-acetylcysteine has been reported in multiple trials including the Acetylcysteine to Prevent Angiography-Related Renal Tissue Injury trial.^{49,50} But the recently completed, large Acetylcysteine for Contrast-Induced Nephropathy Trial reported by Berwanger and colleagues has cast a doubt on the effectiveness of this agent to prevent this complication. Iodixanol is an iso-osmolar, non ionic dimer used in coronary angiography. It is associated with a significantly lower incidence of AKI after contrast exposure especially in patients with CKD.⁵¹ Finally, biplane angiography is associated with a reduction in angiographic contrast volume in patients with CKD.^{52, 53} Staging complicated intervention can decrease the contrast volume used in a single session and thus decrease the risk of AKI provided a sufficient long interim time period is observed (>10 days). Kumar and colleagues have demonstrated that the prudent use of intravascular iodinated contrast agent and coronary revascularization—with due attention to renal protection—did not hasten the progression to end-stage renal disease. Prevention of contrast-induced AKI is almost certainly a product of multimodality prophylaxis after careful patient selection and pre-, intra-, and post-procedural management.⁴⁹ **Table 1** lists caveats concerning nephrotoxic medications and other drugs used in routine management with suggestions to possibly reduce adverse events with coronary angiography.

Medications	Cardiovascular and Renal Effects	Recommendation
NSAIDs	Inhibition of production of vasodilatory prostaglandins leading to vasoconstriction of afferent arterioles, increased risk of AKI, fluid retention, and the development of heart failure	Discontinue at least 3 days prior to contrast exposure, switch to narcotics or alternative pain treatment
Antihypertensive medications *Special mention ACE inhibitors	Reduce the decline in renal function Can impair tubuloglomerular feedback	Continue Consider holding before angiography
Loop, thiazide, and other diuretics	Volume depletion, electrolyte abnormalities	Hold day of procedure
Aminoglycosides	Interstitial and medullary renal injury	Avoid if possible, close monitoring by levels if no alternative
Vancomycin	Enhance nephrotoxic potential of other nephrotoxic medications, direct chemotoxicity	Continue, closely monitor drug levels

Medications	Cardiovascular and Renal Effects	Recommendation
Amphotericin B	Acute renal vasoconstriction and distal tubular epithelial damage, loss of concentrating ability	Avoid if possible. Intensive monitoring of renal function, hydration and acid base status if no alternative or switch to newer less nephrotoxic agents such as caspofungin
Metformin	Increased risk of lactic acidosis if continued after glomerular filtration rate drops	Hold the day of contrast procedure, and generally recommended for another 10 days
Statins	May be protective against contrast-induced AKI	Continue
Cyclosporine, tacrolimus	Hypertension, dyslipidemia, diabetes mellitus, powerful inhibitor of CYP450 isozyme 3A4 and increases levels of some statins including lovastatin, atorvastatin, and simvastatin	Hold for three days prior to procedure. CCB and ACEI preferred choice for hypertension. To treat dyslipidemia, consider lowering dose, change to tacrolimus, diet control and/or lipid-lowering drugs usually statin with preference to pravastatin or rosuvastatin therapy. Watch for statin induced muscle toxicity/ rhabdomyolysis. Avoid toxic levels of cyclosporine and monitor blood glucose closely. Initiate early therapy for post-transplantation diabetes mellitus.
Sirolimus	Dyslipidemia, no significant impact on hypertension or post-transplant diabetes mellitus. It may interact with drugs metabolized by CYP450 isozyme system.	Treat dyslipidemia with diet control plus lipid-lowering drug therapy usually statins with preference to pravastatin or rosuvastatin. Consider lowering dose and/or change to alternative immune-suppressant drug if resistant dyslipidemia.
Corticosteroids	Hypertension, dyslipidemia, hyperglycemia, diabetes mellitus	Treat hypertension with CCB, ACEI or beta-blockers. Treat dyslipidemia with diet control plus lipid-lowering drug therapy. Monitor blood sugar levels closely and initiate early therapy for post transplantation diabetes mellitus. Use of lower dosing, if possible.
Mycophenolate mofetil and Azathioprine	Both pose low cardiometabolic risks.	Monitoring for hypertension, diabetes mellitus and dyslipidemia when used in conjunction with any of the above mentioned immunosuppressant drugs.

Table 1. Common medications and caveats with respect to coronary angiography in renal transplant candidates or recipients.

5. Coronary revascularization in transplant candidates

Jones et al divided 250 transplant candidates based on coronary angiography into group 1 with less than 50% stenosis, group 2 with more than 50% stenosis in 1 vessel, and group 3 with more than 50% stenosis in 2 or more vessels. Survival was significantly worse in group 3 when compared to groups 1 and 2. However survival was much better in patients who received transplantation in all 3 groups. Therefore severe coronary artery disease should not delay or disqualify a CKD patient from receiving renal transplantation.³¹ Coronary intervention in CKD patients is associated with multiple complicated issues that determine the outcome. Dialysis patients with coronary stenosis of more than 70% have a higher risk of cardiac events and death than patients without coronary artery lesions.¹⁴ The Coronary Artery Revascularization Prophylaxis (CARP) trial examined the impact of coronary revascularization in patients requiring major vascular surgery. Revascularization was not associated with any benefit in survival except in patients with left main coronary artery disease. Similarly, the American College of Physicians does not recommend prophylactic revascularization of asymptomatic patients undergoing noncardiac surgery, stressing the fact that asymptomatic low risk pretransplant candidates do not need coronary revascularization for renal transplantation.³² Kasiske et al suggested that revascularization of significant coronary artery stenosis should occur prior to renal transplantation.¹³ The prolonged survival benefit was confined to left main coronary artery stenosis, left main equivalent disease, triple vessel disease with abnormal left ventricular function, and two vessel disease with more than 75% stenosis of the left anterior descending artery. Revascularization is recommended for left main disease and its equivalents and symptomatic patients refractory to medical treatments.³³ Manske et al randomized 26 diabetic pretransplant candidates with significant coronary artery disease into revascularization and medical therapy groups prior to renal transplantation. The outcome of patients managed medically was significantly inferior to those treated by revascularization. Only 2 out of 13 revascularized patients had cardiovascular end points when compared to 10 out of 13 in the medically managed group.³⁴ Coronary revascularization in renal patients is associated with a three fold increase in mortality when compared to patients not requiring renal replacement therapy.³⁵ Compared to percutaneous coronary intervention, coronary artery bypass grafting is associated with approximately three time greater short term risk of postoperative hemodialysis dependence among non-hemodialysis dependent CKD patients.³⁶ Similarly, survival rates are significantly lower in dialysis patients at 2 years when compared to the general population.³⁵ Percutaneous coronary intervention is shown to have a better in hospital and 30 day survival in dialysis patients when compared to coronary artery bypass surgery. However coronary artery bypass surgery has better long term survival.³⁷ It also appears that there is a higher rate of restenosis of revascularized vessels in patients with CKD.³⁸ The use of drug eluting stents may decrease the incidence of restenosis, however these stents mandate the use of aspirin and clopidogrel for at least 1 year as per the present guidelines. Premature discontinuation of an antiplatelet agent is associated with significant risk of stent thrombosis. Thus, the combined use of aspirin and clopidogrel may delay renal transplantation. For that reason, if coronary intervention is contemplated, bare metal stent, balloon angioplasty or bypass grafting should be considered if the anatomy is feasible.³⁹

6. Angiography in patients after renal transplantation

Coronary angiography continues to be the gold standard for identifying coronary artery disease even in post transplant patients. Renal transplantation does not protect one from the adverse effect of contrast on the kidney. Transplant recipients are at high risk of CI-AKI due to chronic allograft dysfunction and the high prevalence of diabetes and concomitant use of immunosuppressants like cyclosporine and tacrolimus. Agrawal et al found a 15.4% incidence of contrast induced nephropathy among post transplant patients undergoing coronary angiography. Intravenous hydration, bicarbonate infusion, N-acetylcysteine and the use of iso-osmolar contrast agent show varying efficacy in reducing its incidence.⁴⁴ Thus, the renal transplant recipient, appears to be at enhanced risk for CI-AKI compared to patients with similar glomerular filtration and bilateral native kidneys. Renal transplant recipients should be informed of this increased risk and unnecessary or optional contrast exposure should be avoided.

7. Conclusions

There are specific cardiovascular benefits to early renal transplantation in CKD patients including improved left ventricular function, enhanced overall functional capacity and quality of life, and decreased morbidity and mortality. Delay in renal transplantation and longer duration of hemodialysis decreases the likelihood of normalization of cardiac systolic dysfunction after transplantation. CKD patient with cardiac dysfunction should be thoroughly evaluated for underlying ischemia and aggressively treated with anti-anginals, angiotensin converting enzyme inhibitors or angiotensin receptor blockers and beta blockers before, perioperatively, and after renal transplantation. Every effort must be made to promote early renal transplantation when feasible with a living donor.¹² An early cardiovascular assessment, preferably by cautious coronary angiography utilizing the above mentioned renoprotective measures should be performed if indicated, to decrease the cardiovascular event rate associated with transplant surgery. A multidisciplinary approach involving a cardiologist, an interventionist, a nephrologist, a cardiothoracic and transplant surgeon can expedite the process and thus improve post transplant morbidity, mortality, functional capacity and overall quality of life.

8. Abbreviations

KT = Kidney transplantation,
CAD = Coronary artery disease,
CHF = Congestive Heart Failure,
EKG = Electrocardiogram,
EF = Ejection Fraction,
MI = Myocardial infarction,
DM = Diabetes mellitus,
AS = Aortic stenosis,
MR = Mitral regurgitation,
LDL = Low density lipoprotein,
PVOD = Peripheral vascular disease,

CI-AKI = Contrast induced acute kidney injury,
 NSAIDs = Non steroidal anti-inflammatory drugs,
 AKI = acute kidney injury,
 CCB = calcium channel blockers,
 ACEI = angiotensin converting enzyme inhibitors,
 eGFR = estimated glomerular filtration rate,
 MDRD = Modification of Diet in Renal Disease,
 AKI = Acute Kidney Injury,
 CKD = Chronic Kidney Disease,
 ESRD = End Stage Renal Disease

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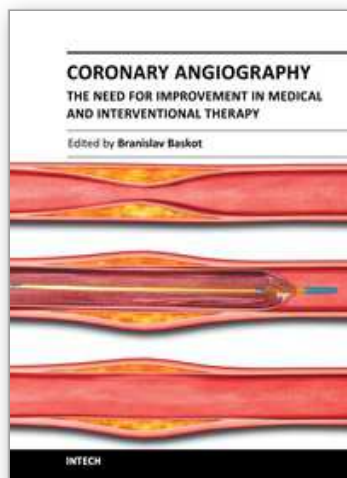
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In this book we examined a periprocedural complication of coronary angiography, and coronary intervention. That includes related to cardiac catheterization and diagnostic coronary angiography, and those that occur as a consequence of the specific equipment. However, improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incident of major periprocedural complications. This book giving knowledge and experiences many of interventional cardiologists from all over the world, and provide possibility to recognize new approach in this domain. Book gives lecture on how we image and how we decide on what to treat, how to treat it, and then results of that treatment. They offer many answers to what we have today and what we will have tomorrow.

How to reference

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