Trends in Transplant. 2011;5:128-32

Coronary Artery Disease in Candidates for Kidney Transplantation: Should We Do Pre-Emptive Revascularization?

Jose Jayme G. De Lima[1], Luis Henrique W. Gowdak[1] and Flavio J. de Paula[2]

[1]Heart Institute (InCor), Hospital das Clínicas, University of São Paulo Medical School, São Paulo, Brazil; [2]Renal Transplant Unit, Hospital das Clínicas, University of São Paulo Medical School, São Paulo, Brazil

Abstract

Coronary artery disease exerts an important negative influence on the survival of patients with chronic kidney disease before, during, and after transplantation. Myocardial revascularization is recommended for chronic kidney disease patients with unstable cardiac symptoms or for whom coronary intervention offers a long-term survival benefit as documented in the general population. Pre-emptive coronary intervention should not be indicated based only on the possibility of future transplantation. The question whether pre-emptive myocardial revascularization should be preferred instead of medical treatment, when the two options are equally appropriate by current guidelines, can only be answered by a prospective randomized study that does not yet exist. It is likely that such a study will show that coronary intervention should be recommended for some chronic kidney disease patients in whom the appropriateness of coronary intervention is now deemed uncertain by current guidelines. Surgery offers better long-term survival compared to angioplasty or stent. Modern medical treatment provides adequate protection in selected chronic kidney disease patients with significant coronary artery disease. **(Trends in Transplant. 2011;5:128-32)**

Corresponding author: Jose Jayme G. de Lima, jose.lima@incor.usp.br

Key words

Myocardial revascularization. Coronary artery disease. Chronic kidney disease. Renal transplantation. Pre-emptive coronary intervention. Transplant waiting list.

Introduction

Renal transplantation is the treatment of choice for many patients with chronic kidney disease (CKD). Recipients of transplants enjoy a better quality of life and have better long-term survival compared to patients who remain on dialysis[1]. Nowadays, the most common causes of graft loss are chronic allograft nephropathy and cardiovascular death with a functional graft[2,3]. Because an important proportion of cardiovascular events are due to coronary artery disease (CAD), it is generally agreed that a coronary assessment must be part of the pretransplant work-up. In spite of this, a significant number of coronary events

Correspondence to:
Jose Jayme G. de Lima
Unidade de Hipertensão
Instituto do Coração (InCor)
Rua Eneas Carvalho Aguiar 44
05403, São Paulo, SP, Brazil
E-mail: jose.lima@incor.usp.br

still take place during the first few months after transplantation and, sometimes, even during the surgery, suggesting that we still need a better strategy for diagnosis and treatment of CAD in patients on the waiting list. That is why a broad discussion on the appropriateness criteria to recommend pre-emptive coronary intervention in patients with CAD who may also be candidates for kidney engraftment is necessary. But, before starting, it is useful to consider the current practices for cardiac evaluation and coronary assessment in this particular group of patients.

Current Practices for Coronary Assessment in Patients Scheduled for Renal Transplantation

There is no definitive guideline for preoperative cardiovascular evaluation for renal transplant candidates. However, it is well known that patients with CAD have a worse prognosis, whether on dialysis or after transplantation[4,5]. As a consequence, assessment for CAD in renal transplant candidates is an accepted practice in the majority of centers. As a rule, patients are evaluated by a cardiology consultant, applying the current guidelines for appropriateness of coronary angiography[6,7], as established for the general population, that combine clinical risk factors and the presence or absence of ischemia on a noninvasive stress test. This approach may be the source of problems because of the reduced sensibility of noninvasive testing in patients with CKD[5,8]. For instance, we have data indicating that clinical risk factors are more accurate than noninvasive testing to define the probability of future cardiovascular events in patients with end-stage renal disease[9]. Nevertheless, the reported prevalence of significant CAD in renal transplant candidates is fairly constant and close to 50% in many studies[4,8-10] and not different from that observed in nonrenal patients scheduled for major vascular surgery[11].

Pre-emptive Coronary Intervention for Renal Transplant Candidates with High-Risk Coronary Artery Disease

Because of the absence of large randomized prospective studies to define the appropriateness criteria for coronary intervention in patients with CKD, we have to rely on the guidelines conceived for the general population[6,7]. It is accepted that preoperative myocardial revascularization should be reserved for patients with unstable cardiac symptoms or for whom coronary intervention offers a long-term survival benefit[12,13]. This treatment is recommended for both renal and nonrenal patients, independently of the possibility of future surgery. As we have shown, patients on the waiting list in whom intervention was indicated, according to international guidelines, but who refused the procedure, had a very poor outcome compared to individuals that underwent revascularization[10]. Therefore, up to this point, there is no reason for controversies. The problem arises when we consider patients who, according to current guidelines, could be managed either by medical treatment or by coronary intervention. That is because there is no conclusive evidence in the literature favoring either type of treatment for some patients with significant CAD; this scenario can be found in asymptomatic patients or in patients with less severe symptoms of angina (class I-II), or in patients with low-risk results in noninvasive tests, excluding those with high-risk coronary anatomy (e.g. left main disease). For those patients with intermediate-risk CAD, as of today, the benefit of myocardial revascularization is uncertain.

Pre-emptive Coronary Intervention in Renal Transplant Candidates with Intermediate-Risk Coronary Artery Disease

In the general population, due to advances in the medical treatment of CAD in

recent years, there is a tendency to give preference to medical treatment when intervention is also an option. It may be argued, however, that this does not necessarily apply to patients being considered for major surgical operations because surgery itself may predispose to coronary events[14]. In such individuals, a more aggressive treatment of CAD has been proposed[15]. The subject was evaluated prospectively in a large group of patients with stable CAD scheduled for major vascular surgery, who were randomly assigned to undergo either myocardial revascularization or no revascularization before surgery[11]. The main finding was that myocardial revascularization before elective vascular surgery does not significantly alter the long-term outcome. The authors concluded that the decision to indicate coronary intervention should not take into consideration the possibility of future surgery. Another prospective investigation[16] also asserted that prophylactic myocardial revascularization did not improve the short-term outcome in a similar group of patients with a more severe degree of CAD that underwent vascular surgery. Therefore, these studies question the usefulness of routine pre-emptive coronary intervention before major surgery to prevent events.

For patients on the waiting list for transplantation, there is no large, prospective, randomized study to settle this matter. Under these circumstances, some centers, like ours, rely on the current guidelines for the general population to indicate intervention in patients with intermediate-risk CAD. Because the perioperative mortality of myocardial revascularization is at least three-times greater for dialysis patients compared to nonrenal patients[17], we usually opt for medical management when the two modalities of treatment are considered adequate by current guidelines. We do not take into consideration the possibility of transplantation to recommend myocardial revascularization either by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). Using this approach, we indicated coronary intervention (CABG/stent) in only 46/230 patients with important (≥ 70% stenosis) CAD[10]. Others, however, recommend revascularization before transplantation for all patients with significant CAD, whether symptomatic or asymptomatic[4,18]. It is argued that because of the low sensitivity of noninvasive tests to detect ischemia, we may be denying intervention to patients that otherwise could benefit from the operation compared to medical therapy. Anatomy should then be the most important factor influencing the decision to intervene. A compromise between strict observation of guidelines and revascularization for all patients with significant CAD should be extending intervention only to patients with significant (≥ 70%) proximal left anterior descending (LAD) stenosis, irrespective of symptoms or results of noninvasive testing. This approach, however, still needs sufficient observational evaluation to be accepted.

Pre-emptive Myocardial Revascularization versus Pharmacologic-Based Treatment for Patients Being Considered for Renal Transplantation: Data from the Literature

The question whether pre-emptive myocardial revascularization for candidates for renal transplantation should be preferred instead of medical treatment when the two options are equally appropriate by current guidelines can only be answered by a prospective randomized study that does not yet exist. It is likely that such a study will show that coronary intervention should be recommended for some CKD patients for whom the appropriateness of coronary intervention is now deemed uncertain by current guidelines. We have already started an investigation in our center with that objective. Meanwhile, we have to resort to data from the literature, the majority of which is retrospective. The safety of coronary intervention

in patients undergoing hemodialysis was analyzed in a large retrospective investigation comprising more than 15,000 patients in the USA[17]. The in-hospital mortality was 8.6% for surgery, 6.4% angioplasty, and 4.1% stent. The two-year all-cause survival was 56.4% for surgery, 48.2% angioplasty, and 48.8% stent. The data indicate that surgery offers the best long-term survival in spite of increased in-hospital mortality and suggest that coronary intervention is safe. However, the study did not include results from medical treatment. This and other studies indicate that surgery (CABG) should the preferred modality of intervention, especially for diabetic patients[17-19].

The only prospective randomized work comparing medical versus surgical revascularization was conducted in 26 diabetic patients on dialysis, and concluded that coronary intervention was associated with reduced incidence of cardiac events (2 of 13 re-vascularized and 10 of 13 of medically managed patients)[20]. However, the medical treatment available when the study was undertaken (aspirin and niphedipine) is of questionable efficacy by modern standards. More recent works, all retrospective, also favor intervention[21,22]. Again, either medical treatment was not optimal by accumulated evidence or there were insufficient data to decide on their efficacy. We conducted an observational, nonrandomized, prospective investigation comparing the outcome of patients with stable CAD that underwent renal transplantation, receiving medical treatment or medical treatment plus pre-emptive coronary intervention, either CABG or stent[23]. The decision to intervene was based on AHA/ACC guidelines[6,7] and statins, beta-blockers, aspirin, and rennin-angiotensin system inhibitors were administered to all individuals. Both types of treatment provided adequate posttransplant survival and the incidence of cardiac events and of death by any cause did not differ between groups. On the other hand, for patients that did not receive a graft but remained on the list, coronary intervention was associated with a 22% greater long-term, event-free survival in spite of more severe CAD[10], lending support to the claim that guidelines usually underestimate coronary risk in CKD.

Current evidences advocate that modern pharmacological treatment results in adequate protection for an increasing proportion of renal patients. However, they also suggest that the coronary risk in patients with CKD is underestimated by the guidelines. These considerations emphasize the urgent need for in-depth evaluation of the appropriateness of coronary intervention in patients with CKD, whether on the waiting list for transplantation or not.

Conclusion

Myocardial revascularization is recommended for CKD patients with unstable cardiac symptoms or for whom coronary intervention offers a long-term survival benefit as documented in the general population. There are no data to recommend a strategy for coronary intervention based on the possibility of future transplantation. The question whether pre-emptive myocardial revascularization should be preferred instead of medical treatment when the two options are equally appropriate by current guidelines can only be answered by a prospective randomized study that does not yet exist. It is likely that such a study will show that coronary intervention should be recommended for some CKD patients for whom the appropriateness of coronary intervention is now deemed uncertain by current guidelines. The challenge that we have to face is how to correctly identify those individuals for whom the risk/benefit ratio is favorable.

Considering the increased risk of complications and death related to coronary intervention in this population and the encouraging

results with modern medical treatment in selected patients, we do not recommend myocardial revascularization based exclusively on the anatomy of the coronary arteries. Instead, we favor combining clinical risk factors with some anatomic coronary features, especially proximal LAD stenosis and multivessel disease. We estimate that a negative noninvasive test for ischemia contributes little to the decision because of its low sensitivity in CKD patients; however, a positive test is a reliable index of severity and thus helps in the decision process.

Acknowledgement

Supported by Fundação de Amparo à Pesqisa do Estado de São Paulo (FAPESP) and Fundação Zerbini, São Paulo, Brasil.

References

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341:1725-30. **Demonstrates the benefit of transplantation compared to dialysis.*
2. Briggs JD. Causes of death after renal transplantation. Nephrol Dial Transplant. 2001;16:1545-9.
3. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. Kidney Int. 2000;57:307-13. **Shows that post-transplant cardiac events are more frequent during the early months after the operation.*
4. De Lemos JA, Hills LD. Diagnosis and management of coronary artery disease in patients with coronary artery disease on hemodialysis. J Am Soc Nephrol. 1996;7:2044-54.
5. De Lima JJ, Sabbaga E, Vieira ML, et al. Coronary angiography is the best predictor of events in renal transplant candidates comparing with noninvasive testing. Hypertension. 2003;42:263-8. **Shows the importance of angiography to evaluate the cardiovascular risk in patients on the waiting list for transplantation.*
6. Gibbons RJ, Abrams J, Chatterjee K, et al.; American College of Cardiology; American Heart Association Task Force on Practice Guidelines. Committee on the Management of Patients with Chronic Stable Angina. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina-summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation. 2003;107:149-58.
7. Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness criteria for coronary revascularization. A report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology. J Am Coll Cardiol. 2009;53:530-53. ***Fundamental to indicate coronary intervention.*
8. Pilmore H. Cardiac assessment for renal transplantation. Am J Transplant. 2006;6:659-65.
9. Arantes RL, Gowdak LH, Paula FJ, et al. Myocardial scintigraphy and clinical stratification as predictors of events in renal transplant candidates. J Nephrol. 2010;23: 314-20.
10. De Lima JJG, Gowdak LHW, de Paula FJ, et al. Treatment of coronary artery disease in hemodialysis patients – a registry study. Transplantation. 2010;89:845-50. **Shows the impact of modern medical treatment on prevention of cardiac events and the importance of coronary intervention in patients on the waiting list for transplantation.*
11. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004;351:2795-804. ***Important paper on the subject of pre-emptive coronary intervention before elective surgery.*
12. American College of Physicians. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. Ann Intern Med. 1997;127:309-12.
13. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol. 2002;39:542-53.
14. Durazzo AES, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial J Vasc Surg. 2004;39:975-6.
15. Pierpont G, Moritz T, Goldman S, et al. Disparate opinions regarding indications for coronary artery revascularization prior to elective vascular surgery. Am J Cardiol 2004;94: 1124-8.
16. Poldermans D, Schouten O, Vidakovic R, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: The DECREASE-V Pilot Study. J Am Coll Cardiol. 2007; 49:1763-9.
17. Herzog CA, Ma JZ, Collins AJ. Comparative survival of dialysis patients in the United States after coronary angioplasty, coronary stenting, and coronary artery bypass surgery and impact of diabetes. Circulation. 2002;106:2207-21. **Large study showing the results of coronary intervention in dialysis patients.*
18. Braun W, Marwick T. Coronary artery disease in renal transplant recipients. Cleve Clin J Med. 1994;61:370-85.
19. Rinehart AL, Herzog CA, Collins AJ, Flack JM, Ma JZ, Opsahl JA. A comparison of coronary angioplasty and coronary artery bypass grafting outcomes in chronic dialysis patients. Am J Kidney Dis. 1995;25:281-90.
20. Manske CL, Wang Y, Rector T, et al. Coronary revascularization in insulin-dependent diabetic patients with chronic renal failure. Lancet. 1992;340:998-1002. ***The first and sole randomized, prospective, controlled study comparing medical versus interventional treatment of CAD in CKD patients.*
21. 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.
22. Opsahl JA, Husebye DG, Helseth HK, et al. Coronary artery bypass surgery in patients on maintenance dialysis: long-term survival. Am J Kidney Dis. 1988;12:271-4.
23. De Lima JJG, Gowdak LHW, de Paula FJ, et al. Influence of coronary artery disease assessment and treatment in the incidence of cardiac events in renal transplant recipients. Clin Transplant. 2010;24:474-80.