Coronary Artery Bypass Grafting vs. Drug-Eluting Stent Implantation for Multivessel Disease in Patients with Chronic Kidney Disease

Se Hun Kang, MD1, Cheol Whan Lee, MD2, Sung-Cheol Yun, PhD2, Pil Hyung Lee, MD2, Jung-Min Ahn, MD2, Duk-Woo Park, MD2, Soo-Jin Kang, MD2 Seung-Whan Lee, MD3, Young-Hak Kim, MD3, Seong-Wook Park, MD3, and Seung-Jung Park, MD2

1Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, 2Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 3Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background and Objectives: There is currently a limited amount of data that demonstrate the optimal revascularization strategy for chronic kidney disease (CKD) patients with multivessel coronary artery disease (CAD). We compared the long-term outcomes of percutaneous coronary intervention (PCI) with drug-eluting stents (DES) versus coronary artery bypass graft surgery (CABG) for multivessel CAD in patients with CKD.

Subjects and Methods: We analyzed 2108 CKD patients (estimated glomerular filtration rate <60 mL/min/1.73 m²) with multivessel CAD that were treated with PCI with DES (n=1165) or CABG (n=943). The primary outcome was a composite of all causes of mortality, myocardial infarction, or stroke. The mean age was 66.9±9.1 years.

Results: Median follow-up duration was 41.4 (interquartile range 12.1–75.5) months. The primary outcome occurred in 307 (26.4%) patients in the PCI group compared with 304 (32.2%) patients in the CABG group (adjusted hazard ratio [HR], 0.941; 95% confidence interval [CI], 0.79–1.12; p=0.493). The two groups exhibited similar rates of all-cause mortality (adjusted HR, 0.91; 95% CI, 0.77–1.09; p=0.295), myocardial infarction (adjusted HR, 1.86; 95% CI, 0.85–4.07; p=0.120) and stroke (3.2% vs. 4.8%; HR, 0.93; 95% CI, 0.57–1.61; p=0.758). However, PCI was associated with significantly increased rates of repeat revascularization (adjusted HR, 4.72; 95% CI, 3.20–6.96; p<0.001).

Conclusion: Among patients with CKD and multivessel CAD, PCI with DES when compared with CABG resulted in similar rates of composite outcome of mortality from any cause, MI, or stroke; however, a higher risk of repeat revascularization was observed. (Korean Circ J 2017;47(3):354-360)

KEY WORDS: Coronary artery bypass; Coronary disease; Percutaneous coronary intervention; Renal insufficiency.
Subjects and Methods

Study population

The Asan Multivessel Registry is a single-center, prospective study designed to evaluate the treatment effects of PCI with DES and CABG for multivessel CAD. Briefly, this registry involves a prospective, single center recruitment of patients with multivessel CAD who received PCI with DES or isolated CABG at the Asan Medical Center (Seoul, Korea) between January 2003 and December 2013. Patients with a history of prior CABG, those who underwent concomitant valvular or aortic surgery, and those who had experienced an acute myocardial infarction (MI) within 24 h before revascularization or presented with cardiogenic shock were excluded. Among these patients, 2108 consecutive patients with CKD and multivessel CAD who underwent PCI with DES (n=1165) or CABG (n=943) were identified. The present study was approved by the local institutional review board.

PCI was performed according to current practice guidelines. The specific type of DES was selected based on the operator’s discretion. Antiplatelet therapy and periprocedural anticoagulation followed standard regimens. Following the procedure, patients were prescribed aspirin indefinitely and clopidogrel for at least 6 months, regardless of DES type. Surgical revascularization was performed using standard bypass techniques; whenever possible, the internal thoracic artery was preferentially utilized for revascularization of the left anterior descending artery.

Definitions and study outcomes

The primary outcome was a composite of mortality from any cause, MI, or stroke. The secondary outcomes were individual components of primary outcome and repeat revascularization. The diagnosis of acute MI was defined as either complications at the index admission (defined as new pathologic Q waves after index treatment) or follow-up MI requiring subsequent hospitalizations (defined as an emergency admission with a principal diagnosis of MI), as described previously. Stroke, as indicated by neurological deficits, was confirmed by a neurologist based on imaging studies. Repeat revascularization included target vessel revascularization and non-target vessel revascularization. In the PCI group, stent thrombosis was defined as definite or probable events, according to the Academic Research Consortium classification.

CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², which was calculated using the modification of diet in renal disease equation for at least three months. The renal replacement therapy (RRT) group was defined as patients that received hemodialysis or peritoneal dialysis.

Clinical, angiographic, procedural or operative, and outcome data were prospectively recorded in the dedicated PCI and surgical databases by independent research personnel. Clinical follow-up was performed at one month, six months, and one year, and subsequent follow-up was performed annually by either office visit or telephone.

Statistical analysis

Continuous and categorical covariates were summarized as the mean±standard deviation or the count (%). Baseline variables of the patients between the two treatment groups were compared with the t test or Wilcoxon rank-sum tests for continuous variables and with the chi-square statistics or Fisher’s exact test for categorical variables. Survival curves were constructed using Kaplan-Meier estimates and were compared with the log-rank test. Unadjusted and adjusted Cox proportional hazard models were used to assess the long-term rates of clinical outcomes between the two treatment strategies among the total population and subgroups. Covariates that were statistically significant on univariate analysis and/or those that were clinically relevant were considered as candidate variables in the multivariate models. Adjusted covariates included age, hypertension, diabetes mellitus, dyslipidemia, history of myocardial infarction, stroke, peripheral arterial disease, heart failure, history of PCI and CABG, extent of CAD, involvement of left main coronary artery, presence as acute coronary syndrome, and treatment strategy. In the Cox model, the proportionality assumptions were assessed by the Schoenfeld residual test and no relevant violations were detected. All reported p-values are two-sided, and p values<0.05 were considered statistically significant. Analysis was performed with SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The mean age of the patients was 66.9 years, 68.3% of the patients were men, and 1121 (53.2%) patients had diabetes mellitus. Baseline characteristics of patients according to treatment strategy are shown in Table 1. The results indicated that patients who received PCI were younger, had a lower incidence of diabetes mellitus, history of heart failure, and three-vessel disease, and had a higher incidence of left main disease compared with CABG patients. The number of implanted stents per patients was 2.3±1.2 in the PCI group, and the number of grafts used was 2.9±1.0 in the CABG group.
Clinical outcomes

During the 41.4-month follow-up period (interquartile range, 12.175.5 months), primary outcomes occurred in 307 (26.4%) patients in the PCI group and 304 (32.2%) patients in the CABG group (hazard ratio [HR], 0.866; 95% confidence interval [CI], 0.739–1.015; p=0.076). The Kapan-Meier curve did not show a significant difference in primary outcomes up to 1 year (p=0.839) and up to 5 years (p=0.075) between the PCI and CABG groups. In unadjusted analysis, the risks of all-cause mortality, MI, or stroke were similar between the two treatment strategies, whereas repeat revascularization was increased in PCI patients (Table 2).

Adjusted analysis also demonstrated that there were no significant differences in the cumulative incidence of primary outcomes (adjusted HR, 0.941; 95% CI, 0.791–1.120; p=0.493), all-cause mortality (adjusted HR, 0.907; 95% CI, 0.765–1.089; p=0.295), or stroke (HR, 0.926; 95% CI, 0.569–1.607; p=0.758) between the two treatment strategies. However, PCI was associated with higher risks of repeat revascularization compared with CABG (adjusted HR, 4.718; 95% CI, 3.198–6.959; p<0.001, Table 2, Fig. 1).

Subgroup analysis

Survival curves were created with Kaplan-Meier estimates in various subgroups to determine whether the non-significant effect observed for the treatment strategy in the overall population was consistent. There were no significant differences in the rates of primary outcome, mortality, MI, or stroke up to 1 and 5 years between the two treatment strategies among patients receiving hemodialysis or peritoneal dialysis (Table 3, Fig. 2). Similarly, no significant differences in the cumulative incidence of primary outcomes up to 1 and 5 years in patients with three-vessel disease, diabetes mellitus, or left ventricular ejection fraction less <40% were detected (Fig. 2).
Discussion

Among patients with CKD and multivessel CAD, the risks of a composite outcome of mortality from any cause, MI, or stroke were similar between the PCI and CABG groups, whereas PCI was associated with a higher risk of repeat revascularization. These findings were consistent in major clinical subgroups, including RRT, three-vessel disease, diabetes mellitus, or decreased LV function.

CKD represents an important high-risk subgroup of patients undergoing revascularization. PCI in patients with CKD is associated with a higher risk due to its increased incidence of repeat revascularization, acute renal failure, and mortality. In addition, patients with CKD have a poor prognosis after CABG, as CKD is associated with increased postoperative bleeding rates, longer postoperative mechanical ventilation time, and increased hospital stay. As CKD progresses, some patients exhibit chronic renal failure and these patients should receive RRT, but limited data are available on the prognosis of RRT patients with CAD.

Table 1. Baseline characteristics based on treatment strategy

| Variables                              | PCI (n=1165) | CABG (n=943) | p      |
|----------------------------------------|-------------|-------------|--------|
| Age (years)                            | 67.3±9.5    | 66.4±8.4    | 0.023  |
| Male                                   | 779 (66.9)  | 661 (70.1)  | 0.351  |
| Acute coronary syndrome                | 550 (47.2)  | 527 (55.9)  | <0.001 |
| BMI (kg/m²)                            | 24.6±3.0    | 24.6±3.0    | 0.948  |
| Hypertension                           | 884 (75.9)  | 716 (75.9)  | 0.980  |
| Diabetes mellitus                      | 574 (49.3)  | 547 (58.0)  | <0.001 |
| Treatment with insulin                 | 160 (13.7)  | 157 (16.6)  | <0.001 |
| History of smoking                     | 486 (41.7)  | 418 (44.3)  | 0.454  |
| History of dyslipidemia                | 402 (34.5)  | 334 (35.4)  | 0.170  |
| History of myocardial infarction       | 93 (8.0)    | 101 (10.7)  | 0.095  |
| Prior PCI                              | 213 (18.3)  | 140 (14.8)  | 0.072  |
| Family history of CAD                  | 64 (5.5)    | 56 (5.9)    | 0.896  |
| History of heart failure               | 50 (4.3)    | 59 (6.3)    | 0.043  |
| History of stroke                      | 137 (11.8)  | 121 (12.8)  | 0.747  |
| History of peripheral arterial disease | 51 (4.4)    | 49 (5.2)    | 0.379  |
| History of chronic lung disease        | 25 (2.1)    | 25 (2.7)    | 0.217  |
| LVEF                                   | 55.9±11.4   | 51.4±13.2   | <0.001 |
| LVEF ≤40                               | 98 (8.4)    | 206 (21.8)  | <0.001 |
| CKD stages                              |             |             | 0.002  |
| Stage 3 (eGFR 30-59 mL/min/1.73 m²)    | 877 (75.3)  | 63 (70.3)   |        |
| Stage 4 (eGFR 15-29 mL/min/1.73 m²)    | 62 (5.3)    | 86 (9.1)    |        |
| Stage 5 (eGFR ≤15 mL/min/1.73 m² or dialysis) | 226 (19.4) | 194 (20.6) |        |
| Disease extent                         |             |             | <0.001 |
| 2-vessel                               | 660 (56.7)  | 182 (19.3)  |        |
| 3-vessel                               | 505 (43.3)  | 761 (80.7)  |        |
| Left main disease                      | 182 (15.6)  | 276 (29.3)  | <0.001 |
| DES generation                         |             |             |        |
| 1st generation DES                     | 744 (63.9)  | -           |        |
| 2nd generation DES                     | 421 (36.1)  | -           |        |
| Total stents per patient               | 2.3±1.2     | -           |        |
| On pump CABG                           | -           | 484 (51.3)  |        |

Values are presented as mean±standard deviation or number (%). PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, BMI: body mass index, CAD: coronary artery disease, LVEF: left ventricular ejection fraction, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, DES: drug eluting stents
Several studies have compared PCI and CABG in patients with multivessel CAD. Early studies have demonstrated that long-term clinical outcomes were equivalent in patients who underwent PCI or CABG, although the subsequent revascularization rate was significantly higher in the PCI group.\(^\text{22,23}\) In the bare metal stent era, PCI with bare metal stent or balloon angioplasty and CABG for multivessel CAD exhibited similar rates of mortality and a composite of mortality or MI; however, CABG demonstrated a survival advantage in patients with diabetes or older patients.\(^\text{24}\)

In the DES era, the FREEDOM trial showed that CABG was superior...
to PCI with DES in that CABG significantly reduced mortality rates and MI in patients with diabetes and multivessel CAD. Likewise, CABG, as compared with PCI with DES, significantly reduced the long-term risk of mortality in nondiabetic patients with multivessel CAD. Therefore, in the DES era, despite advances in stent technology, CABG demonstrated improved clinical outcomes of mortality in patients with multivessel CAD compared to PCI, supporting the hypothesis that CABG is the preferred strategy for the majority of patients with multivessel CAD.

CKD is a poor prognostic factor of mortality or morbidity after revascularization with PCI or CABG, and some studies reported that PCI with DES showed comparable results when compared with CABG in patients with multivessel CAD and CKD. In the present study, which included >2000 patients with CKD and multivessel CAD, there were no significant differences in the risk of primary outcomes, mortality, MI, or stroke between the two treatment strategies, and PCI was associated with an elevated rate of repeat revascularization. Similarly, in patients with RRT, there were no significant differences in the rates of primary outcomes, mortality, MI, or stroke between the two treatment groups. In addition, among CKD patients with other risk factors, such as three-vessel disease, diabetes mellitus, or decreased left ventricular dysfunction, there were no significant differences in the occurrence of primary outcomes. Our findings are consistent with those of a recent report, showing that PCI is associated with a similar long-term risk of death compared with CABG in patients with CKD and multivessel CAD.

Altogether, PCI and CABG are similar in hard clinical outcomes for patients with CKD and multivessel CAD, suggesting that PCI with DES is a safe and effective in treating such patients.

Conclusion
Among patients with CKD and multivessel CAD, PCI with DES when compared with CABG resulted in similar rates of a composite outcome of mortality from any cause, MI, or stroke; however, a higher risk of repeat revascularization was observed.

References
1. Blackman DJ, Pinto R, Ross JR, et al. Impact of renal insufficiency on outcome after contemporary percutaneous coronary intervention. Am Heart J 2006;151:146–52.
2. Best PJ, 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.
3. 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.
4. Hillis GS, Croal BL, Buchan KG, et al. Renal function and outcome from coronary artery bypass grafting: impact on mortality after a 2.3-year follow-up. Circulation 2006;113:1056–62.
5. Shlipak MG, Simon JA, Grady D, et al. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. J Am Coll Cardiol 2001;38:705–11.
6. Lee SH, Kim YJ, Kim W, et al. Clinical outcomes and therapeutic strategy in patients with acute myocardial infarction according to renal function: data from the Korean Acute Myocardial Infarction Registry. Circ J 2008;72:1410–8.
7. Joki N, Hase H, Nakamura R, Yamaguchi T. Onset of coronary artery disease prior to initiation of haemodialysis in patients with end-stage renal disease. Nephrol Dial Transplant 1997;12:718–23.
8. Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med 2005;352:2174–83.
9. Javaid A, Steinberg DH, Buch AN, et al. Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention with drug-eluting stents for patients with multivessel coronary artery disease. Circulation 2007;116(11 Suppl):1200–6.
10. BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty
Revascularization Investigation (BARI). Circulation 1997;96:1761–9.
11. Ix JH, Mercado N, Shlipak MG, et al. Association of chronic kidney disease with clinical outcomes after coronary revascularization: the Arterial Revascularization Therapies Study (ARTS). Am Heart J 2005;149:512–9.
12. Park DW, Kim YH, Song HG, et al. Long-term comparison of drug-eluting stents and coronary artery bypass grafting for multivessel coronary revascularization: 5-year outcomes from the Asan Medical Center-multivessel revascularization registry. J Am Coll Cardiol 2011;57:128–37.
13. Park DW, Yun SC, Lee SW, et al. Long-term mortality after percutaneous coronary intervention with drug-eluting stent implantation versus coronary artery bypass surgery for the treatment of multivessel coronary artery disease. Circulation 2008;117:2079–86.
14. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:2574–609.
15. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:652–735.
16. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331–41.
17. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the circulatory system medical devices advisory panel of the Food and Drug Administration center for devices and radiologic health, December 7–8, 2006. Circulation 2007;115:2352–7.
18. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1–266.
20. Gruberg L, Dangas G, Mehran R, et al. Clinical outcome following percutaneous coronary interventions in patients with chronic renal failure. Catheter Cardiovasc Interv 2002;55:66–72.
21. Anderson RJ, O’Brien M, MaWhinney S, et al. Renal failure predisposes patients to adverse outcome after coronary artery bypass surgery. VA Cooperative Study #5. Kidney Int 1999;55:1057–62.
22. Serruys PW, Ong AT, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005;46:575–81.
23. BARI Investigators. The final 10-year follow-up results from the BARI randomized trial. J Am Coll Cardiol 2007;49:1600–6.
24. 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.
25. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.
26. Chang M, Ahn JM, Lee CW, et al. Long-term mortality after coronary revascularization in nondiabetic patients with multivessel disease. J Am Coll Cardiol 2016;68:29–36.
27. Deb S, Wijeysundera HC, Ko DJ, Tsubota H, Hill S, Frenses SE. Coronary artery bypass graft surgery vs percutaneous interventions in coronary revascularization: a systematic review. JAMA 2013;310:2086–95.
28. Asvirth G, Lee VV, Elayda MA, Reul RM, Wilson JM. Short- and long-term outcomes of coronary artery bypass grafting or drug-eluting stent implantation for multivessel coronary artery disease in patients with chronic kidney disease. Am J Cardiol 2010;106:348–53.
29. 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.
30. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Revascularization in patients with multivessel coronary artery disease and chronic kidney disease: everolimus-eluting stents versus coronary artery bypass graft surgery. J Am Coll Cardiol 2015;66:1209–20.