Coronary Artery Bypass Surgery versus Percutaneous Coronary Intervention for Left Main Coronary Artery Disease with Chronic Kidney Disease

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Summary
Percutaneous coronary intervention (PCI) has emerged as an alternative treatment to coronary artery bypass grafting (CABG) in patients with unprotected left main coronary artery disease (ULMCAD). However, the optimal treatment for ULMCAD concomitant with chronic kidney disease (CKD) was rarely addressed. Herein, we compare the long-term outcomes of these patients treated with CABG or PCI.

From January 2004 to December 2010, 185 patients with ULMCAD and CKD undergoing PCI (n = 84) or CABG (n = 101) were matched for the selection criteria. The primary end points included all-cause death, myocardial infarction (MI), stroke, repeat revascularization and major adverse cardiovascular and cerebrovascular event (MACCE).

The mean age was 73.4 ± 10.3 years with male (84%) predominance. Baseline characteristics of both groups were similar, except that patients in CABG group were more frequently associated with significant stenosis of right coronary artery and triple vessel disease. Furthermore, most patients belonged to higher surgical risk population (EuroSCORE ≥ 6, PCI group: 80.9%, CABG group: 75.2%). After treatment, the 30-day mortality was 3.5% in PCI and 8.9% in CABG (P = 0.14). During the median follow-up of 3.5 years, the risk of MACCE (67% versus 55%, P = 0.048), MI (15.5% versus 6.9%, P = 0.024), and repeat revascularization (30.9% versus 7.9%, P < 0.001) was significantly higher in the PCI compared with CABG. There were no significant differences in long-term all-cause death, stroke, and impact on renal function.

CABG was associated with significantly less long-term risk of MI and repeat revascularization in patients with ULMCAD and CKD.

Key words: Coronary artery bypass grafting

According to the report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice guidelines in 2011, Coronary artery bypass grafting (CABG) is in the class I of recommendation for patients with significant unprotected left main coronary artery disease (ULMCAD).1 However, percutaneous coronary intervention (PCI) by using drug-eluting stent (DES) has emerged as a possible alternative treatment in carefully selected patients with ULMCAD. Although short-term and long-term risk of mortality and major adverse cardiovascular and cerebrovascular events (MACCE) were comparable, constantly higher rate of repeat revascularization was concerned.2,3 On the other hand, cardiovascular morbidity and mortality rates are markedly increased in patients with chronic kidney disease (CKD),4,5 and the severity of renal function impairment significantly affected the incidence of MACCE in patients with ULMCAD and stable angina.6 In patients with advanced CKD and CAD, CABG was suggested to be associated with lower risks of acute coronary syndrome, repeat revascularization, and better survival comparing with PCI regardless the severity of CAD.7-10 However, the issue of treatment of ULMCAD in patients with CKD was rarely addressed. Thus, in this study, we aimed to access the short-term and long-term clinical outcomes of patients with ULMCAD and CKD undergoing CABG or PCI in our hospital, including the result of renal function.
Methods

Populations and exclusion criteria: From January 2004 to December 2010, totally 185 patients with concomitant ULMCAD and CKD undergoing PCI (n = 84) or CABG (n = 101) treatment were matched and formed the basis of analysis. Unprotected LM disease was defined as LM coronary artery stenosis > 50% and without patent coronary artery bypass grafts to the left anterior descending or left circumflex arteries. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m². Its classification and stratification were according to National Kidney Foundation practice guidelines for chronic kidney disease.11 Patients with acute coronary syndrome with cardiogenic shock and acute ST segment elevation MI with totally occluded LM coronary artery as the culprit lesion were excluded. Patients who underwent concomitant surgery for valvular, aortic disease, or peripheral arterial occlusive disease were also excluded. The decision to perform PCI or CABG depended on the patient’s or physician’s preference.

Percutaneous Coronary Intervention: PCI was performed according to the standard procedure as described before.12 During the procedure, predilatation with balloon catheter was performed in all cases. For most LM lesions with distal bifurcation involved, stenting across the bifurcation toward the left anterior descending artery (cross-over technique) was attempted, followed by provisional stenting of left circumflex artery (T-stenting or culottes stenting) if there was residual stenosis or dissection over orifice of left circumflex artery. Post-dilation with kissing balloon technique was attempted except in technical difficulty or small non-dominant left circumflex artery. Debubling by means of rotablator was used only in highly calcified lesions, and the use of intravascular ultrasound and glycoprotein IIb/IIIa receptor antagonist were at the discretion of the interventional operators. After the procedure, all patients received aspirin (100 mg/day) indefinitely and clopidogrel (300 mg loading dose, followed by 75 mg/day) or ticlopidine (500 mg loading dose, followed by 250 mg twice a day) for at least 1 month for bare metal stent (BMS) and 12 months for DES. Other medications (calcium channel blocker, beta-blocker, nitrate, angiotensin-converting enzyme inhibitors, and statins) for previous heart disease such as angina pectoris would be continued.

Coronary artery bypass grafting: After midline sternotomy, atherosclerosis and/or calcification of ascending aorta was evaluated by palpation and transesophageal echocardiography for whether or not to clamp the aorta. Traditional arrested CABG was performed for most patients. Ascending aorta canulation and 2-stage venous canulation to right atrium were performed to initiate the cardiopulmonary bypass and moderate hypothermia. After an aortic cross-clamp, cardiopulogic solution was given via antegrade infusion with or without retrograde infusion. Beating heart technique with or without cardiopulmonary bypass was done while severe atherosclerosis or calcification of ascending aorta not amenable to clamp. The left internal mammary artery (LIMA) was harvested to bypass the left anterior descending coronary artery in all possible cases. Complete revascularization was attempted whenever possible using arterial conduits or saphenous vein grafts. Life-long aspirin and/or clopidogrel would be prescribed soon after the surgery. Other medications had been used before the surgery was continued.

Follow-up: The clinical follow-up data were collected by scheduled monthly clinic evaluations, medical record review, or direct telephone contact. Follow-up angiography was performed only when there were ischemic symptoms or signs and/or non-invasive evidence of ischemia. The primary end-point included all-cause death and the first-ever MACCE, which were defined as all-cause death, myocardial infarction (MI), stroke, and clinical-driven repeat revascularization. MI was defined as the presence of significant new Q waves in at least 2 electrocardiographic leads or of symptoms compatible with MI associated with increase in creatinine kinase-MB fraction ≥ 3 times than the upper limit of the reference range. Stroke with neurological deficit was diagnosed by a neurologist on the basis of imaging study. Repeat revascularization was defined as any repeat PCI or coronary artery bypass surgery after index procedure. The surgical risk was evaluated according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE),13 which was computed by two experienced cardiologists unaware of the clinical course of patients. EuroSCORE ≥ 6 was considered as high surgical risk. Estimated GFR was calculated according to the simplified version of the Modification of Diet in Renal Disease Study prediction equation formula, further modified by Ma, et al.14 for Chinese patients with chronic kidney disease [eGFR = 175 × (plasma creatinine)^1.254 × age^{0.993} × 0.79 (if female)].14 The study protocol was approved by the Institutional Review Board at Taipei Veterans General Hospital and informed written consent was obtained from each participant.

Statistical analysis: All continuous variables were presented as mean ± standard deviation, and categorical variables as numbers and percentages. The differences of continuous variables were compared by two-sample t-test, and that of categorical variables by Chi-square or Fisher’s exact test between two groups. Long-term actuarial event-free survival curves of both groups were estimated by use of the Kaplan-Meier method and were compared using the log-rank test. Multivariable Cox regression analysis was performed to determine independent predictors of clinical outcomes. The hazard ratio and 95% confidence intervals were calculated. A p-value of less than 0.05 was considered to be statistically significant. The SPSS 17.0 (SPSS Inc., Chicago, Illinois, US) software package was used for statistical analysis.

Results

Patient characteristics: The patients’ characteristics of both groups are summarized in Table I. The mean age of was 73.4 ± 10.3 years with male (84%) predominance. More than half patients were presented as non-ST segment elevation acute coronary syndrome (122 patients, 65.9%). In particular, 99 patients (53.5%) and 60 patients (32.4%) suffered from diabetes and heart failure (LVEF < 40%), respectively. The median additive EuroSCORE was
8.0 (25%-75%, range: 6.0-11.0), and 144 patients (77.8%) were considered to be high surgical risk with EuroSCORE ≥ 6. There were 33 patients (18%) patients who underwent regular hemodialysis (without CAPD in our series). These features suggested that these patients belonged to a higher risk population. There were no significant differences in the pre-procedural variables between PCI group and CABG group, except that more patients with smoking went regular hemodialysis (without CAPD in our series).

Among the patients surviving for more than 30 days, 8 developed end-stage renal disease and required permanent hemodialysis after the procedure, with 1 patient of PCI group (1.2%) and 7 patients of CABG group (6.9%) (P = 0.078). We further analyzed renal function change in single stent with cross-over technique (50 patients). In patients treated with more than one stent, T-stenting with final kissing balloon post-dilatation (13 patients, 15.4%) was used more often than other techniques.

**CABG and procedural characteristics:** In the CABG group, 96 patients underwent on-pump CABG, and the rest 5 underwent off-pump CABG (OPCAB). Left anterior descending artery was revascularized with LIMA in 75 patients (74.2%). Left radial artery was harvested once.

**PCI and procedural characteristics:** PCI procedure was angiographically successful in all patients. DES was used in 46 patients, included 1st generation (sirolimus-eluting stent, Cypher; and paclitaxel-eluting stent, Taxus) in 29 patients and 2nd generation (everolimus- and zotalimus-eluting stents) in 17 patients. The majority of patients with distal bifurcation involvement were treated with a PCI T-stent or final kissing balloon post-dilatation. DES was used more often than other techniques. The mean bypass graft number was 3.0 ± 0.76.

**Outcomes:** All patients were follow-up completely without loss. The median follow-up period was 3.5 years (25%-75% range: 1.5-5.9 years). Table II summarizes 30-day and long-term results. In 30-days outcome, there were 3 mortalities (who presented as acute/subacute stent thrombosis) in the PCI group, and 9 (6 cardiac death and 3 septic shock) in the CABG group. One patient in PCI group had MI, and 1 patient in CABG group had stroke.

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Table II. 30-Day and Cumulative Long-Term Outcomes

|                      | PCI (n = 84) | CABG (n = 101) | P     |
|----------------------|-------------|----------------|-------|
| 30-day outcomes      |             |                |       |
| All-cause death      | 3 (3.5%)    | 9 (8.9%)       | 0.14  |
| Myocardial infarction| 1 (1.2%)    | 0 (0%)         | 0.27  |
| Stroke               | 0 (0%)      | 1 (1%)         | 0.36  |
| Repeat revascularization | 0 (0%) | 0 (0%) | 1.0   |
| MACCE                | 3 (3.5%)    | 9 (8.9%)       | 0.14  |
| Long-term outcomes   |             |                |       |
| All-cause death      | 40 (48%)    | 51 (51%)       | 0.84  |
| Myocardial infarction| 13 (15.5%)  | 7 (6.9%)       | 0.024 |
| Stroke               | 1 (1.2%)    | 5 (4.9%)       | 0.15  |
| Repeat revascularization | 26 (30.9%) | 8 (7.9%) | <0.001|
| MACCE                | 52 (67%)    | 56 (55%)       | 0.048 |
| New permanent hemodialysis | 1 (1.2%) | 7 (6.9%) | 0.078 |

MACCE indicates major adverse cardiovascular and cerebrovascular event, included all-cause death, myocardial infarction, stroke, and repeat revascularization. P value of 30-day outcomes and long-term outcomes was measured by log-rank test.

Figure 1. Renal function change in patients who were not on hemodialysis (HD) before the intervention according to chronic kidney disease (CKD) staging.

In the long-term clinical outcomes, overall there were 91 all-cause deaths, 20 MIs, 6 strokes, and 34 repeat revascularizations, all via PCI during the follow-up period. By Kaplan-Meier analysis, the risk of MI, repeat revascularization, and MACCE was significantly higher in PCI group (MI, \( P = 0.03 \); repeat revascularization, \( P < 0.001 \); and MACCE, \( P = 0.048 \)) than those in CABG group, though there was no difference in all-cause death between both groups (Table II and Figure 2). The multivariable Cox regression analysis showed that age and eGFR were identified as independent factors for all-cause death and MACCE (Table III). In contrast, LVEF was identified as an independent protective factor for all-cause death (\( P = 0.03 \)) and CABG as a protective factor for repeat revascularization (\( P < 0.001 \)). Furthermore, CABG was identified as the only independent protective factor against MI in the multivariable Cox analysis (\( P = 0.045 \)).

Discussion

In this retrospective observational study, no difference in the 30-day outcomes was noted between PCI and CABG in patients with ULMCAD and CKD. However, CABG was associated with lower risk of MI, repeat revascularization, and MACCE compared with PCI in the long-term follow-up.

Chronic renal insufficiency has been identified as an independent risk for death and adverse cardiovascular events. Patients with CKD undergoing either PCI or
CABG were associated with increased procedural risk and poor long-term outcome compared with those without CKD. Furthermore, CABG has been reported to have a survival benefit over PCI using DES in patients with CKD and multi-vessel CAD, though patients with left main CAD was excluded in these studies. On the other hand, while CABG is the golden treatment for patients with ULMCAD, PCI with DES has been regarded as an acceptable alternative for these patients with high surgical risk. Previous studies have shown that, compared with CABG, PCI in ULMCAD was associated with similar long-term risk of cardiovascular death and MACCE, but increased rate of repeat revascularization. However, the treatments of patients with concomitant ULMCAD and CKD have been less addressed. To the best our knowledge, our study is the first study comparing the short-term and long-term outcomes of PCI and CABG for patients with CKD and ULMCAD, and our results might be beneficial in the decision making of treatment for this high risk subgroup.

Several studies and meta-analyses comparing PCI and CABG for ULMCAD showed that CABG patients may have reduced risk of MI and repeat revascularization, but PCI is either superior or similar to CABG in term of the peri-procedural risk of stroke. The long-term risk of repeat revascularization and MI in our PCI group re-

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**Table III.** Cox Regression Multivariable Analysis of All-Cause Death, MACCE, Myocardial Infarction, and Repeat Revascularization

| Variables       | All-cause death | MACCE          | Myocardial infarction | Repeat revascularization |
|-----------------|-----------------|----------------|-----------------------|-------------------------|
|                 | HR (95% CI)     | HR (95% CI)    | HR (95% CI)           | HR (95% CI)             |
| Age             | 1.034 (1.009-1.059) | 1.026 (1.004-1.048) | 0.018                | 2.20 (0.994-4.873) | 0.052 |
| ACS             | 1.535 (1.007-2.339) | 0.046          |                       |                         |
| LVEF            | 0.981 (0.965-0.998) | 0.03           |                       |                         |
| CAD extent      | 0.801 (0.622-1.033) | 0.087          |                       |                         |
| eGFR            | 0.973 (0.961-0.984) | < 0.001       | 0.983 (0.973-0.993) | 0.001                   |
| CABG/PCI        | 0.39 (0.154-0.980) | 0.045          | 0.19 (0.085-0.421) | < 0.001                 |

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and PCI, percutaneous coronary intervention.
mained significantly higher than the CABG group, which is in accordance with previous studies.2,4-7,21-23 However, the risk of stroke is comparable in both groups in our study. Actually, many variables, including calcified ascending aorta and operative techniques (on-pump or off-pump), may have some impact on the stroke incidence after CABG. Some studies have shown that off-pump CABG may reduce the incidence of post-operative stroke by 20%-30% in comparison to on-pump CABG.22,23 These results addressed the importance of avoidance of aortic manipulation which could minimize the risk of embolization of atheromatic plaque and the usage of composite arterial grafts based on the internal mammary arteries. Furthermore, because ROOBY and CORONARY trials showed that worse anastomotic quality and poorer graft patency in the off-pump CABG24,25, which may have a potential impact on the long-term result of CABG, traditional arrested CABG was used in most cases in our study. We routinely evaluated the aorta before aortic cannulation or cross-clamping by palpation or guidance by transesophageal echocardiography. In addition, we used proximal anastomotic device in patients with calcified ascending aorta, as Gold, et al.26 and Biancari, et al. reported before.27 Taken together, these precautions might contribute to the similar peri-procedural stroke rate in our CABG patients comparing with PCI. However, larger study is needed before any conclusions can be made.

Although our study showed comparable results in both CABG and PCI groups, the 5-year survival rate was only about 50%, and 5-year incidence of MACCE was even higher in both groups. The risk of adverse events in our study was much higher than those reported in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial, which enrolled those with left main and three-vessel disease.19 However, our results were comparable to those of Szczech, et al.,28 who reported similar 7-year survival rate in patients with CKD (serum creatinine > 1.5 mg/dL) and receiving PCI or CABG. The average eGFR in our study is 36.0 ± 18.3 mL/minute/1.73 m². According to the observation of Go, et al., both the risks of death and cardiovascular events increased as the eGFR decreased below 60 mL/minute/1.73 m²: the adjusted hazard ratio is 1.8 for death from any cause and 2.0 for any cardiovascular event with an eGFR of 30-44 mL/minute/1.73 m².29 In addition to eGFR, the differences in clinical characteristics, such as age, comorbidity, and less use of LIMA and DES might explain the great discrepancy in the outcomes between ours and SYNTAX trial.29 Nevertheless, in this extremely high risk population with concomitant CKD and ULMD, more effective therapy to improve survival is needed.

Limitations: There are several limitations in this study. Firstly, it was a retrospective observational study based on a relatively small number of patients from a single-center. Secondly, this study enrolled patients as long as 7-year period. It may have significant heterogeneity in the strategy of treatment. For example, in the PCI group, only half of them received DES implantation, and most of the DES was first-generation. It is known that DES was associated with a lower rate of restenosis and reduced the need for repeat revascularization in CKD patients compared with BMS.30 Furthermore, the use of newer generation DES might be associated with better clinical outcome than 1st generation DES. The EXCEL trial, which compares the safety and efficacy of everolimus-eluting stent with CABG in selected patients with ULMD, may be expected to give more information. Thirdly, the follow-up rate of coronary angiogram was low in both groups, which may cause under-estimation of restenosis rate in PCI group and asymptomatic graft failure in CABG group.

Conclusion

Although currently PCI was regarded as a potential alternative treatment to CABG, in patients concomitant with ULMD and CKD, CABG is still superior to PCI in terms of long-term risk of MI, MACCE, and repeat revascularization.

Disclosures

Conflicts of interest: None.

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