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Impact of prior cerebrovascular events on patients with unprotected left main coronary artery disease treated with coronary artery bypass grafting or percutaneous coronary intervention

Yu Pan[1], Yu Mu[2], Ze-Sen Liu[3], Yu-Chen Zhang[1], Ji-Qiang He[1], Xian-Peng Yu[1], Qi Qiu[2]

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China;
[2]Department of Pharmacy, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China;
[3]Department of Cardiology, Beijing Luhe Hospital, Capital Medical University, Beijing 101100, China.

Treatment of unprotected left main coronary artery (ULMCA) disease with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) has developed rapidly during the past decades. The optimal revascularization strategy has been a subject of debate, with several randomized controlled trials and meta-analyses comparing outcomes of CABG and PCI.[1] However, patients with prior cerebrovascular events (CVEs) were often excluded from coronary revascularization trials. There is a strong association between coronary artery disease (CAD) and prior CVEs.[2] Approximately one in eight patients with CAD has a history of CVEs, and that particular patient is at higher risk of worse outcomes after coronary revascularization than patients with CAD alone.[3] The reason for the co-occurrence of CAD and CVEs might be that atherosclerosis is a diffuse process that may affect different vascular beds including coronary artery and cerebral artery. To date, there are no guidelines providing advice on the optimum modality of revascularization for patients with prior CVEs. It gradually became clear that CABG is the standard care for patients with complex lesions, and PCI with drug-eluting stents (DES) is an acceptable option for patients with less complicated diseases. Thus, CABG seems like a better choice for patients with prior CVEs. But it is also pointed out by trials that more strokes occurred after CABG than PCI.[4] Currently, no study has assessed the impact of prior CVEs and compared outcomes in real-world patients with ULMCA disease and CVEs treated with PCI *vs*. CABG. We conducted a real-world, single-center, retrospective study of patients with ULMCA disease including prior CVEs to facilitate this comparison.

All of the consecutive patients who underwent PCI or CABG were retrospectively analyzed if they were aged >18 years and diagnosed with ULMCA disease (left main artery stenosis ≥50%) in the Department of Cardiology and Department of Cardiac Surgery at Beijing Anzhen Hospital between January 2005 and March 2010. Either DES placement or CABG was performed at the discretion of the cardiologist and patients. Coronary angioplasty and stent implantation were carried out in accordance with the operator's criteria following the center's usual practice. CABG was performed with standard bypass techniques. The internal thoracic artery was preferentially used for revascularization of the left anterior descending artery. The therapeutic effects of the procedures on patients were determined by telephone or timely outpatient follow-up.

The study was approved by the Human Research Committee of Capital Medical University (No. 2019055X). Informed consent was obtained from all individual participants included in the study.

The main purpose of this study was to evaluate the risk of adverse consequences in ULMCA disease patients with previous CVEs undergoing revascularization and to determine whether patients with prior CVEs are more likely to benefit from PCI or CABG. CVEs were defined as prior stroke, transient ischemic attack (TIA), or carotid artery disease. The research team assessed and collected the presence of these events in each patient. The end-point during the follow-up was major adverse cardiac and cerebral events (MACCE), defined as the synthesis of all-cause death, myocardial infarction (MI), stroke, and target vessel revascularization (TVR). We defined TVR as any

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Correspondence to: Qi Qiu, Department of Pharmacy, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China
E-Mail: qiuqi8133@163.com

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surgical or interventional revascularization performed on previously treated vessels.

Categorical variables were presented as absolute values and frequencies. Continuous variables were tested for normality using the Kolmogorov-Smirnov test and were presented as mean standard deviation or median (interquartile range). Differences between groups were tested using χ^2 test or the Fisher exact test for discrete variables and Student's *t* test or Wilcoxon rank-sum test for continuous variables, as appropriate. The Kaplan-Meier and log-rank methods were performed to compare event rates. Univariable and multivariable Cox proportional hazard models were constructed to compare risks for the outcomes between groups. Variables with $P \leq 0.1000$ and clinically relevant covariates irrespective of their statistical relevance (such as sex and age) in univariable analyses were candidates for inclusion in the multivariable Cox proportional hazard models. The relationship between prior CVEs and PCI *vs.* CABG on prognosis was further explored through interaction analysis. All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Institute Inc., Chicago, IL, USA). A two-sided $P < 0.0500$ was considered statistically significant.

All of the 2043 ULMCA disease patients enrolled had data regarding prior CVEs status recorded in the electronic system, 274 (13.4%) of whom had prior CVEs. The baseline characteristics, angiographic, and procedural findings of the entire study population are shown in Supplementary Table 1, http://links.lww.com/CM9/A673. Overall, patients with prior CVEs were older with a significantly higher incidence of hyperlipidemia, hypertension, and peripheral vascular disease. Additionally, patients with prior CVEs were more likely to have chronic total occlusion (CTO) and were less likely to achieve complete revascularization than those without CVEs. There were no significant differences in the distributions of sex, smoking history, previous revascularization, left ventricular ejection fraction, creatinine, family history of CAD, multivessel disease (MVD), modality of revascularization, old myocardial infarction, and other relevant diseases between patients with and without prior CVEs. Among 274 patients with prior CVEs, 130 and 144 underwent PCI and CABG, respectively. Among 1769 patients who did not have prior CVEs, 918 and 851 underwent PCI and CABG, respectively.

The median follow-up period was 21.53 (interquartile range 14.00–28.33) months. The incidence of endpoints for patients with or without prior CVEs are shown in Supplementary Table 2, http://links.lww.com/CM9/A673. Overall, patients with *vs.* those without prior CVEs experienced significantly higher rates of MACCE (32.3% *vs.* 23.6%; hazard ratio [HR]: 1.96; 95% confidence interval [CI]: 1.37–2.81; $P < 0.0001$) driven by increased rates of MI (8.4% *vs.* 7.3%; HR: 3.02; 95% CI: 1.51–6.04; $P < 0.0001$), with no significant differences in all-cause death (both cardiovascular and non-cardiovascular) or TVR. The incidence of stroke in patients with CVEs was higher than those without CVEs, but the difference was not significant (3.7% *vs.* 3.0%; HR: 2.15; 95% CI: 0.78–5.94; $P = 0.0550$).

After adjusting for age, history of hyperlipidemia, hypertension, peripheral vascular disease, and other relevant influential factors, the Cox regression analysis showed a higher MACCE incidence (adjusted HR: 2.11; 95% CI: 1.54–2.89; $P < 0.0001$), a higher MI incidence (adjusted HR: 2.24; 95% CI: 1.28–3.91; $P = 0.0050$), and a higher stroke incidence (adjusted HR: 3.64; 95% CI: 1.24–10.74; $P = 0.0190$) in the patients with *vs.* without prior CVEs. There were still no differences in the incidence of all-cause death or TVR between patients with and without prior CVEs.

The baseline characteristics, angiographic, and procedural findings of patients with prior CVEs are shown in Supplementary Table 3, http://links.lww.com/CM9/A673. There were no significant differences between patients who undergone PCI and CABG. The incidences of endpoint for patients with or without prior CVEs stratified by different revascularization modalities are shown in Supplementary Table 4, http://links.lww.com/CM9/A673. The mortality was higher after PCI in patients with prior CVEs but lower after PCI compared with CABG in patients without prior CVEs ($P_{interaction}$: 0.7500). In patients with prior CVEs, MI occurred in 12.7% (16/130) of patients after PCI and in 4.4% (6/144) of patients after CABG (HR: 3.03; 95% CI: 1.19–7.75), whereas in those without CVEs, the MI rates were 13.7% (30/918) and 2.4% (18/851), respectively (HR: 1.62; 95% CI: 0.90–2.90) ($P_{interaction}$: 0.6200). A significant interaction was present such that the rate of stroke was lower after PCI compared with CABG in patients with and without prior CVEs ($P_{interaction}$: 0.0200) but the rate of TVR was higher after PCI compared with CABG in patients with and without prior CVEs ($P_{interaction}$: <0.0001). As a result, the composite rate of death, MI, stroke, and TVR favored CABG in patients with and without prior CVEs ($P_{interaction}$: 0.5400). Kaplan-Meier survival curves are shown in Supplementary Figure 1. http://links.lww.com/CM9/A750.

The current retrospective observational cohort study evaluated and compared outcomes after revascularization with PCI *vs.* CABG in real-world patients with ULMCA disease and known CVEs. The key research findings are as follows: (1) compared with patients without prior CVEs, those with CVEs were more likely to have comorbidities; (2) the rate of composite endpoint, MACCE, was remarkably increased in patients with *vs.* without prior CVEs, driven by increased rates of MI after both PCI and CABG; (3) the rates of all-cause death, MI, and TVR favored CABG but the stroke rate favored PCI in patients with and without prior CVEs; and (4) the composite rate of death, MI, stroke, and TVR favored CABG in patients with and without prior CVEs.

ULMCA disease patients with prior CVEs were older with a higher incidence of hyperlipidemia, hypertension, peripheral vascular disease, and CTO compared with those without CVEs. These statuses are linked to similar predisposing risk factors and genetic predisposition. The reason might be that atherosclerosis is a diffuse process that may affect different vascular beds with considerable overlaps between coronary, cerebrovascular, and peripheral arterial disease.[5] Moreover, atrial fibrillation caused

by aging and systemic vascular risk factors can also result in embolic stroke.[6] Clinical variables including patient's age, comorbidities, as well as coronary anatomy were considered in the decision-making whether to conduct a complete or incomplete revascularization strategy.[7] Patients with CVEs often present with MVD and comorbidities, thus they were less likely to undergo complete revascularization in PCI.

The incidents of all-cause death, MI, and TVR favored CABG but stroke favored PCI. The interaction between CVEs and revascularization modality for stroke and TVR was significant, leading to a higher rate of MACCE in PCI patients. Information about whether patients with prior CVEs more suitable for PCI or CABG remains limited. Consistent with prior studies, CABG is associated with a higher risk of perioperative stroke than PCI. Although the incidence of perioperative stroke gradually decreases over time, the rate remains 2.1% to 5.2%, and the mortality remains 0% to 38%.[8] Since stroke is one of the most fatal and devastating complications of CABG surgery, the etiology of stroke after CABG surgery is complex and multifactorial. Early strokes often arise from particulate and gaseous embolism during surgery. The reason for delayed strokes is likely the prothrombotic postoperative state causing by continuous cellular inflammatory responses and platelet activation. However, patients with the previous stroke also showed higher risks for all-cause death and stroke after PCI than those without stroke.[9] Given all these data, our findings support the view that previous CVEs should not be the reason to favor PCI instead of CABG. Therefore, the heart team should consider all factors that may affect the prognosis in an all-round way, and then choose the revascularization modality.

Although this is the first real-world analysis of its kind to date, it does have the limitations of retrospective design and non-randomized nature leading to selection bias and ascertaining bias. Because it is a single-center study, a modest number of patients (274) had prior CVEs, and subsequent analysis is inherently underpowered. Owing to insufficient data to calculate the score, our registry did not capture data on the SYNTAX score of patients, a factor that affects outcomes, and therefore, did not appear in the regression analyses. Larger trials are necessary to determine whether PCI is beneficial to patients with previous CVEs.

Conflicts of interest

None.

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