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Gender Differences in Clinical Outcomes of Patients with Coronary Artery Disease after Percutaneous Coronary Intervention

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Abstract

With the increasing incidence of coronary artery disease, the percutaneous coronary intervention (PCI) has become one of the most effective treatments for coronary artery disease. After more than 40 years of clinical application, development and research, and continuous improvement, it has been widely used around the world. In recent years, due to the continuous innovation of drug-eluting stents, equipment, drugs, and interventional technology, the indications for treatment have been continuously broadened, many heart centers can deal with complete revascularization for high-risk indicated patient session, and the efficacy has been further improved. However, studies have shown that there are gender differences in the clinical prognosis of patients with coronary artery disease after percutaneous coronary intervention, which are affected by many related risk factors of gender differences, but there is lack of systematic and comprehensive review of relevant factors. The purpose of this review is to evaluate the possible causes of gender differences in the clinical outcomes of patients after percutaneous coronary intervention and to put forward recommendations for primary prevention and secondary prevention.

Keywords: coronary artery disease, percutaneous coronary intervention, gender, differences

1. Introduction

Coronary artery disease is the most common cardiovascular disease caused by myocardial ischemia, hypoxia, and necrosis due to coronary stenosis, spasm, or occlusion. Since the first application of percutaneous coronary intervention (PCI) to myocardial infarction by Gruentzig in 1977, it has become the most common method to recover myocardial reperfusion under various states, significantly improving the survival and quality of life of patients with coronary artery disease [1]. Notably, PCI has been considered as the cornerstone of management for

patients with or without ST elevation acute coronary syndromes [2–4]. In the past two decades, with the emergence of drug-eluting stent, the indication of PCI in high-risk patients with coronary artery disease has been tremendously broadened. In recent years, the progress of interventional techniques has also fundamentally changed the treatment of coronary artery disease. Moreover, since balloon angioplasty has been used in patients with coronary artery disease, the influence of gender on clinical outcomes after PCI has been continuously investigated. In particular, previous studies have reported that the incidence of adverse outcomes in female patients with coronary artery disease after PCI is higher than that in male patients with those after PCI, including short- and long-term mortality, major adverse cardiovascular events (MACE), and revascularization. On the one hand, some studies have shown that gender differences in clinical outcomes persist after adjusting for multivariate factors, such as age, prior peripheral vascular disease, prior myocardial infarction, prior PCI, and chronic renal failure [5–8]. On the other hand, other studies have demonstrated that gender is not an independent factor in the clinical outcome [9–11]. Due to the protection of estrogen, a large number of studies have revealed that the onset age of female patients with coronary artery disease is approximately 5–10 years later than that of male patients with those. Additionally, the prevalence of hypertension, diabetes mellitus, and hyperlipidemia was higher in female individual than that in male individual, while the prevalence of former or current smokers was more in male individual. Therefore, the purpose of the present review is to summarize the gender differences in clinical studies of patients with coronary artery disease after PCI and to put forward suggestions for improving primary and secondary prevention strategies.

2. Representative researches

In a Japanese observational study including 43,231 patients with non-ST-segment elevation acute coronary syndrome who underwent PCI from January 2014 to December 2014, the authors concluded that female patients had a higher risk of hospital complications than male patients, especially bleeding [5]. Another large-scale cohort study involving 95,030 male and 35,955 female patients from a clinical registry of PCI procedures revealed that female gender remained as an independent predictor for mortality of patients with coronary artery disease underwent PCI after multivariable adjustment from January 2006 to February 2011 [6]. A multi-center study from the United Kingdom and Sweden, which included 338,462 male and 119,799 female patients, indicated that female patients with coronary artery disease after PCI had a higher all-cause mortality than male patients with those and the age was also a strong predictor of mortality [7]. Moreover, a retrospective cohort study from Germany showed that female patients with ST-segment elevation myocardial infarction undergoing PCI harbored a 20% higher age-adjusted risk of death and ischemic cardiac and cerebrovascular events [8].

A systematic review involving 21 studies with 21,666 patients from the Netherlands showed that crude short- and long-term mortality was higher in female patients with ST-segment elevation myocardial infarction than that in male patients with those. However, the abovementioned gender differences generally disappeared after adjusting for baseline characteristics [12]. A comprehensive meta-analysis from the United States reported that there were gender differences in patients with coronary artery disease who underwent PCI, including short- and long-term mortality. Nevertheless, these differences were also gradually weakened after adjusting for the clinical differences and/or hospitalization course [13]. Although there were no significant gender differences in long-term mortality after adjustment, the

short-term mortality of female patients with coronary artery disease undergoing primary angioplasty was still higher than that of male patients with those. Meanwhile, a meta-analysis involving 48 studies from Italy to explore the gender differences in clinical outcomes for patients with ST-segment elevation myocardial infarction who underwent PCI [14] indicated that female patients with ST-segment elevation myocardial infarction undergoing PCI had higher rates of bleeding and stroke and the early mortality was lower than that of male patients with those, but not in the mid-term.

Both previous qualitative and quantitative studies have suggested that there are gender differences in clinical outcomes of patients with coronary artery disease after PCI, which are mainly reflected in the fact that the mortality rate of female patients with those is higher than that of male patients with those; however, the above systematic review and meta-analysis results were only limited to patients with ST-segment elevation myocardial infarction who underwent PCI. In order to determine the prognosis other than mortality, a systematic review was performed, which suggested that the prognosis of male patients with coronary artery disease after PCI was better than that of female patients with those, including mortality, MACE, and short-term revascularization, except for long-term revascularization [15]. Based on the results of previous studies, it is necessary to analyze the possible causes of these gender differences.

3. Related factors of gender differences

3.1 Risk factors

It is clear that the elderly patients not only have a higher risk of cardiovascular disease but also have a higher risk of mortality. The major reason for the delayed onset of female patients with coronary artery disease is the protective effect of estrogen, which can be delayed to female patients with postmenopause. Estrogen can directly protect myocardial cells, reduce myocardial apoptosis, and prevent plaque rupture through sarcKATP channels and β -estrogen receptor [16, 17]. Nevertheless, female patients with coronary artery disease were facing the same risk factors as male patients with those. Female patients with coronary artery disease frequently had hypertension in clinical practice, which can damage endothelial cells, lead to endothelial dysfunction, and accelerate atherosclerosis. Meanwhile, hypertension is associated with chronic alterations of renin-angiotensin-aldosterone system and overexpression of angiotensin II receptor 1/renin-angiotensin-aldosterone system, which can increase myocardial fibrosis, cardiomegaly, extracellular matrix, and diastolic dysfunction. Besides, elevated blood pressure can also increase infarct size of patients with myocardial infarction [18]. In addition, previous studies have shown that more female patients with cardiovascular disease had diabetes mellitus and dyslipidemia, which can impair the endothelial cells of coronary artery and strengthen the functions of coagulation factor VIII and platelets, which can thereby further accelerate the occlusion of the coronary artery and arteriosclerosis. It has been shown that hyperuricemia and hyperhomocysteinemia are independent predictors of female patients with coronary artery disease. Uric acid crystals can deposit on the vessel wall, which can promote inflammation and atherosclerosis [19]. Hyperhomocysteinemia can affect the functions of vascular endothelial cells and lipid metabolism and increase platelet aggregation and adhesion [20, 21]. All of these risk factors may contribute to the occurrence of adverse prognosis events in female patients with coronary artery disease after PCI.

3.2 Anatomy and pathophysiology

Some studies have elucidated that gender differences in the prognosis of patients with coronary artery disease after PCI are due to the fundamental differences in physiology, pathophysiology, pathological anatomy, and other aspects between male and female. Anatomically, the coronary arteries of female patients with coronary artery disease are smaller than that of male patients with those, and the smaller blood vessels can cause higher risks of bleeding complications and vascular damage [22]. In general, male patients with coronary artery disease are prone to complex lesions, such as left main artery lesions, chronic total occlusion lesions, and long lesions, while female patients with coronary artery disease tend to have small vessel lesions, which are more likely to show no significant stenosis of the coronary artery during coronary angiography [23]. Meanwhile, coronary microvascular reactivity and myocardial response to ischemia are also different between male and female individuals. It is suggested that the hemodynamic state of female patients with coronary artery disease is worse than that of male patients with those, which leads to differences of cell cycle process and apoptosis-related protein levels of cardiac fibroblasts between different genders [24]. In addition, female patients with myocardial infarction often show atypical symptoms [25]. As a result, such patients will not be paid much attention to, and physicians may be misled or underestimate the possibility of acute coronary syndrome, thereby prolonging the time from myocardial infarction to revascularization [26]. These pathophysiology and anatomy differences are irreversible factors. If the physiological and pathological characteristics of female patients with coronary artery disease can be identified in time, appropriate coronary intervention strategies will be selected to reduce complications and improve their clinical prognosis.

3.3 Ischemia-reperfusion time

According to the statistics of the time from the onset of coronary artery disease to reperfusion ischemia time, the interval of female patients was longer than that of male patients, including the prehospital delay and the time from door to balloon [27–30]. A study by Lichtman et al. has revealed that the cardiovascular risk of female patients with coronary artery disease, especially young female patients with those, is not easy to be accurately assessed, which may lead to be delayed diagnosis of acute myocardial infarction, thereby affecting treatment and prognosis [31]. Another registration study from one of 11 centers in Switzerland providing primary PCI around the clock, which has demonstrated that female patients with acute myocardial infarction between 2005 and 2010 may be discriminated when they receive PCI [32]. It is speculated that this situation may also exist in other countries. The prognosis of female patients with coronary artery disease who are discriminated in clinic is partly poor. Moreover, a study from the United States has found that female patients with coronary artery disease were less likely to undergo PCI than male patients with those and more female patients with those had delayed time of ischemia-reperfusion [33]. These controllable factors can lead to the failure of female patients with coronary artery disease to improve myocardial ischemia effectively in a short period of time, which is one of the important factors of poor prognosis. The duration of ischemia-reperfusion may be longer in female patients with these atypical symptoms than in male patients, which is another factor of higher mortality and MACE in female patients with coronary artery disease after PCI.

3.4 MACE

MACE is one of the factors that significantly affect the prognosis for patients with coronary artery disease after PCI. Previous study has indicated that the incidence of MACE is lower in male patients with coronary artery disease after PCI than that in female patients with those [9, 10, 23, 34]. A prospective, multicenter, cohort study by Glaser et al. has exhibited that female patients with non-ST-segment elevation acute coronary syndrome undergoing PCI at the age of 65 was more likely to have MACE than male patients with those at the same time [28]. Further analysis has shown that the incidence of congestive heart failure was higher in female patients with ST-segment elevation myocardial infarction than that in male patients with those, and the former was more likely to have cardiogenic shock when myocardial infarction occurred [5–7]. High incidence of ventricular septal rupture and severe mitral regurgitation during cardiogenic shock can be considered as important factors affecting the poor prognosis of female patients with myocardial infarction in the hospital. In a word, the above pathological factors can lead to the high incidence of MACE in female patients with coronary artery disease after PCI.

3.5 Revascularization

A study has demonstrated that the low incidence of revascularization in female patients with coronary artery disease may also be attributed to the lower follow-up rate, atypical symptoms, difficulty identifying myocardial ischemia, unwillingness to undergo invasive investigations, and prejudice against female patients [9]. In addition, the mortality of female patients with coronary artery disease was higher during the short- and long-term follow-up compared with male patients with those, which may also reduce the chance of revascularization [23, 34]. Furthermore, male patients with coronary artery disease who underwent PCI often have more complex lesions, which may be also an independent predictor of revascularization [23]. In terms of pathophysiology, the male subjects are more likely to have atherosclerotic plaque rupture, platelet-rich thrombus, and micro-embolism [35], while the platelets are more sensitive to aggregation stimulation in female patients, and this pathophysiological difference may also increase the risk of male patients with coronary artery disease who underwent PCI or CABG [36]. Moreover, some studies have shown that male patients with coronary artery disease have a higher PCI or CABG history than the female with those, which may be another reason for the higher incidence of overall revascularization in male patients with those [7, 8].

3.6 Other risk factors

Earlier evidence has supported that the female individuals would experience depression after the initial diagnosis of coronary artery disease and acute cardiac events, leading to all-cause mortality and the risk of MACE in the following months [37, 38]. Breast cancer is one of the most important causes of female individual death worldwide. However, the administration of estrogen receptor modulators in anti-breast cancer treatments may increase the incidence of coronary artery disease [39]. The incidence of autoimmune diseases for female individuals is also high, especially systemic lupus erythematosus, which is more common in female individuals. The pathogenic antibodies of the disease can cause antiphospholipid antibody syndrome (thrombosis, thrombocytopenia), thereby involving coronary artery and even resulting in acute myocardial infarction [40]. Therefore, it is important

to prevent and reduce the incidence of female high-risk diseases and to reduce the mortality and MACE of female patients with coronary artery disease after PCI.

4. Primary and secondary prevention

For population with high risk of cardiovascular events in the future and population who have already suffered from coronary artery disease, it is very important to implement the primary and secondary prevention of coronary artery disease. At present, various academic institutions around the world have formulated relevant suggestions, scientific statements, expert consensus documents, and clinical practice guidelines and put forward many measures for the primary and secondary prevention for patients with coronary artery disease and its PCI. However, the latest study shows that there are still significant gender differences for the primary and secondary prevention of cardiovascular disease. Compared with male patients, female patients with high risk of cardiovascular disease in the next 10 years are difficult to control their blood pressure, blood lipid, and body weight, while female patients who suffered from cardiovascular disease were worse in taking guideline-directed medications [41]. Therefore, the secondary prevention is particularly important for patients with coronary artery disease after PCI. On the basis of adherence to long-term drug treatment, the risk factors should be managed and controlled, and appropriate exercise should be performed, especially female coronary artery disease patients with higher risk factors and poor prognosis after PCI.

5. Conclusions

PCI has long been the main treatment method for patients with coronary artery disease, which significantly reduces the mortality of myocardial infarction and improves the quality of life of patients. However, compared with male patients with coronary artery disease, female patients with those have a higher MACE and mortality after PCI, while male patients with those have advantages in revascularization. Hypertension, diabetes mellitus, and dyslipidemia are the traditional risk factors of arteriosclerosis disease, which seriously affect the occurrence and development of coronary artery disease. Female patients with coronary artery disease are faced with more cardiovascular risk factors and adverse factors affecting the prognosis of PCI, which is a major challenge for female patients with PCI. In addition, it is necessary to pay attention to the management of non-cardiovascular risk factors for postmenopausal female. Meanwhile, psychological diseases should be identified and intervened in patients with coronary artery disease in time. Finally, it should be emphasized that the prevention and treatment of coronary artery disease should not be ignored for individuals with more than 65 years and population with vulnerable region of medical resources.

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