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Surgical revascularization in women: focus on factors worsening the prognosis

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ABSTRACT

In recent years, there has been an increase in the number of women undergoing coronary artery bypass grafting (CABG). Although the evidence of gender effects on outcomes is controversial, a number of publications have reported less favorable outcomes of CABG in women. The aim of this paper was to review the literature regarding factors that worsen short- and long-term prognosis in women undergoing surgical myocardial revascularization.

Gender differences in early outcomes of CABG are largely explained by gender distribution of baseline clinical characteristics. Women, compared to men, undergo CABG at an older age and have a worse profile of cardiovascular disease (CVD) risk factors (RF), comorbidity burden, structural and functional cardiac pathology, and coronary lesions. In women, complete myocardial revascularization is less frequent than in men, venous shunts are used more frequently, and the left internal mammary artery is less frequently used as a conduit. In addition to the baseline characteristics, higher incidence of perioperative myocardial infarction (MI), higher prevalence of anxiety and depression, lower quality of life and social adaptation after CABG, and lower involvement of women in rehabilitation programs, compared to men, may contribute to a less favorable long-term prognosis after CABG in women.

There is a need for more information for physicians about the specifics of CVDs and anatomical and surgical aspects of CABG in women. It is also necessary to raise patients' awareness of RF correction and to involve them in educational technologies. Recommendations for diagnosis and treatment of CVDs should be developed taking into account gender. Further research is also required to develop and implement sex-specific models for predicting surgical risks. Long-term follow-up is appropriate in women with recent MI and a history of diabetes mellitus. To further improve clinical outcomes of CABG in women, development of approaches that facilitate more complete revascularization and reduce the incidence of perioperative complications, such as MI and pneumonia, is needed. More answers to questions regarding gender differences in long-term outcomes of CABG may be obtained by analyzing further studies involving a larger number of female patients.

Keywords: coronary artery bypass grafting, female sex, women, complications, predictors, prognosis

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Хирургическая реваскуляризация у женщин: фокус на факторы, ухудшающие прогноз

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РЕЗЮМЕ

В прошедшие годы отмечается рост количества женщин, перенесших операцию коронарного шунтирования (КШ). Хотя данные о влиянии пола на исходы операции неоднозначны, в ряде публикаций сообщается о менее благоприятных результатах КШ у женщин. Целью данной работы явился анализ литературы в отношении факторов, ухудшающих краткосрочный и долгосрочный прогнозы у женщин, подвергнутых хирургической реваскуляризации миокарда.

Гендерные различия в ранних исходах КШ в значительной мере объясняются особенностями распределения между полами исходных клинических характеристик. У женщин, по сравнению с мужчинами, КШ осуществляется в более старшем возрасте, и они имеют более отягощенный профиль факторов риска (ФР) сердечно-сосудистых заболеваний (ССЗ), коморбидной нагрузки, структурно-функциональной патологии сердца и поражения коронарных артерий (КА). В отдельных случаях у женщин реже, чем у мужчин, осуществляется полная реваскуляризация миокарда, чаще используются венозные шунты, реже в качестве кондута используется левая маммарная артерия. Кроме исходных клинических характеристик менее благоприятному отдаленному прогнозу после КШ у женщин могут способствовать более высокая частота периперационного инфаркта миокарда (ИМ), более высокая распространенность тревоги и депрессии, менее высокий уровень качества жизни и социальной адаптации, а также меньшая вовлеченность женщин в реабилитационные программы по сравнению с мужчинами.

Существует потребность в дополнительном информировании врачей относительно особенностей течения ССЗ и анатомо-хирургических аспектов КШ у женщин. Также необходимо повышение осведомленности пациентов в вопросах коррекции ФР, привлечение их к участию в обучающих технологиях. Рекомендации по диагностике и лечению ССЗ целесообразно разрабатывать с учетом пола. Также необходимы дальнейшие исследования, направленные на разработку и практическое внедрение поло-специфических моделей прогнозирования хирургического риска. Долгосрочное наблюдение целесообразно у женщин с недавним ИМ и сахарным диабетом в анамнезе. Существенное значение имеет компенсация коморбидных состояний. Для улучшения клинических результатов КШ у женщин необходимо дальнейшее развитие подходов, способствующих осуществлению более полной реваскуляризации, а также снижению частоты периперационных осложнений, таких как ИМ и пневмония. Больше ответов на вопросы относительно гендерных различий в отдаленных исходах КШ может быть получено при анализе дальнейших исследований с участием большего числа пациентов женского пола.

Ключевые слова: коронарное шунтирование, женский пол, женщины, осложнения, предикторы, прогноз

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INTRODUCTION

It is well known that cardiovascular diseases (CVDs) are one of the leading causes of death, in particular among women, and they continue to be the subject of close attention of scientists. Understanding

the potential influence of gender on the development of not only CVDs but also their complications is currently of paramount importance to eliminate gender differences in approaches to the diagnosis and treatment of this group of diseases. A characteristic feature of coronary artery disease (CAD) is that this patholo-

gy has clinical manifestations mainly in patients over the age of 40 years. Development of many chronic diseases (multimorbidity) with age is explained by involutionary processes, and the deterministic possibility of their combination (comorbidity) remains a very urgent problem for scientific research, both among men and women [1–3].

One of the most effective methods for improving long-term prognosis and quality of life (QoL) in patients with severe CAD is coronary artery bypass grafting (CABG) [4]. About a million CABGs are performed annually in the world among patients with chronic CAD. Attention is drawn to repeated reports of a less favorable immediate and long-term prognosis after CABG in women [5–7]. Predictors that affect the immediate and long-term outcome of CABG have been actively studied over the past decades. At the same time, the factors explaining the gender difference in the outcome of surgical treatment for CAD have not been fully determined yet. The aim of this work was to review the literature regarding factors that explain gender differences in the immediate and long-term prognosis after CABG.

According to research data, the mortality rate from CAD among women is higher than among men and amounts to 23 and 21%, respectively [8]. According to the US Society of Thoracic Surgeons, a study of 344,913 patients who underwent CABG showed a higher rate of operative mortality among women (4.5 vs. 2.6% in men, $p < 0.001$) [9]. The results of other studies also support this standpoint. Thus, in a large meta-analysis, it was noted that postoperative mortality was significantly higher in women than in men (relative risk (RR) = 1.77; 95% confidence interval (CI): 1.67–1.88) [10].

When CABG is performed with the aid of cardiopulmonary bypass (CPB), in-hospital mortality among women is also higher than among men. M. Alam et al. revealed higher mortality among women compared to men, not only in the short term, but also in the medium and long term after CABG [10]. A less favorable long-term prognosis in women after CABG is also confirmed by other works [6, 11–13]. At the same time, the analysis of CABG cases in the period from 2003 to 2015 showed that the 30-day survival rate in women (average age 67 years) was lower, but the long-term survival, on the contrary, was higher than in operated men (average age 64 years) [14]. J.F. ter Woort et al. noted lower rates of long-term mortality (120 days) in women after CABG performed without the use of CPB compared to the traditional revascularization

method. No such difference was found in men [15]. A similar pattern was previously identified in the work by S.P. Fu et al. [16].

Despite the fact that criteria for selecting patients for surgery have been developed, hospital-acquired complications remain relevant in cardiac surgery practice. The most common complications are perioperative myocardial infarction (MI), neurological and infectious complications, systemic inflammatory response, as well as development of renal failure and various arrhythmias [17–20]. A number of studies have noted that in-hospital mortality and a higher proportion of severe complications (MI, stroke, acute kidney injury with the development of renal failure) after the intervention are more characteristic of women [21–23]. In women, angina pectoris recurs more often, there is higher incidence of intraoperative MI, acute heart failure, or chronic decompensation, respectively [24, 25]. In the long term after CABG, women were more likely to have repeated hospitalizations for MI and congestive heart failure than men, but survival did not differ between the genders [26].

However, in the available literature there are data that do not confirm the prognostic value of gender. For example, in a study by C.R. Herman et al. [27] that evaluated immediate outcomes of cardiac surgery, no gender effect on the development of a composite end point (infection, stroke, acute renal failure, death) was revealed. Among age-matched patients under 65 years, gender-specific mortality did not show statistically significant differences [28]. Other authors note that perioperative mortality among women was no higher than among men, and differences in the immediate CABG outcomes related only to infectious wounds, neurological complications, the frequency of re sternotomy, and the duration of inpatient treatment [29]. A number of studies have shown that gender did not have a significant impact on the long-term prognosis [30, 31]. Thus, the data on the effect of gender on the immediate and long-term prognosis after CABG are ambiguous: in some studies, prognostic parameters in women do not differ from those in men, in others, they show less favorable trends.

Of the factors potentially influencing gender differences in the outcomes of CABG we should first of all consider the effect of age. According to the results of numerous studies, it has been established that men are 3 times more likely to undergo CABG than women, which is due to an earlier onset of CAD [9]. However, the situation changes with age: among candidates for CABG over the age of 65 years, women prevail

[32]. According to domestic and foreign researchers, women are admitted for surgical treatment for CAD at an older age than men [33–35]. It is also worth noting that the maximum gender differences in the incidence of MI and other cardiovascular complications in most studies are detected at a relatively early age and significantly decrease after the age of 65 years.

A study conducted in Germany showed the relationship between gender, age, and early mortality after CABG. It was found that in the group of young women under the age of 50 years, postoperative mortality was 2.4 times higher than in men, while in 80-year-old women, mortality was similar to that of men of the same age [36]. In another study, however, the largest gender difference in early mortality after CABG (180 days) was noted in the age group of 70–79 years, with higher mortality rates in women [5]. At the same time, the difference between the genders in relation to the risk of in-hospital mortality was leveled after adjusting for gender differences in the distribution of preoperative risk factors. A similar age pattern was revealed in the study by American researchers, who showed that in-hospital mortality was higher in women than in men in all age groups, but it was most pronounced among patients under 50 years of age (3.4 vs. 1.1%) [37].

Similar differences were noted among patients aged 50–59 years – the probability of death among women was 2.4 times higher (2.6 vs. 1.1%) [37]. In older age groups, these differences were less pronounced ($p < 0.001$). There were also no gender differences in early prognosis after CABG among 70–84-year-old patients in an observational study presented by Turkish cardiologists that included 223 patients [38]. Thus, the severity of gender differences in relation to the immediate prognosis after CABG largely depends on age. The reported age limits for the maximum gender effect are controversial, but there is a trend toward the most pronounced gender differences among relatively young patients and toward a gradual decrease in the differences as the age approaches 80 years and older.

A characteristic feature of the clinical manifestations of CAD in women is significant severity of symptoms of the disease [39, 40]. Women who subsequently undergo CABG seek surgery with more severe symptoms of CAD and higher urgency for cardiac surgery [6]. The possibility of systematic delays in recognizing and diagnosing the severity of CAD in women, resulting in a less favorable outcome of CABG, cannot be ruled out [6, 41]. This, in turn, can be facilitated by a number of factors: in women, an atypical course of

CAD is detected more often, the sensitivity of non-invasive methods for diagnosing this disease is lower, diagnostic angiography is performed less frequently, stenosing coronary atherosclerosis is detected less often, and CAD develops 7–10 years later than in men [42]. However, American researchers showed that if women are admitted for CABG sufficiently early, this improves both the immediate outcomes of the surgery and patients' QoL later after the surgery [43].

It should also be noted that until 2013, the classical anatomical EuroSCORE (European System for Cardiac Operative Risk Evaluation) risk scale was used. Undoubtedly, this scale helped in choosing the optimal method of revascularization, since it made it possible to identify patients with a high risk of adverse events after percutaneous intervention. This scale had a significant drawback – it did not take into account clinical parameters and gender. This drawback was corrected when a new scale had been developed – EuroSCORE II, which made it possible to assess the surgical risk of CABG with account of gender-associated comorbidities [13].

Less favorable outcomes of CABG in women are partly explained by gender differences in the prevalence of major CVD risk factors. It is known that the prevalence of risk factors leading to the development of CVD also differs among men and women. Thus, according to the epidemiological analysis, gender differences are found both in the cardiovascular mortality and in the prevalence of the leading risk factors for CVD, such as smoking, obesity, diabetes mellitus (DM) [44]. In men, the predominant risk factors for CAD are smoking, age, arterial hypertension, high levels of low-density lipoproteins; in women – age, overweight, diabetes, and high triglycerides, respectively. Women with a high triglyceride level have worse long-term survival rates (HR = 1.5; 95% CI: 1.1–2.1) compared to men with high triglyceride concentration (HR = 1.1; 95% CI: 0.9–1.3) [45]. A number of studies report higher prevalence of obesity, DM, and arterial hypertension in women undergoing CABG [6, 46].

Higher incidence of complications after CABG in women is largely due to greater comorbidity burden compared to men [33, 43, 47]. Important factors of early mortality after CABG in women are previous MI and acute cerebrovascular accident (ACV) [36]. Higher incidence of stroke in history in women is predictable, since it has been found that a cerebrovascular event (stroke and transient ischemic attack) in women marked the onset of CVD 1.5–2 times more

often than in men [9, 48]. In a study by V. Vaccarino et al. it was noted that women who were referred for CABG more often had a history of unstable angina and congestive heart failure in the preoperative period [35]. Several studies reported significantly higher prevalence of comorbidities in women, such as DM, chronic kidney disease, and chronic lung disease [46]. According to the American group of researchers, among women who underwent CABG, unstable angina and a higher grade of angina pectoris were more common, they more often suffered from congestive heart failure, although left ventricular ejection fraction (LVEF) did not significantly differ depending on gender [35].

It is believed that a number of perioperative risks in women come from the mechanisms of hormonal regulation, which are different in men and women. Before menopause in women, estrogen plays a protective role in preventing the development of CAD, which has a cardioprotective effect through specific estrogen receptors [49]. With the onset of menopause, a loss of this protective component leads to a cascade of pathological processes, such as deterioration of endothelial function, increased systemic vascular resistance, activation of the platelet link of hemostasis, and a trend toward platelet aggregation [50, 51]. Estrogen deficiency in young women increases the risk of CAD by 7 times. Estrogen replacement therapy in the postmenopausal period does not show a protective effect. Operated women have more frequent microcirculation disorders, which is associated with hormonal deficiency and higher prevalence of DM compared to men [52]. Also, females are characterized by vascular hypersensitivity to serotonin, which is also considered as a causal factor in the development of adverse events after CABG [53].

An important role among the predictors of an immediate and long-term prognosis after CABG is attributed to baseline parameters reflecting the structural and functional state of the heart and coronary bed. Traditionally, predictors of early postoperative complications include LVEF < 50% and the degree of CA stenosis > 70% [9]. Compared to men, women undergoing CABG are more likely to have low LVEF [35] and more pronounced changes in the coronary bed [36].

The prognosis after CABG may be influenced by anatomical and operative factors. In particular, compared to men, CAs in women have a smaller diameter and are more often tortuous, which can make it difficult to perform more complete revascularization.

In their work, O'Connor et al. found that anterior descending artery diameter less than 1.5 mm increased the risk of in-hospital mortality [36]. It is reported that in women during CABG surgery, fewer distal anastomoses are applied, venous bypasses are used more often, and the left mammary artery is less commonly used as a conduit. At the same time, there are no differences between the genders in the remote patency of arterial bypasses, while lower rates are reported for venous bypasses in women. The reasons for these patterns continue to be the subject of discussion, in particular, the anatomical aspects already mentioned above are actively discussed. Another characteristic of the female population is insufficient development of the collateral circulation in severe stenosis or occlusion of the CA, especially in DM and postmenopausal women. The combination of these factors can affect both the duration of the surgery and its immediate outcomes [5, 6, 39, 40, 52].

Among the factors complicating the prognosis after surgical myocardial revascularization in women, one cannot but note psychosocial variables and QoL. Compared to men, women who underwent CABG had both more pronounced depression and a lower level of social adaptation. Since there is more pronounced comorbidity burden in operated women, they have lower QoL compared to men, both at baseline and six months after the intervention [35, 54].

Summarizing the above, we can conclude that a significant proportion of gender differences in terms of an early prognosis after CABG is explained by differences between men and women in baseline clinical characteristics, such as age, prevalence of risk factors for CVD and comorbid conditions, structural and functional state of the heart, and severity of CAD. Also, the gender effect can be influenced by anatomical and operative factors, in some cases limiting the possibility of complete myocardial revascularization in women.

As has been repeatedly noted, the gender difference in hospital outcomes of CABG is largely due to gender differences in baseline clinical characteristics. However, the situation changes in the longer term, in particular 3–6 months after the intervention. At this time, according to a number of studies, there is a discrepancy between the incident curves for clinically significant outcomes with less favorable trends observed in the female population [6, 10–12]. In these terms, the impact of operative factors on the further prognosis gradually decreases, and the most important issue in terms of long-term outcomes after

CABG is the effectiveness of secondary prevention of CVD [45].

One of the key approaches to improve the effectiveness of secondary prevention of CVD after CABG is cardiac rehabilitation. Participation in rehabilitation programs improves survival regardless of age, gender, program type, and intensity of moderate physical activity [45]. At the same time, along with the elderly and people with low socioeconomic status, women belong to a specific population which is less frequently referred for cardiac rehabilitation [55]. Subjectively, women tolerate CABG surgery relatively worse [24], it is more difficult for them to self-organize in the treatment of CAD due to fatigue, anxiety, depression, and the need to deal with household chores [56]. Another problem is that, in the long term, women are less committed to physical activity than men. Thus, 35% of women stop physical training 3 months after the end of the cardiac rehabilitation program [57]. These features can serve as potential barriers that reduce the effectiveness of secondary prevention of CVD in women after CABG.

Thus, apart from baseline clinical, structural, and functional variables, the long-term prognosis after CABG is largely influenced by the effectiveness of secondary prevention of CVD. A less favorable course of the late postoperative period in the female population may be due to higher incidence of perioperative MI, higher prevalence of anxiety and depression, lower QoL and social adaptation, and less active participation in rehabilitation programs compared to men.

CONCLUSION

In recent years, there has been an increase in the number of women undergoing CABG. At the same time, a number of publications report less favorable outcomes of CABG in women. In the course of this work, the review of the literature was carried out on factors explaining such gender differences. It was established that gender differences in early outcomes of CABG are largely explained by the peculiarities of the distribution of the baseline clinical characteristics between the genders. Compared to men, women undergo CABG at an older age, which largely explains a more burdened profile of CVD risk factors, comorbidity burden, structural and functional pathology of the heart, and CAD observed in them. In some cases, women are less likely than men to undergo complete myocardial revascularization, venous shunts are used more often, and the left mammary artery is less commonly used as a conduit. In addition to the baseline

clinical characteristics, a less favorable long-term prognosis after CABG in women may be contributed by higher incidence of perioperative MI, higher prevalence of anxiety and depression, lower QoL and social adaptation level after CABG, as well as less active involvement of women in rehabilitation programs, compared to men.

Thus, there is a need for raising doctors' awareness about the characteristics of the CVD course and the anatomical and surgical aspects of CABG in women. It is also necessary to increase the awareness of patients about RF correction and to involve them in educational technologies. Recommendations for the diagnosis and treatment of CVD should be developed taking into account gender. Further research is required to develop and implement gender-specific models for predicting surgical risks. Long-term follow-up is reasonable in women with a history of recent MI and DM. Correction of comorbidities is also essential. To further improve the clinical outcomes of CABG in women, it is necessary to develop approaches that promote more complete revascularization and reduce the incidence of perioperative complications, such as MI and pneumonia. More answers to questions about gender differences in long-term outcomes of CABG may be obtained by analyzing further studies with more female patients.

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