

Depression following coronary artery bypass grafting surgery revisited

Koroner arter baypas greftleme sonrası depresyon: Yeniden gözden geçirme

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Summary– Coronary artery bypass grafting (CABG) is the most common cardiac surgical procedure. Depression is a frequent comorbidity in patients with ischemic heart disease that can affect the course of the disease and the process of recovery after CABG. Depression after CABG is more common in women and is an independent predictor of mortality in long-term. However, fewer than half of cardiologists ask about depression symptoms in their patients, and with screening measures not being routinely utilized, depression remains under-recognized in this patient population. Treatment of depression in patients with ischemic heart disease can be challenging, considering unwanted medication side effects and interactions. The present report is a review of risk factors, prognosis, prevention, and treatment of depression in patients following CABG.

Depression is a recurrent comorbidity in patients with coronary artery disease (CAD) that can affect the course of the disease and the process of recovery after coronary artery bypass grafting (CABG). Depression is very common among patients suffering from cardiovascular disease (CVD). Between 31% and 45% of patients with CAD, including those with stable angina, unstable angina, or myocardial infarction (MI), have clinically significant depressive symptoms, and 15% to 20% of patients with CAD fulfill the diagnostic criteria for major depressive disorder (MDD).

^[1] The prevalence of MDD is 2 to 3 times higher in patients with CVD compared to general population.

^[2] The prevalence of depression after cardiac surgery is also influenced by the complexity of the surgical procedure (isolated CABG vs CABG with valve re-

Özet– Koroner arter baypas greftleme (KABG) en yaygın kalp cerrahisi girişimidir. İskemik kalp hastalarında depresyon sık görülen bir komorbidite olup hastalığın seyrini ve KABG sonrası derlenme sürecini etkileyebilmektedir. Koroner arter baypas greftleme sonrası depresyon kadınlarda daha sık olup uzun vadede mortalitenin bağımsız bir öngördürücüsüdür. Ancak kardiyologların yarısından azı hastalarında depresyon semptomlarını sorgulamakta olup rutin olarak tarama ölçümleri kullanılmadığından bu hasta popülasyonunda depresyon hâlâ düşük oranda tanınmaktadır. Diğer taraftan ilaçların yan etkileri ve etkileşimleri göz önüne alındığında iskemik kalp hastalığı olanlarda depresyon tedavisi zorlayıcı olabilmektedir. Burada KABG sonrası hastalarda depresyonun risk faktörleri, prognozu, önlenmesi ve tedavisi üzerine bir derleme sunuyoruz.

pair/replacement). Few studies have focused on patients undergoing CABG combined with valve surgeries. Oxlad et al.^[3] reported that 15.7% of patients undergoing such procedures had depression when evaluated in the first week after surgery.

Pirraglia et al.^[4] reported that poor social support, lower education level, less access to medical care, longer stay in intensive care unit after cardiac surgery and presence of at least 1 life stressor in the previous year were associated with depression after CABG.

Abbreviations:

CABG	Coronary artery bypass grafting
CBT	Cognitive behavioral therapy
CAD	Coronary artery disease
CVD	Cardiovascular disease
MDD	Major depressive disorder
MI	Myocardial infarction
PHQ	Patient health questionnaire
SSRI	Serotonin reuptake inhibitors
SNRI	Serotonin-norepinephrine reuptake inhibitor
TCA	Tricyclic antidepressant

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Less family support and living alone also increased the occurrence of depression following CABG. A study on depression after CABG in different age groups showed a higher prevalence among patients older than 73 years.^[5] On the other hand, in a study assessing 31 CABG cases, depression was more common among younger subjects 2 weeks and 4 weeks after surgery.^[6] Additionally, a higher preoperative score on the Beck Depression Inventory (BDI) was found to be a strong predictor of developing depression after CABG.^[7] Post-CABG depression, similar to its other forms, is more common in women.^[8] There could also be a familial tendency for development of depression after CABG.

A longitudinal cohort study from Duke Medical Center concluded that depression is, in fact, an important independent predictor of 12-year mortality after CABG, so patients with depression need to be closely monitored and appropriately treated.^[9] In another study, the presence of depression 1 month after CABG was an independent predictor of morbidity up to 5 years after surgery.^[10] In a prospective study with 1-year follow-up, patients with depression postoperatively experienced more cardiac events.^[11] Despite the significance of proper management of perioperative depression, studies reveal that cardiologists do not pay enough attention to detect depressive symptoms in patients undergoing CABG.

In a survey completed by 796 cardiovascular physicians, fewer than half said that they ask their CAD patients about symptoms of depression.^[12] The American Heart Association has suggested using self-administered depression screening questionnaire for patients suffering from CAD.^[13] We believe that screening patients undergoing CABG for depression prior to surgery and afterwards raises awareness among patients and their family members, thereby increasing the likelihood of reporting subtle mood changes and seeking early medical advice. One of the practical tools of depression assessment is patient health questionnaire (PHQ). The brief version of this

questionnaire (PHQ-2) comprises 2 questions about the symptoms of a major depressive episode: 1) Little interest or pleasure in daily activities, and 2) feeling down, depressed or hopeless.^[14] The complete questionnaire (PHQ-9) consists of 9 items including all symptoms of an episode of major depression.^[15] If there is a positive answer to either of the questions in PHQ-2, it should be followed by PHQ-9 (available online from http://www.phqscreeners.com/sites/g/files/g10016261/f/201412/PHQ-9_English.pdf). If the PHQ-9 score confirms the presence of depression, patient should be referred to a psychiatrist or psychologist. In a new meta-analysis, the important role of depression before and after CABG is highly emphasized.^[16] Considering the treatable nature of depression, systematic perioperative screening of patients for depression is crucial due to the hindering effects of depression on recovery after CABG.^[16] Table 1 provides examples of various perceptions and behaviors seen in patients presenting with depression following CABG.

Depression usually fades away in a few months after CABG; however, it may persist for years in patients with preexisting depression. In 2012, a group of researchers from Poland published a follow-up study of 53 patients who had undergone CABG. During the follow-up period, 7 patients died and 9 were lost to follow up. Among the remaining 37 patients 11 were still employed, 14 were disabled, 11 were retired and 1 was unemployed.^[17] Preexisting depression in patients who underwent CABG was associated with earlier recurrence of cardiac symptoms as well as increased readmission rates and immediate mortality.^[18] In a prospective study by Blumenthal et al.,^[9] risk of mortality was doubled in patients with preexisting moderate to severe depression prior to CABG.

Postoperative depression is also associated with adverse outcomes during recovery from CABG. Depression after CABG impairs physical and emotional healing^[19] and increases morbidity and mortality.^[5] Postoperative depression is also associated with de-

Table 1. Examples of patients' perceptions and behaviors when presenting with depression following CABG

Sense of uselessness and hopelessness	Sense of impending death
Inability to feel pleasure, sadness	Excessive crying and loss of interest in daily activities
Reluctance to communicate with family and friends	Physical and mental fatigue

CABG: Coronary artery bypass grafting.

layed wound healing, increased frequency of wound infections and higher risk of adverse cardiac events.^[20] Depression is associated with morbidity and mortality after surgery; anxiety disorders are most often associated with sudden cardiac death, in which ventricular dysrhythmia is suggested as underlying pathophysiological process.^[21]

With new advances and the improved outcome of CABG, the patient population undergoing CABG has grown older compared to earlier years. In Germany, 42.8% of patients who underwent CABG in 2002 were older than 70 years of age; however, this age group constituted only 24.9% of the cases in year 1994. Advanced age is a risk factor for mortality during perioperative period and is always present in the risk assessment tools used to predict mortality.^[22] With regard to the specific cluster of depressive symptoms, 2 new studies indicate that cognitive-affective symptoms (e.g., feeling worthlessness, pessimism, and self-blame) are associated with doubled risk of morbidity and mortality after CABG.^[23,24]

Increased morbidity attributable to the emotional distress in the setting of CAD can be explained with behavioral and biological mechanisms. Epidemiological studies have shown that the prevalence of risk factors for CAD such as obesity, hypertension, dyslipidemia, diabetes mellitus, sedentary lifestyle, and nicotine-dependence are high in individuals with psychoaffective disorders.^[15] In patients with anxiety and depression hypothalamic pituitary adrenal axis and serotonergic pathways are deregulated. Dysregulation of the monoamine balance in the central nervous system further affects inflammatory responses and platelet aggregation, 2 main processes that are crucial in the pathogenesis of atherosclerosis.^[25] Hormonal fluctuation plays an important role in cardiopathic effects of depression, as there is a surge in cortisol levels with subsequent activation of the adrenergic system and both contribute to vasospasm and activation of clot formation.^[26] In addition to a decrease in oxygen supply, there is an increase in myocardial oxygen demand as heart rate escalates and rate variability decreases in patients with significant mood disorders.^[25,26]

There is an ongoing National Institutes of Health-funded study that is examining pre-surgical blood flow in the brain as an independent risk factor for depression after CABG.^[27] Cerebrovascular disease may contribute to late-life depression (vascular depres-

sion hypothesis). Involvement of certain locations in the process could potentially predispose to or protect against depression.^[28] This concept is of clinical significance considering the potential implications for prevention and treatment strategies.

The incidence of depression is relatively high following CABG, especially after redo cardiac surgery in patients who live alone, smoke, and have had pre-existing anxiety disorders, as well as in patients with more severe and complex cardiac problems. Constant apprehension regarding the outcome of surgery can also provoke depression. Post-CABG depression particularly becomes problematic for patients in whom such an occurrence is not expected. During an interview with *The New York Times*, a cardiologist who had undergone CABG and a second operation at a later time for a ruptured appendix stated that the depression following CABG is different, probably due to the prolonged anesthesia or cardiopulmonary bypass process.^[29] He explained that he recovered much more quickly after his appendix operation.

In low-risk group of patients, physicians generally do not preoperatively discuss with them the possibility of mood disorders such as debilitating depression. Majority of patients develop depression at home after they have been discharged from the hospital, and it may be difficult for immediate family members to fully appreciate their mood changes after CABG. Delayed onset of depressive symptoms, along with the fact that most cardiac centers do not screen their patients for presence of depression at the time of discharge, generally results in decreased levels of vigilance in family members for mood alterations. Therefore, they may falsely attribute the resultant common symptoms of depression to failure in revascularization or surgical complication.

As is true for cognitive dysfunction after CABG, postoperative occurrence of depression is also affected by the duration of cardiopulmonary bypass, aortic cross clamping, perioperative anemia, and presence of coexisting cardiac disease. We acknowledge that most of these risk factors are not amenable to modification in order to decrease the probability of post-CABG depression. However, patients should be flagged as "high-risk" if they had more intra-operative contributory events, and in these patients, the extent of psychological screening should be increased. Patients who develop depression after CABG usually recover

within 6 months; however, during this period, they may need medical treatment or behavioral therapy and they definitely need strong social support. Treatment of depression after CABG may be different, but acknowledging the patient's emotions is of utmost importance, irrespective of the therapeutic modality. As a result, it is advisable to discuss the possibility of post-CABG depression before surgery so that patients are prepared to deal with depression even prior to CABG.

Treatment of depression in patients with CAD can be challenging, considering the unwanted side effects and interactions of various medications. One encouraging study published in 2006 reports that 50% of cardiologists try to treat depression once they notice depressive symptoms in patients with CAD.^[12] Physicians should be familiar with the adverse pharmacological effects of tricyclic antidepressants (TCAs) on the cardiovascular system, as they are particularly capable of producing serious dysrhythmia. It is reported that TCAs have more adverse cardiac effects than selective serotonin reuptake inhibitors (SSRIs) in patients with ischemic heart disease.^[30] Among this class of antidepressants, nortriptyline was once used to treat depression in patients with CVD. However, with the advent of SSRIs, these antidepressants are no longer prescribed in modern practice of psychiatry. In 1999, Shapiro et al.^[31] studied the efficacy and safety of SSRIs in patients with cardiac disease for the first time and found that sertraline was effective in treating patients with depression after MI without an increase in cardiac adverse effects.

In a large, randomized clinical trial from Canada (CREATE study), the efficacy of citalopram and interpersonal psychotherapy for treatment of depression in 284 patients with stable CAD was investigated. Citalopram was superior to placebo in reducing symptoms of depression in patients with CAD (higher remission rate and reduction in the scores on BDI-II and Hamilton Depression Rating Scale).^[32] Citalopram was well tolerated by the patients and its adverse cardiac effects were no different from the controls.^[32] Rollman et al.,^[33] in a study conducted in Pittsburg University, suggested citalopram as the treatment of choice for depression in patients with CAD and who were naïve to SSRIs, due to its minimal drug interactions in comparison to other medications in this class. In patients who already take SSRIs, it is recommended to

increase the dose of the medication. They also recommend trying 2 different SSRIs before prescribing other classes of antidepressants.

There are limited studies focusing on the efficacy and safety of additional classes of antidepressants in patients with cardiac disease. Mirtazapine, an antagonist of class-2 endogenous neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) receptors, has been studied on patients following an acute MI. Mirtazapine also possesses an antagonistic function on alpha-2 receptors and is well tolerated in patients convalescing from recent MI. In a randomized clinical trial, mirtazapine was effective in decreasing depressive symptoms with no effect on the incidence of recurrent cardiac events or mortality. However, mirtazapine causes weight gain and hyperlipidemia, which makes it unsuitable for patients with CVD.^[34]

In both clinical trials, bupropion was used as the back-up medication to treat depression in case of treatment failure. Bupropion is a serotonin-norepinephrine reuptake inhibitor (SNRI) with relatively lesser effect on the cardiovascular system and should be considered as the second choice for patients with CVD.^[35] Venlafaxine and duloxetine, which are both SNRIs, have not been investigated in patients with cardiac disease. However, considering the fact that venlafaxine possesses potential for raising blood pressure, it should not be used in patients with CVD unless the first line treatment with SSRIs fails.^[33]

Non-pharmacological treatment of patients with depression following CABG includes cognitive behavioral therapy (CBT) and supportive stress management. In a well-designed randomized clinical trial from Washington University, 123 patients who had developed major or minor depression within 1 year of CABG, were randomly assigned into 3 groups:^[36] 1) Forty patients received usual care by primary care or other physicians, 2) 41 patients received 12 weeks of CBT sessions for a duration of 50–60 minutes conducted by 2 clinical psychologists and 1 trained clinical social worker, and 3) 42 patients received 12 weekly sessions of supportive stress management with duration of 50–60 minutes, conducted by 2 clinical psychologists and 1 trained clinical social worker. Brief phone contacts and biweekly sessions as needed were also available. After 3 months, most patients in CBT group (71%), more than half (57%) in stress management group and one-third (33%) in usual

care group experienced remission of their depression symptoms. Within 6 months, the differences between the groups diminished, but in 9 months the differences increased, reaching 73% in CBT group, 41% in stress management group and 23% in the usual care group. It is clear that CBT is an effective therapeutic modality for depression after CABG. Supportive stress management is also effective in these patients; however, its efficacy is lower than that of CBT. Enrollment in cardiac rehabilitation programs has also been shown to have psychological benefit and reduce the level of depression and anxiety following coronary revascularization.

Conclusion

Depression frequently occurs following CABG, particularly in women, and is recognized as an independent predictor of long-term mortality. Depression remains under-recognized, as fewer than half of cardiologists ask about depressive symptoms in their patients. Additionally, screening measures remain underutilized in cardiology community. Citalopram is generally regarded as the treatment of choice for depression in patients with CAD in view of its minimal drug interactions. As for non-pharmacological treatment modalities, CBT has been shown to be effective for depression after CABG.

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