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Does the patient's physical activity affect the course of cardiac surgery - a comprehensive approach to cardiac surgery patients.

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ABSTRACT

Cardiovascular diseases represent a leading cause of morbidity worldwide. Over the past years, the field of cardiac surgery has significantly evolved. Globally, more than 2 million cardiac surgeries are performed annually. Among the main procedures are coronary artery bypass grafting (CABG), valve replacements, and heart transplants. The increasing number of patients requiring such treatment and, consequently, the rising number of procedures performed imply an improvement in their quality. With advancements in surgical techniques, the scope of patients eligible for procedures has also expanded. Patients undergoing cardiac surgeries are increasingly older and often suffer from significant comorbidities, such as hypertension and diabetes. Effective cardiac surgery significantly enhances the quality of life. When caring for a patient undergoing cardiac surgery, many aspects of the patient need to be considered to approach them holistically, while simultaneously creating an individualized treatment pathway. Not only the cardiac aspect but also various other factors need to be taken into account, including the patient's diet, medications, comorbidities, mental state, and physical activity. In this work, we emphasize the role of both postoperative and preoperative care for cardiac surgery patients, which, when properly executed, can be the key to the patient's recovery.

Key words: cardiac surgery, physical activity, cardiovascular diseases, comprehensive approach

INTRODUCTION

Cardiovascular diseases are the leading cause of disease burden globally [1]. In recent years, the field of cardiac surgery has advanced significantly. Annually, over 2 million cardiac surgeries are performed worldwide [2]. Major procedures in this field include coronary artery bypass grafting (CABG), valve replacement, and heart transplantation [3]. The increasing number of patients requiring such treatments, and consequently the rising number of procedures performed, necessitates an improvement in their quality. Alongside advancements in surgical techniques, the range of patients eligible for these procedures has also expanded. Patients undergoing cardiac surgery are increasingly older and often suffer from significant comorbidities such as hypertension and diabetes [4]. While successful cardiac surgery can substantially enhance quality of life, it is essential to remember that postoperative care for these patients is a crucial component of treatment. During this period, patients are at the highest risk for various life-threatening complications [3]. In the care of patients undergoing cardiac surgery, numerous aspects of the patient must be considered to adopt a holistic approach. These include the patient's nutrition, particularly potassium-related dietary considerations, medications, comorbidities, psychological state, physical activity, and many other factors that may be critical for some patients.

THE ROLE OF THE PRIMARY CARE PHYSICIAN

Firstly, it is important to mention the role of the primary care physician (PCP) in the care of patients undergoing cardiac surgery. Often, a patient who has been qualified for surgery by a specialist will visit their PCP during the preoperative period. The family doctor has certain responsibilities in preparing the patient for the planned surgery. A patient scheduled for cardiac surgery may ask their family doctor about the risks associated with their operation. To provide information on surgical risk, the family doctor can use existing tools in cardiac surgery to assess the risk of death. The most popular and widely used scale in Europe is the EuroScore and EuroScore Logistic scoring systems [5]. The scale is based on factors such as age, gender, coexisting heart, lung, or vascular diseases, and the type of planned surgical procedure. A score of 0 to 2 indicates low risk, with an estimated risk of less than 1%. A score of 3 to 5 indicates a moderate risk of death, approximately 3%. Patients with a score of 6 to 11 are considered

high-risk, with an estimated perioperative mortality exceeding 11%. Patients with a EuroScore above 12 are in the very high-risk group, and their qualification for surgery or disqualification must always be preceded by a detailed specialist analysis [6]. Information about coexisting diseases, especially potential heart rhythm disorders or hormonal issues, is crucial for the cardiac surgeon. Information on allergies, addictions, or the patient's psychological state can also be critical. It is essential to thoroughly review the medications, dietary supplements, and foods consumed by the patient daily, and, if necessary, modify treatment and diet. Special attention should be given to modifying anticoagulant therapy if the patient is taking such medications. It is also important to ensure that necessary tests are performed for the surgical procedure, including having a valid, confirmed blood group result and other tests previously ordered by the specialist, such as imaging tests (e.g., coronary angiography, echocardiography, ultrasound, endoscopy) and necessary consultations (e.g., dental), especially in the context of coexisting diseases (e.g., diabetes, kidney failure, neurological and psychiatric disorders). An analysis of the patient's lifestyle and the implementation of recommendations regarding preoperative exercise and physiotherapy are also advisable [5].

THE USE OF ANTICOAGULANTS

A cardiac surgery patient is often a patient with multiple medications. In this paper, we want to focus on the treatment with oral anticoagulants, which patients frequently take before and after cardiac surgery procedures. Anticoagulant treatment with oral medications for patients with heart and chest diseases is often associated with the use of vitamin K antagonists such as warfarin. The recent introduction of new oral anticoagulants (NOACs) targeting factor Xa or thrombin represents a novel approach to anticoagulant therapy. Cardiac surgeons must become familiar with these medications, as an increasing number of preoperative patients will be taking NOACs. Their rapid action, wide therapeutic range, and steady therapeutic state without the need for monitoring have made these new drugs more attractive in these indications than warfarin. Warfarin inhibits the vitamin K-dependent synthesis of calcium-dependent clotting factors and regulatory proteins C and S. Numerous food and drug interactions complicate the use of warfarin. Its narrow therapeutic index, requiring frequent monitoring, makes treatment difficult due to the need for frequent dose adjustments. The long half-life of warfarin (approximately 60 hours) means it takes several days to restore therapeutic anticoagulant levels after discontinuation. In emergencies, the effects of warfarin can be reversed with fresh frozen plasma, allowing patients to safely undergo surgery. Vitamin K provides an excess cofactor for

ongoing carboxylation of clotting factors in the presence of irreversible warfarin inhibition and thus requires the synthesis of new clotting factors to be effective. NOACs have many advantages over warfarin. One of the main advantages compared to NOACs is their reversibility. Currently available NOACs include rivaroxaban, apixaban, dabigatran etexilate, and edoxaban. They are more convenient to use than warfarin and have fewer drug-drug and food-drug interactions. Numerous large randomized clinical trials have confirmed the safety and efficacy of these NOACs. The number of clinical indications, such as the prevention and treatment of venous thromboembolism and stroke prevention in patients with non-valvular atrial fibrillation, is increasing. Currently, these drugs are not indicated for anticoagulant treatment of mechanical prostheses. In the future, cardiac surgeons will encounter more patients taking these drugs. Knowledge of the pharmacokinetic profile, discontinuation and resumption of surgical treatment, and management of severe bleeding is important in treating patients taking these drugs [7].

VITAMIN K

Vitamin K is essential in several physiological processes, such as blood clotting, where it serves as a cofactor in converting peptide-bound glutamate to γ-carboxyglutamate in vitamin K-dependent proteins. Vitamin K also performs functions independent of carboxylation. It acts as an electron carrier in ATP production in some organisms and prevents ferroptosis, a type of cell death characterized by lipid peroxidation [8]. Vitamin K-dependent proteins require carboxylation for their activity. The amount of vitamin K in the diet often limits the carboxylation reaction. For example, osteocalcin is fully carboxylated only when the diet is supplemented with vitamin K [10]. It is widely accepted that intestinal bacteria can also supply vitamin K [9]. Vitamin K1 appears to be primarily taken up by the liver, while vitamin K2 seems to accumulate preferentially in the arteries and extrahepatic tissues [11,12]. The enzymes involved in vitamin K-dependent carboxylation include gamma-glutamyl carboxylase (GGCX), vitamin K epoxide reductase (VKOR), and vitamin K reductase (VKR). Vitamin K's hydrophobic properties mean that these enzymes are likely integral membrane proteins found in the endoplasmic reticulum. Therefore, studying the structure and function of these enzymes presents a significant challenge [13].

HEALTH BENEFITS OF VITAMIN K

The health benefits of vitamin K extend beyond blood homeostasis and are associated with chronic low-grade inflammatory diseases such as cardiovascular diseases, osteoarthritis, dementia, cognitive impairment, and mobility disabilities. Naturally occurring vitamin K includes phylloquinone (vitamin K1) and a range of menaquinones collectively referred to as vitamin K2. These differ in their sources, absorption rates, tissue distribution, bioavailability, and target actions. The main sources of vitamins K1 and K2 are foods, with a notable increase in the selection of dietary supplements, primarily those derived from marine sources.

Vitamin K1 is a final product of the shikimate pathway in photosynthesis, thus it is found in all photosynthetic organisms, including plants, algae, and cyanobacteria. Major dietary sources of vitamin K include green leafy vegetables such as kale, romaine lettuce, broccoli, cabbage, and spinach. Vegetable oils, such as soybean, sunflower, olive, and canola oils, are the next best sources of dietary vitamin K1. Smaller amounts of K1 can also be found in fruits, grains, meat, and dairy products. Vitamin K2 is primarily produced by bacteria, except for MK-4, which can be synthesized by tissue-specific conversion from vitamin K1 in animals. This reaction is catalyzed by an enzyme containing the UbiA prenyltransferase domain 1, which uses menadione as an intermediate. Other main sources of vitamin K2 include meat, especially chicken, bacon, and ham. Additionally, egg yolks and high-fat dairy products such as hard cheeses provide appreciable amounts of this vitamin [14].

The most commonly prescribed oral anticoagulants worldwide are vitamin K antagonists (VKAs), including warfarin. Factors affecting the pharmacokinetics of VKAs are crucial because deviations from their narrow therapeutic window can result in bleeding due to excessive anticoagulation or thrombosis due to inadequate anticoagulation. Besides pharmacodynamic interactions, interactions with drugs, food, herbs, and over-the-counter medications can impact the risk-benefit ratio of VKAs [15].

When using VKA therapy, a therapeutic INR range of 2.0–3.0 is recommended for the prevention of embolic complications in non-valvular atrial fibrillation, and for the treatment of deep vein thrombosis and pulmonary embolism [16]. Warfarin is characterized by significant variability in individual dose response and a narrow therapeutic window (the international normalized ratio [PT-INR] must be maintained between 2.0 and 3.0 for most indications). Clinical outcomes are strongly correlated with the time that patients' PT-INR values remain within the appropriate range [15]. Patients whose mean individual time in the therapeutic range

is >70% are at low risk of experiencing a major bleeding or thromboembolic event [17]. Therefore, frequent monitoring of PT-INR values and dose adjustments are necessary for the safe and effective use of warfarin [18].

Warfarin absorption decreases with the concomitant use of cholestyramine and sucralfate [19]. Since warfarin is highly protein-bound, other substances or medications competing for protein binding sites (e.g., ibuprofen, quinidine, fenofibrate, losartan, valsartan, amlodipine, felodipine, sulfinpyrazone, phenylbutazone, and the major metabolite of chloral hydrate, i.e., trichloroacetic acid) displace warfarin, enhancing the anticoagulant effects of VKAs [20]. Long-term consumption of St. John's wort results in a clinically significant reduction in the pharmacological effect of warfarin. Soy extracts can attenuate the anticoagulant effects of warfarin, as they contain substantial amounts of vitamin K. The most important advice for patients is to maintain their usual diet, as warfarin-food interactions generally have no clinical implications when patients adhere to a consistent diet [15].

MENTAL HEALTH

It is important to remember that every somatic patient also has psychological needs that require care and should not be neglected. Depression is highly prevalent in the general population; however, among patients undergoing cardiac surgery, the incidence of depression is significantly higher. Between 20-47% of this population suffers from preoperative depression, and postoperative depression affects approximately 23-61% of patients following cardiac surgeries [21-27].

The main risk factors for postoperative depression after cardiac surgery include female gender, younger age, previous depressive episodes or a family history of depression, and a history of preoperative depression. Social factors, such as lower educational level, lower level of social support, or social isolation, also contribute. Emergency surgery and longer hospital stays increase the likelihood of developing postoperative depression. The risk factors for preoperative depression are similar but also include exertional and resting dyspnea (leading to a higher NYHA classification) and a history of myocardial infarction. Knowing these risk factors is crucial in identifying patients vulnerable to depressive disorders and ensuring they receive timely psychiatric/psychological care. Screening questionnaires for depression in cardiac surgery patients include the Patient Health Questionnaire 9 (PHQ-9), the Centre for Epidemiological Study of Depression (CES-D), the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale (HADS), and the Cardiac Depression Scale (CDS) [3].

Depression is an independent risk factor for developing heart diseases. Individuals with depression have twice the risk of dying from cardiovascular diseases (CVD) [28]. This condition may also lead to smoking, reduced physical activity, poor dietary choices, and even less adherence to medical recommendations [29-32]. Such health behaviors can necessitate surgical intervention due to worsening heart disease. Preoperative depression is associated with a poorer quality of life, poor functional status, increased postoperative pain, longer hospital stays, and higher mortality after CABG and valve surgery [33-36].

Postoperative depression is also associated with greater postoperative pain, lack of functional improvement in patients six months post-surgery, a twofold increase in the risk of hospital readmission, a significant risk of atherosclerotic complications, and increased mortality after coronary artery bypass grafting (CABG), as well as increased overall mortality within ten years after cardiac surgeries. Thus, both preoperative and postoperative depression are linked with poor clinical outcomes and prognosis. Therefore, understanding the pathophysiology underlying depression after cardiac surgery and finding effective methods to prevent and treat depression in this population is crucial [3]. The pathophysiology of depression in patients with cardiovascular diseases includes physiological and behavioral factors. The former group consists of dysregulation of the autonomic nervous system (ANS), dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, inflammation, and platelet abnormalities. The latter group includes reduced adherence to medical recommendations, decreased cardiac rehabilitation, poor diet, and physical inactivity. These factors are summarized in the diagram below.

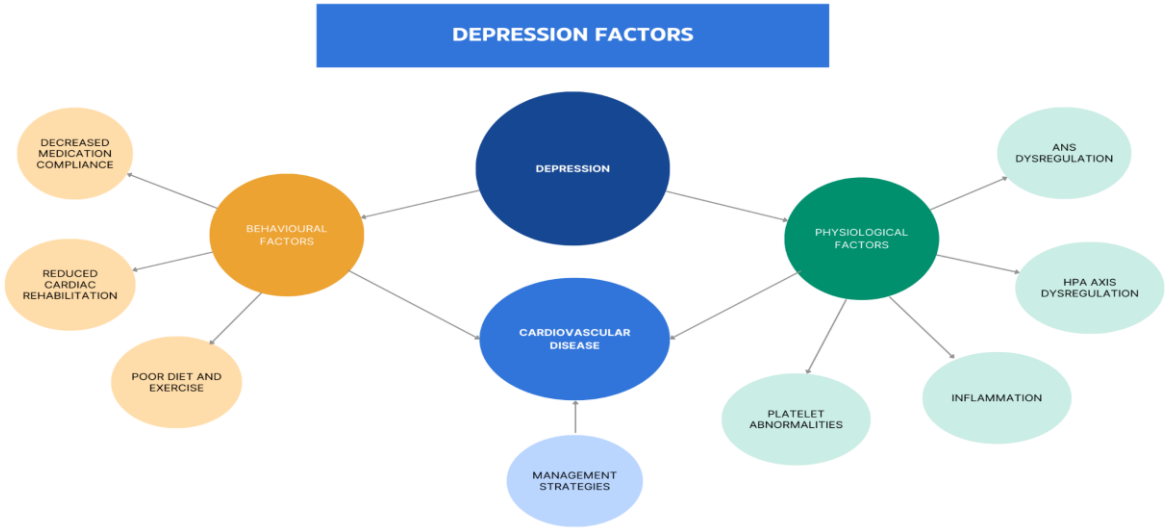

Fig. 1. Factors of Depression
Source: Diagram created based on the article: Vu T, Smith JA. The pathophysiology and management of depression in cardiac surgery patients. Front Psychiatry. 2023 Oct 20;14:1195028. doi: 10.3389/fpsyt.2023.1195028. PMID: 37928924; PMCID: PMC10623009, made in Canva

As for the methods to cope with depression in these patients, we can distinguish between preventive and management strategies. Preventive strategies include preoperative and postoperative education and cardiac rehabilitation. Meanwhile, therapeutic strategies can be divided into pharmacological and non-pharmacological approaches. Pharmacological treatments include statin therapy and antidepressants, while non-pharmacological approaches encompass psychotherapy and education. A summary of these methods is presented in the diagram below.

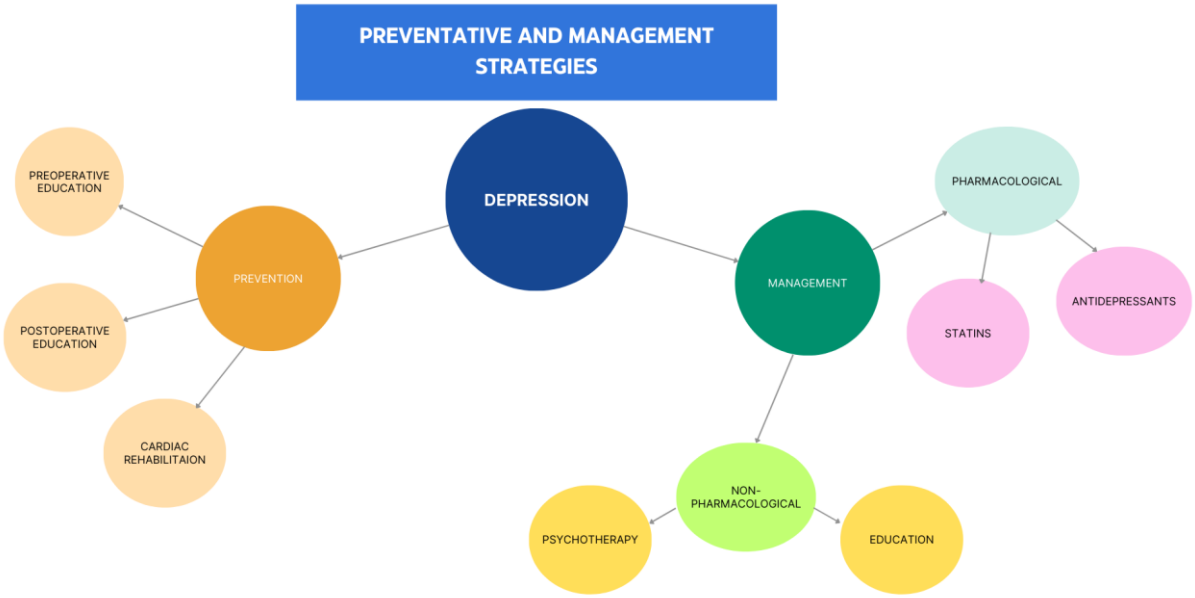

Fig. 2. Strategies for Prevention and Coping with Depression

Source: Diagram created based on the article: Vu T, Smith JA. The pathophysiology and management of depression in cardiac surgery patients. Front Psychiatry. 2023 Oct 20;14:1195028. doi: 10.3389/fpsyt.2023.1195028. PMID: 37928924; PMCID: PMC10623009, made in Canva

In summary, it is important to remember the significance of psychiatric assessment of patients undergoing surgery, both before and after the procedure, maintaining heightened vigilance among high-risk patients, and ensuring all patients receive adequate support, counseling, and treatment.

One way to assist patients may be through social support. It has been demonstrated that social support in the first month after surgery can reduce the likelihood of postoperative

depression and impairment in activities of daily living (ADL) six months after the procedure. In clinical psychology, three fundamental stages of managing cardiac surgery patients can be distinguished: preparing the patient for surgery, postoperative ward contact, and psychoeducation before discharge. Clinical psychologists' interventions in these patients focus on two complementary areas. The first area involves emotional state and tension relief related to the surgery. This is where patients can express their concerns, moods, and thoughts about the procedure. The second area involves cognitive level and aims to provide necessary information about the surgery and recovery process. Interventions in both areas should complement each other, forming a direct response to the patient's presented needs. The goal is to shape realistic, genuine, and accurate expectations regarding the postoperative period and promote appropriate patient attitudes.

Postoperative pain is an inherent element of surgical procedures. Many studies show that effective management of postoperative pain significantly reduces hospitalization time and costs, as well as the number of complications associated with surgery, especially in high-risk patients and those undergoing extensive operations. At the same time, commonly used methods are often not adequately tailored to patients, making their rehabilitation more challenging and prolonging their return to full physical activity. It is essential to address PPP - persistent postoperative pain, which is a significant complication of cardiac surgery procedures. The most common methods for postoperative pain management include non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, often in combination with various local anesthesia techniques, such as infiltration and epidural anesthesia. As for the method of drug administration, continuous opioid infusion, patient-controlled analgesia (PCA), peripheral nerve blocks, analgosedation, preventive analgesia, and epidural anesthesia can be used [38]. In the conducted observational study [38], 216 patients operated on surgical wards of the University Clinical Hospital in Bialystok were examined in late 2017 and 2018, including a group of 112 patients from the Department of Cardiac Surgery undergoing procedures such as coronary artery bypass grafting (CABG), transcatheter aortic valve implantation (TAVI), ascending aortic aneurysm surgery, aortic arch aneurysm repair, minimally invasive direct coronary artery bypass (MIDCAB), and procedures performed due to congenital and acquired heart defects. The way the patient was admitted to the hospital, the type of procedure performed, the condition of the postoperative wound, the type of analgesic drugs used, and their effectiveness were analyzed. A 10-item questionnaire and a numerical pain rating scale (NRS) were used. Pain was monitored for 0 to 10 days after the procedure. The researchers concluded that the form of patient admission to the hospital, the condition of the postoperative wound, and the use of an

appropriate pain relief method significantly influenced the level of pain experienced. Patients operated on in an emergency mode were characterized by significantly higher pain intensity on the NRS scale compared to patients hospitalized in a planned manner. The least intense pain after the procedure was experienced by patients who did not have postoperative wound drainage. The most effective methods of postoperative pain management were analgosedation, PCA, and preemptive analgesia. Researchers are also looking for non-pharmacological methods of pain management in cardiac surgery patients. Studies are being conducted using methods such as hypnosis and virtual reality [39,40]. Due to the existence of many pain management methods and their varying levels of effectiveness, it is essential to find which method of managing postoperative pain is the best and how to adapt it to each patient.

REHABILITATION

Hospitalization and immobilization of a patient, which are inherent parts of cardiac surgical procedures, are associated with an increased risk of long-term cognitive and physical impairments. Therefore, it is crucial to turn towards appropriate rehabilitation, which can facilitate the patient's return to health.

A study was conducted to assess the role of cardiac rehabilitation and its effects on patients after heart valve surgery [41]. Patients were randomly assigned to two groups. The early rehabilitation group performed exercises in sitting, standing, and walking positions, followed by endurance training. The control group received usual care without engaging in any physical activity. Physical fitness was assessed using the Short Physical Performance Battery (SPPB) and other measurement tools. The results of the SPPB and 6-minute walking test at hospital discharge showed that early rehabilitation significantly improved physical endurance. Patients in the intervention group also achieved better long-term outcomes after 6 months compared to the control group. Additionally, participation in early cardiac rehabilitation was associated with a significant reduction in mortality. This occurs because early cardiac rehabilitation contributes to a positive return to physical function after surgery and shortens hospital stays. Physical activity positively affects low-density lipoprotein cholesterol levels and blood pressure regulation, thereby preventing mortality. Therefore, early cardiac rehabilitation appears to be an effective method for improving physical fitness and survival rates in patients after heart valve surgery.

Another interesting method of perioperative patient care is ERAS, which stands for Enhanced Recovery After Surgery, also known as Fast Track Surgery (FTS). By definition,

ERAS is a multimodal and multidisciplinary evidence-based approach to surgical nursing aimed at optimizing perioperative management and prognosis to reduce the patient's response to surgical stress, lower postoperative complications, promote functional recovery, shorten hospital stays, and achieve rapid rehabilitation effectiveness [42]. The ERAS method includes preoperative, intraoperative, and postoperative care. Preoperative ERAS involves pre-admission counseling, screening tests/support for nutrition, medical optimization of chronic diseases, avoiding prolonged fasting, carbohydrate loading, antibiotics, and, if necessary, thromboprophylaxis. Intraoperative ERAS includes minimally invasive surgical techniques, standardized anesthesia techniques, selective drain use, avoiding fluid overload, and maintaining normal body temperature. Postoperative ERAS, aimed at improving rehabilitation and patient recovery, includes avoiding nasogastric tube placement, early oral fluid and solid intake, early removal of urinary catheters and intravenous infusion tubes, preventing nausea and vomiting, using non-opioid pain medications, early mobilization, and preparation for early discharge. There are reports that these measures can be applied to cardiac surgery patients to accelerate their rehabilitation, shorten extubation time and length of hospital stay, and improve their satisfaction with nursing care. ERAS nursing, therefore, accelerates postoperative recovery, improves treatment outcomes, and is highly accepted by patients [43].

It should be emphasized that in recent decades, physical exercises in patients with heart diseases, alongside pharmacological treatment or lifestyle changes, have become an essential treatment method, which cannot be underestimated.

Another aspect worth addressing in the context of cardiac surgical patient rehabilitation is preoperative exercises. The relationship between preoperative exercises and postoperative recovery after cardiac surgery has been analyzed in many studies, which were subjected to meta-analysis [44]. According to it, active preoperative exercises in cardiac surgery patients can be helpful in postoperative recovery. In the included studies, exercise programs included inspiratory muscle training, aerobic exercise, resistance training, and stretching. It has been shown that physical activity has a positive impact on many physiological processes in cardiac patients. It reduces oxygen consumption by the heart muscle and cardiac workload, improves lipid metabolism and carbon dioxide in the blood, and increases cardiac reserve. Active exercises can increase heart rate, improve cerebral blood flow, increase ventilation, and promote body regeneration. They can also effectively improve and correct the imbalance of coronary artery endothelial function, promoting the rehabilitation process in patients with coronary heart disease. Physical therapy can improve joint range of motion, stimulate blood circulation, increase muscle tension, regulate the function of major organs, and improve mood

and ability to perform daily activities. Exercises can improve cerebral blood flow, increase heart rate, increase ventilation, and promote regeneration. It has been shown that active physical activity in the preoperative period can shorten the stay in the postoperative intensive care unit and reduce postoperative complications in patients undergoing CABG. Also, physical fitness after surgery was better in the exercising group before surgery compared to the non-exercising group. Researchers have also shown that prophylactic physiotherapy involving preoperative inspiratory muscle training for 5 days before cardiac surgery increases the intensity of inspiration, reduces the frequency of postoperative lung complications, and shortens hospital stay. This training improves forced vital capacity, forced expiratory volume in one second, and maximum voluntary ventilation in the first second of cardiac surgery, which can improve cough ability, sputum expectoration, and reduce postoperative pulmonary complications. Therefore, not only postoperative rehabilitation but also appropriate preoperative exercises have a significant impact on the healing process of cardiac surgical patients [44].

PREHABILITATION

A good summary of the comprehensive approach to a patient undergoing cardiac surgery is to focus on the concept of prehabilitation. It is a procedure aimed at improving the overall health and well-being of the patient before planned surgical treatment to modify the risk factors for treatment-related complications, increase physiological reserves, and improve the body's tolerance to stress. This procedure is currently a rapidly evolving area of comprehensive perioperative care, which plays a significant role in surgery, especially planned surgery. It includes finding patient-dependent factors that reduce the risk of treatment-related complications, such as good physical fitness, proper nutrition, motivation, optimization of coexisting diseases, and lack of active addictions. Key to improving treatment outcomes is to create a path for the patient that includes systemic support throughout the treatment process, from the beginning to its full completion. Despite many limitations encountered in implementing prehabilitation into the healthcare system, such as lack of appropriate education, financial, time, and social limitations, it is worth striving to introduce at least some of its elements into patient care. With proper patient and medical staff education, and above all, cooperation of involved individuals at various levels, prehabilitation can be crucial in improving treatment effectiveness. Finally, we present a table illustrating comprehensive patient care, including rehabilitation elements at various stages of treatment [45].

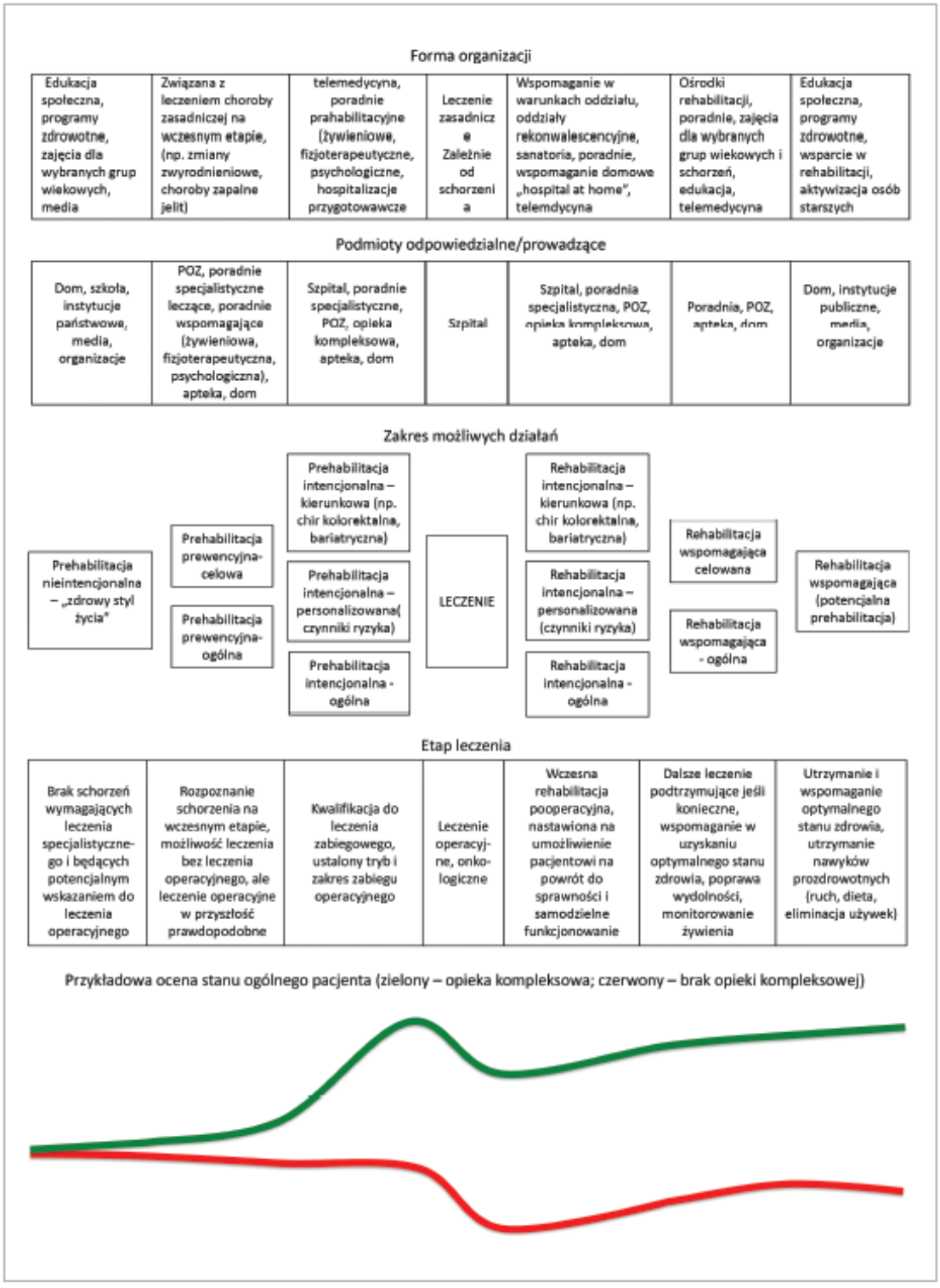

Fig. 3 Comprehensive patient care, including prehabilitation elements at each stage of treatment.

Source: Banasiewicz T, Kobiela J, Cwaliński J et al. Recommendations for the use of prehabilitation, i.e., comprehensive patient preparation for surgical procedures. Pol Przegl Chir. (2023);95(4):61-91. https://doi.org/10.5604/01.3001.0053.8854.

CONCLUSION

According to many data sources, the number of cardiac surgical patients will increase over the years. This means that physicians of various specialties will increasingly encounter these patients, and it is important for them to know how to care for them. There is a need for more research to create more accurate guidelines for the care of cardiac surgical patients and to establish a consistent, holistic pre- and post-operative management plan that allows for an individual approach to each patient. Chronic patient treatment, comorbidities, dietary habits, physical activity, psychological care, and social support should all be taken into account. It is also important to remember that the healing process of a cardiac surgical patient does not end with the operation; rather, it is actually the beginning of their recovery. The success of the entire therapy depends on a well-managed postoperative and preoperative period.

DISCLOSURE

Author'scontribution

Conceptualization, GRS, DM, PSR, KK; methodology, GRS; software, KK; check, GRS, PSR, KK and DM; formal analysis, DM; investigation, PRS; resources, KK; data curation, DM; writing - rough preparation, PSR; writing - review and editing, GRS; visualization, GRS; supervision, KK; project administration, PSR; receiving funding, no specific funding.

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The authors deny any conflict of interest

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