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# Cardiovascular Diseases in Patients with Renal Transplantation

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Daniela Loncar and Selma Hodzic

Additional information is available at the end of the chapter

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## Abstract

Kidney transplantation has become the primary method of treating severe chronic renal failure. The first successful kidney transplant was performed in 1954 in Boston, the graft was in function for 7 years, and patient died because of the heart disease. Cardiovascular disease is the leading cause of death in patients with a transplanted kidney. Despite the fact that patients with a transplanted kidney are highly susceptible to infections and have an increased tendency to develop malignant diseases, these patients die mainly of cardiovascular disease. Patients with a transplanted kidney are exposed to atherogenic risk which is associated with previous dialysis treatment and the use of immunosuppressive drugs. An excessive risk of developing cardiovascular disease in patients with a transplanted kidney is due to the high frequency and accumulation of atherogenic risk factors before and after transplantation. Pre-transplant cardiovascular disease is a major risk factor for the development of post-transplant cardiovascular disease. Risk factors for the development of cardiovascular diseases in patients with a transplanted kidney are divided into traditional and nontraditional. Traditional risk factors such as immutable (age, gender, and inheritance) and variable (smoking, hyperlipidemia, hypertension, obesity, diabetes mellitus, physical activity, stress). Nontraditional risk factors such as risk factors related to the status of transplantation and its treatment and risk factors associated with chronic regression in allograft function. The most common cardiovascular diseases in patients after kidney transplantation are as follows: ischemic heart disease, congestive heart failure and left ventricular hypertrophy. Of all cardiovascular complications, ischemic heart disease is by far the most common cause of mortality (more than 50%) in patients with a transplanted kidney. Frequency of left ventricular hypertrophy ranges from 50 to 70% in patients with a transplanted kidney. Early detection of high-risk patients for the development of cardiovascular diseases allows timely application of an appropriate therapeutic strategy that ensures high survival rates for patients with a transplanted kidney.

**Keywords:** kidney transplantation, risk factors, traditional risk factors, nontraditional risk factors, cardiovascular disease

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## 1. Introduction

### 1.1. History of transplantation

Organ transplantation is one of the greatest achievements in history of medicine in the twentieth century. Kidney transplantation has become the primary method of treating severe chronic renal failure. The first successful kidney transplant was performed in 1954 in Boston, the graft was in function for 7 years, and patient died because of the heart disease. Over the past decades, organ transplantation has achieved incredible proportions through the development of surgical techniques, organ preservation methods, new diagnostic procedures, but, in particular, through discovery of powerful immunosuppressants.

### 1.2. Kidney transplant recipients

#### 1.2.1. *Becoming a kidney recipient*

Kidney transplantation has become the primary method of treating severe chronic renal failure. After kidney transplantation, life is better, more quality and longer than during dialysis. It is recommended that all patients in end-stage kidney disease should be considered as potential kidney transplant recipients no matter of absolute contraindications. Because of the lack of available organs for transplant and all possible risks of immunosuppressive drugs, careful consideration and adequate preparation of patients are indispensable. All studies related to the preparation of the transplant patient are covered by a protocol that includes detailed medical history, physical examination, system review including an examination by a psychologist. To be considered as transplant recipient, patient should be put on the transplant program's waiting list. To select recipients from a deceased donor in our country, we use the prescribed criteria. Among these criteria, an important place includes a blood type, match between the recipient and the donor, tissue typing, length of time on the dialysis and sensibility of the recipient [1].

#### 1.2.2. *Contraindications for kidney transplantation in the recipient*

Contraindications for kidney transplantation in the recipient may be absolute, relative and temporary. Absolute contraindications: contraindications for general anesthesia or surgery, metastatic malignancy, refractory cardiac decompensation, chronic respiratory insufficiency, advanced coronary or cerebrovascular disease, coagulopathy, chronic infection, mental retardation, psychosis, alcoholism, drug addiction. Relative contraindications: frequent respiratory infections, heart failure with frequent exacerbations, frequent digestive bleeding, previous malignancy, primary renal disease with a high degree of postoperative recurrence.

Temporary contraindications: tuberculosis and other chronic infections, bleeding, unexplained focal infection, unresolved bladder anomalies, arterial hypertension with complications, pronounced secondary hyperparathyroidism.

### **1.3. Kidney transplant donors**

The kidney can be transplanted from deceased-donor (cadaveric transplantation) or from living-donors: genetically related (living-related) or nonrelated (living-unrelated) transplants, depending on whether a biological relationship exists between the donor and recipient. The basic prerequisite is for the donor to be mentally and physically healthy and willing to give the kidney. Numerous studies have shown that there are no proteinuria, hypertension or renal insufficiency in the carefully selected donors at 10 and 20 years after the kidneys in relation to the healthy population.

### **1.4. Pre-emptive kidney transplant**

A pre-emptive kidney transplant (before kidney function deteriorates to the point of needing dialysis) should be offered to all candidates for transplantation who have a potential live donor. Earlier kidney transplants from a cadaveric donor can be offered to all potential recipients, but of particular importance are for children and patients with diabetes mellitus. To do the preemptive kidney transplantation, two conditions must be fulfilled: the patient must have irreversible and progressive renal impairment and the creatinine clearance must be less than 15 ml/min. Numerous studies have shown that survival of patients and calves after pre-emptive kidney transplantation was the same or even better than the transplantation done after the dialysis began [2].

### **1.5. Surgical procedures in kidney transplantation**

Transplantation of the kidneys is a surgical procedure where the donor's kidney is placed in the lower part of the abdominal cavity of the recipient. The renal artery and veins connect to the large pelvic artery and vein of the recipient. The urinary tract of the transplanted kidney is attached to the recipient's bladder.

### **1.6. Immunosuppressive therapy**

Renal transplantation is an important form of treatment for patients with terminal renal insufficiency. However, an obstacle to the success of the greatest number of transplants represents the immune response of a recipient directed against the transplanted kidney.

Due to the constant immunological response to renal allograft, permanent immunosuppressive therapy is carried out to prevent graft rejection. Theoretically, it should not be used only on identical twins. The basis of immunosuppression is a calcineurin inhibitor that is combined with corticosteroids and mycophenolate mofetil (Cellcept). Immunosuppressive drugs have enabled the success of organ transplantation, but they do not only act to prevent rejection of the transplanted organism but also they have numerous side effects on the body. Important

side effects of immunosuppressants are the increased risk of infection and the atherogenic effect of immunosuppressive therapy.

### 1.7. Transplantation complications

The early period after kidney transplantation relates to the first 2 months after the surgery [3]. Acute surgical complications (bleeding, thrombosis of the transplanted kidney) are common in first few days after surgery, other clinical and immunological complications occur later.

Reactions of graft rejections are classified into four types based on the clinical picture, but differ in pathogenesis, histomorphological picture, and reactions own flow [4]. Those are hyperactivity, acceleration, acute and chronic rejection. Hyperacute rejection occurs in the first minutes or hours after kidney transplantation. Accelerating rejection begins 5–7 days after kidney transplantation and is demonstrated by rapid deterioration of the graft function. Acute rejection usually occurs from the fifth day to the end of the third month after kidney transplantation, but it can occur later on. Chronic graft rejection signifies the process in which transplanted kidney progressively deteriorates for several months and years, although the transplantation was successful in the first place. Other complications after kidney transplant are: urological complications, cardiovascular diseases, infections, gastrointestinal tract and liver diseases, malignant tumors, skin, bone and muscle diseases [4].

## 2. Risk factors for cardiovascular disease after kidney transplantation

Risk factors for the development cardiovascular diseases in patients with a transplanted kidney are more common than the risk factors in the general population.

They include traditional risk factors, such as arterial hypertension, diabetes mellitus, hyperlipidemia, and nontraditional risk factors associated with reduced glomerular filtration, such as anemia, hyperhomocysteinemia, or factors typical for transplantation, including direct effects of immunosuppression or rejection [5].

Patients with a transplanted kidney are exposed to atherogenic risk which is associated with previous dialysis treatment and the use of immunosuppressive drugs. An excessive risk of developing cardiovascular disease in patients with a transplanted kidney is due to the high frequency and accumulation of atherogenic risk factors before and after transplantation. Pre-transplant cardiovascular disease is a major risk factor for the development of post-transplant cardiovascular disease [6].

Cardiovascular diseases represent the most frequent cause of morbidity and mortality in patients at the end stage of renal diseases. Left ventricle hypertrophy occurs in 75% of patients treated by chronic dialysis. The prevalence of coronary heart disease in patients who are treated by chronic hemodialysis is 40%. The frequency of congestive heart failure in patients undergoing hemodialysis is 46%. Cardiac diseases represent the leading cause of death of dialyzed patients of which sudden cardiac death is the most frequent that is responsible for

around 25% of all deadly outcomes. The rate of cardiovascular mortality in patients undergoing chronic dialysis is nearly 9% per annum. In patients treated by chronic dialysis, the risk of development of CVD is 10–20 times higher than in general population. Uremic milieu contributes to occurrence of atherosclerosis and atherosclerotic cardiovascular complications and often the development of accelerated, galloping atherosclerosis is present. The patients undergoing chronic dialysis are exposed to traditional and nontraditional risk factors for the development of cardiovascular complications. Nontraditional risk factors are the consequences of the uremic milieu and are related with the dialysis technique itself, and they are divided into hemodynamic and metabolic risk factors. Hemodynamic risk factors are anemia, retention of sodium and water, arteriovenous (AV) fistula, while the metabolic risk factors are hyperhomocysteinemia, hypoalbuminemia, oxidative stress, microinflammation and secondary hyperparathyroidism.

Risk factors for cardiovascular diseases in patients with a transplanted kidney are divided into traditional and nontraditional [5]: traditional risk factors are: immutable (age, gender, and inheritance), variable (smoking, hyperlipidemia, hypertension, obesity, diabetes mellitus, physical activity, and stress); and nontraditional risk factors are: risk factors related to the status of transplantation and its treatment (immunosuppressive agents, graft rejection, and viral infection – cytomegalovirus) and risk factors associated with chronic regression in allograft function (anemia, volume load, hyperhomocysteinemia, oxidative stress, secondary hyperparathyroidism, and microinflammation).

### 2.1. Traditional risk factors

Smoking is not only a risk factor for the development of cardiovascular diseases, but is also associated with the risk of developing chronic kidney disease defined as a reduction in glomerular filtration to  $<45 \text{ ml/min/1.73 m}^2$ . Long-term smoking of more than 20 cigarettes per day is associated with 1.52 times higher relative risk of chronic kidney disease [7]. For comparison, smoking and obesity are associated with a 1.77 times higher relative risk of chronic kidney disease. These risks are more conspicuous in men than in women. Smoking begins and improves the process of atherosclerosis in the blood vessels. In various studies, it has been shown that smoking leads to cardiovascular complications, reduces survival of the patient and graft, and its effect on patient survival is similar to the same one on patients with diabetes mellitus [8]. Smoking cigarette is an independent risk factor for the development of cardiovascular events in patients with a transplanted kidney. In the population of patients with transplanted kidney, the prevalence of smoking is 25%, and the smoking cessation includes pharmacological therapy – NRT (nicotine replacement therapy).

Risks of cardiovascular diseases increase with increasing body weight because it increases the blood pressure, serum lipids, and glucose intolerance. A particularly harmful factor is the central obesity characterized by an increase in intra-abdominal fat tissue. Central obesity (waistline  $>88 \text{ cm}$  for women and  $>102 \text{ cm}$  for men) is a risk factor for declining allograft function in patients with a transplanted kidney. Obesity fosters the development of the insulin resistance, diabetes mellitus, ischemic heart disease, and reduces survival of allograft [9].

A cohort study by Adabag of 14,941 men and women, aged 45–64 years, showed that obesity was associated with an increased risk of sudden cardiac death [10]. According to research by Chan, obesity is a risk factor for the development of cardiovascular disease following kidney transplantation [11]. Although the role of obesity in the pre-transplant period is uncertain, after kidney transplantation, obesity increases the risk of graft failure and mortality.

Weight loss reduces and changes other risk factors for the development of cardiovascular disease [12]. Metabolic syndrome is a risk factor for the development of cardiovascular disease in patients with a transplanted kidney. It is characterized by obesity (central type of obesity), physical inactivity, hypertension (arterial blood pressure greater than 130/80 mmHg), hyperlipidaemia (triglycerides greater than 1.7 mmol/l, HDL cholesterol less than 1.0 mmol/l in men and less than 1.3 mmol/l in women) and systemic insulin resistance (fasting blood sugar greater than 6.5 mmol/l). Six years after kidney transplantation, 63% of patients have criteria for metabolic syndrome, reduced survival of allograft and an increased number of cardiovascular incidents [9].

Diabetes mellitus is one of the most common causes of renal disease, this disease independent and in itself increases the risk of cardiovascular disease. The results of two large clinical studies, Framingham Study and Multiple Risk Factor Intervention Trial (MRFIT) show that diabetes mellitus doubles the possibility of coronary artery disease in men and triples the risk of coronary artery disease in women [13]. Diabetes mellitus is a relatively common complication after kidney transplantation and is defined as a fasting glucose greater than 7 mmol/l. The incidence of diabetes mellitus is between 3.6 and 18% and depends mainly on immunosuppressive therapy. Kidney transplantation can lead to the deterioration of existing diabetes mellitus or to the development of “de novo” diabetes mellitus. The most common cause of post-transplantation diabetes mellitus is corticosteroid therapy, and it depends on immunosuppressive therapy. The two main mechanisms by which corticosteroids cause diabetes mellitus are inducing insulin resistance and increasing body weight [14]. Immunosuppressive drugs can lead to the development of diabetes. The prevalence of post-transplant diabetes in patients treated with cyclosporin ranges from 2.5 to 20%. The treatment of diabetes in hospitalized transplant recipients requires attention to a multitude of factors that can impact glycemic control and influence the risk for adverse effects. Methods to manage hyperglycemia vary among transplant centers and also vary according to whether the patient is immediately post-transplant or is being admitted in the post-transplant setting for another issue. Immediately after transplantation in post-transplant we use frequently require IV insulin infusion protocol. Once iv requirements are established and stable, switch to insulin every 8 h plus fast-acting correction insulin every 4–6 h.

The prevalence of post-transplant hypertension is between 60 and 85%. Causes of hypertension in patients with a transplanted kidney are as follows: stenosis of graft renal artery, presence of native kidneys, immunosuppressive therapy, graft dysfunction, genetic predisposition of donors and recipients. Native kidneys and pre-transplant hypertension have been described as independent factors associated with post-transplant hypertension. Native kidney of recipient can cause systemic hypertension through the renin-angiotensin system. Immunosuppressive drugs are also responsible for the appearance of hypertension in patients with a

transplanted kidney. It is believed that corticosteroids aggravate hypertension through hemodynamic and hormonal disorders as well as retention of salt and water. The role of cyclosporin in the development of hypertension in the transplantation of the heart, liver and bone marrow, as well as in patients with uveitis and diabetes mellitus, has been demonstrated, while its role in kidney transplantation is controversial. On the one hand, cyclosporin can cause hypertension with its nephrotoxic effect, and on the other hand, if cyclosporin prevents chronic rejection, it may delay the occurrence of hypertension. In two large retrospective studies with a follow-up period of 2 and 3 years, the prevalence of hypertension remained stable over time, but in the group of patients treated with cyclosporin, the prevalence of hypertension increased by 25% compared to patients treated with azathioprine [15]. Tacrolimus therapy causes hypertension, whose mechanism is probably similar to cyclosporin-induced hypertension. It is a general opinion that the main cause of hypertension after renal transplantation is chronic graft dysfunction or chronic graft nephropathy. Hypertension is often the first clinical sign of chronic rejection. It is known that arterial hypertension is a risk factor for cardiovascular disease in the general population. In a retrospective analysis, Ponticelli and associates have found a higher number of cardiac infarcts after kidney transplantation in patients with hypertension than in normotensive patients [16]. Arterial hypertension correlates with cardiovascular disease after transplantation [17]. In most cases for treatment post-transplant hypertension, routine antihypertensive treatment is effective. We can use ACE inhibitors, beta blockers and calcium channel blockers.

Hyperlipidemia is known as the traditional risk factor for the development of cardiovascular diseases, both in the general population and in the population of patients with terminal stage of renal failure. Several observational studies have shown that total cholesterol and low-density lipoproteins (LDL) are one of the most important independent factors of cardiovascular morbidity and mortality [18]. Patients with renal function impairment have significant changes in the metabolism of lipoproteins, whose exact role in the pathogenesis of atherosclerosis in these patients is still controversial [19]. Hyperlipidemia can occur already after 3 months of transplantation and does not resolve spontaneously, and in most patients, it can persist for a very long, even 10 or more years after kidney transplantation [20]. Patients with a transplanted kidney usually have an increased total cholesterol, LDL cholesterol and triglycerides, while HDL cholesterol is usually normal or even high, although its composition may be pathological [21]. Immunosuppressive drugs such as corticosteroids, cyclosporin, tacrolimus and, in particular, sirolimus contribute to the development of post-transplant hyperlipidemia, usually depending on the dose of medicine [22]. Many epidemiological studies of patients with a transplanted kidney showed a correlation between elevated total cholesterol, triglyceride, LDL and incidence of cardiovascular diseases, the same as a low level of HDL is associated with an increase in cardiovascular risk [23]. Hyperlipidemia in patients with a transplanted kidney may affect the progression of chronic graft nephropathy. Based on data about the prevention of cardiovascular disease, it is known that the reduction of LDL-cholesterol by 1 mmol/l over 4–5 years reduces the risk of coronary and cerebrovascular incidents by 25%. Extrapolation from general population studies and some data in kidney transplant patients support the view that the assessment and treatment of dyslipidemias should be part of routine post-renal transplant care. For treating hyperlipidemia in kidney transplant patient, we use statins.

## 2.2. Risk factors related to the status of transplantation and its treatment

In patients who at the moment of transplantation have no signs of atherosclerosis, reduced graft function and immunosuppressive therapy may cause hypertension, dyslipidemia, diabetes mellitus, and proteinuria, which can lead to myocardial infarction, stroke, or peripheral vascular disease.

Allograft function disorder is a risk factor for the development of cardiovascular disease [24]. A year after renal transplantation, chronic allograft disease at stage 3 (glomerular filtration  $<60$  ml/min/1.73 m<sup>2</sup>) has 60%, and in stage 4 (glomerular filtration value  $<30$  ml/min/1.73 m<sup>2</sup>) has 15% of patients [25]. With the decline in the allograft function, nontraditional risk factors appear. They occur when the glomerular filtration value falls below 60 ml/min/1.73 m<sup>2</sup>, and especially when it is below 45 ml/min/1.73 m<sup>2</sup>.

Reduced function of transplanted kidney in transplant recipient is an independent and important risk factor for the development of cardiovascular diseases due to adverse effects on hypertension, anemia, dyslipidemia, hyperhomocysteinemia [26]. The American National Kidney Foundation (NKF) reported that the value of glomerular filtration (GFR) measured or estimated is a better parameter of renal function than serum creatinine only [27]. The prevalence of left ventricular hypertension is inversely proportional to the level of glomerular filtration. In one study, the frequency of left ventricular hypertension was 45, 31 and 27% in patients with creatinine clearance  $<25$ , 25–50, and  $>50$  ml/min [28].

## 2.3. Risk factors relating to chronic decline in graft function

With an increased risk of cardiovascular complications, homocysteine, infection, pathological coagulation and fibrinolysis are associated.

Anemia is a risk factor for the development of cardiovascular disease in patients with a transplanted kidney. The American Society of Transplantation (AST) defines anemia as a hemoglobin concentration lower than 120 g/l in men and lower than 110 g/l in women [29]. Anemia occurs in 20–60% of patients with a transplanted kidney, and its prevalence is the highest in the early post-transplant period (6–12 months after kidney transplantation). The main causes of its development in the early post-transplant period are: blood loss due to surgery, abrupt termination of erythropoietin administration, iron deficiency, bone marrow suppression caused by induction therapy, increased erythropoietin resistance due to infection (viral infection) and/or inflammatory status caused by systemic immune response on the presence of alloantigens, the use of drugs (mycophenolate mofetil). Reduced production of endogenous erythropoietin due to loss of allograft function, erythropoietin resistance due to secondary hyperparathyroidism and chronic microinflammatory disease are the main causes of anemia in late post-transplantation [30].

Post-transplantation anemia (a hemoglobin less than 110 g/l 3 months after renal transplantation) was associated with the development of congestive heart failure, a lower survival rate of allograft and patient, and a higher rate of acute rejection [31]. The relative risk for the cardiovascular incident was 1.32 with a decrease in hemoglobin by 0.5 g/dl, which is just slightly less

than the relative risk of 1.37 related to an increase in systolic pressure of 15 mmHg. Anemia together with hypertension leads to left ventricular hypertrophy.

Treatment of patients with transplanted kidney and post-transplant anemia should be started with erythropoietin, when the hemoglobin concentration is less than 110 g/l and the target hemoglobin level should be 110–120 g/l.

Homocysteine concentration is an independent risk factor for cardiovascular disease after kidney transplantation [32]. In patients with a transplanted kidney, the concentration of homocysteine decreases compared to patients treated with dialysis but is higher than the concentration of homocysteine in healthy population, so hyperhomocysteinemia is common in patients after kidney transplantation [33]. For the treatment of hyperhomocysteinemia, we use folate and Vitamin B (12).

There is clear evidence that elevated levels of fibrinogen, factor VII, and von Willebrand factor in the general population are associated with an increased risk of acute insult or coronary disease [34]. These factors have also been elevated in patients following kidney transplantation, in more patients with cardiovascular disorders than in patients who do not have them.

Secondary hyperparathyroidism is a risk factor for the development of cardiovascular disease in patients with a transplanted kidney [35]. After transplantation of the kidney, hyperparathyroidism is maintained in 50% of patients, characterized by hypercalcaemia, hyperphosphatemia and increased parathormone concentration [36]. Secondary hyperparathyroidism in post-transplantation may also occur new, as a consequence of the decline in the function of the allograft and the lack of calcitriol. The disorder of metabolism of calcium and phosphate results in calcification of peripheral arteries, including coronary artery calcification. Cinacalcet may be useful in the treatment of persistent hyperparathyroidism after kidney transplant.

The effect of local inflammatory stimulus such as products of the oxidation process, the end products of glycosylation and chronic infectious processes alter the blood vessel in terms of the development of atherosclerosis. Microinflammation is a risk factor for the development of atherosclerotic cardiovascular diseases in patients with a transplanted kidney [24]. These patients have a low level of microinflammation as a consequence of a systemic immune response to the presence of all antigens but also because of chronic infections [25]. C-reactive protein (>5 mg/l > 0.5 mg/dl) is associated with an increased risk of developing cardiovascular events in the population of patients with a transplanted kidney.

Proteinuria occurs in one-third of post-transplant patients and is a risk factor for the development of cardiovascular disease in patients with a transplanted kidney [37].

### **3. Cardiovascular disease in patients with transplanted kidney**

Thanks to the progress in histocompatibility testing and better immunosuppressive therapy, graft survival has increased, so that the leading cause of graft loss after transplantation has been the death of a patient with functional graft. Cardiovascular disease is the leading cause of

death in patients with a transplanted kidney [38]. Despite the fact that patients with a transplanted kidney are highly susceptible to infections and have an increased tendency to develop malignant diseases, these patients die mainly of cardiovascular disease. Although kidney transplantation, in contrast to dialysis, reduces the risk of cardiovascular disease by restoring kidney function, it also brings new risk factors related to the status of transplantation and its treatment and risk factors related to the chronic decline in the function of the allograft. The increased incidence of cardiovascular diseases in patients with transplanted kidney is a consequence of the high prevalence of risk factors for the development of cardiovascular diseases in these patients. The incidence of cardiovascular disease in patients with a transplanted kidney is three to five times higher than in the general population [39]. A cardiovascular event with congestive heart failure or coronary heart disease was manifested in almost 40% of patients 36 months after kidney transplantation [9]. Cardiovascular disease is the most common cause of death in transplanted patients, accounting for 35–50% of all causes of death, and occurs at least two times more often than in the general population [40]. Most kidney recipients die with functional graft and half of these patients die due to ischemic heart disease or other vascular diseases [41].

The most common cardiovascular diseases in patients after kidney transplantation are as follows: ischemic heart disease, congestive heart failure and left ventricular hypertrophy [6]. Of all cardiovascular complications, ischemic heart disease is by far the most common cause of mortality (more than 50%) in patients with a transplanted kidney [41]. Frequency of left ventricular hypertrophy ranges from 50 to 70% in patients with a transplanted kidney [42]. Left ventricular hypertrophy is associated with an increased degree of ventricular arrhythmias. In Europe, cardiovascular disease account for 36% of the total mortality of patients with a transplanted kidney [43]. In the United States, the annual mortality rate of cardiovascular diseases in these patients is 0.54% and is approximately twice as high (0.28%) than in the general population [39].

Ischemic heart disease causes 53% of deaths in patients with transplanted kidney and preserved graft function. The risk of mortality from ischemic heart disease is 6.4 times higher in nondiabetic transplanted renal patients, 8.6 times higher in dialysis patients and 20.8 times higher in transplanted renal patients with diabetes than in the general population [41]. Diagnostic strategy for early detection of patients with an increased risk of developing asymptomatic disorders of the systolic and diastolic function of the left ventricle should include: echocardiographic examination, tests for coronary artery disease and tests for the determination of myocardial function (BNP, Tt-pro BNP). In a study of Aakhus and associates on cardiovascular diseases in patients with a transplanted kidney, involving 406 patients with a transplanted kidney, the mean annual mortality was 4.4, and 74% of them were cardiovascular causes of mortality [44].

### **3.1. Left ventricular hypertrophy**

The most significant risk factors for the development of left ventricular hypertrophy are as follows: hypertension, arteriosclerosis, secondary aortic stenosis and anemia.

Left ventricular hypertrophy is a risk factor for the unfavorable outcome of patients with a transplanted kidney. The selection of patients with an increased risk of left ventricular hypertrophy, the timely application of appropriate treatment, the achievement and maintenance of the target values of risk factors, lead to decrease of the development and regression of existing left ventricular hypertrophy, reduction in the rate of cardiovascular morbidity and mortality, and improve the quality of life of patients with a transplanted kidney.

Left ventricular hypertrophy is present in most patients who begin treatment by replacing renal function and are associated with poor outcome. Time spent on dialysis can also affect the development of left ventricular hypertrophy. Transplantation of the kidneys leads to the withdrawal of left ventricular hypertrophy together with the normalization of blood pressure. The regression of left ventricular hypertrophy continues during the first 2 years after transplantation. Older age and hypertension can slow down this process [45].

The presence of left ventricular hypertension as well as the weak systolic function of the left ventricle before transplantation are related to an increased mortality after renal transplantation during 7.5-year follow-up, while other traditional risk factors such as hypertension, hyperlipidemia and smoking did not show such a connection. On cardiography of the heart made 4 months after transplantation, only left ventricular hypertension had a strong association with poor prognosis during monitoring [46].

### **3.2. Heart failure**

Heart failure is a clinical syndrome characterized by reduced tolerance of physical activity and overload volume. The incidence of congestive heart failure in patients with a transplanted kidney is two to five times higher than the incidence in the general population [47]. The incidence of congestive heart failure in patients with a transplanted kidney was 10.2% 12 months after transplantation and 18.3% 36 months after transplantation [48].

In a study of Higashi and associates, 11 out of 190 (5.8%) kidney recipients, with preserved left ventricular systolic function and the presence of diastolic left ventricular dysfunction, developed a postoperative edema of the lungs [49].

Diastolic left ventricular dysfunction is present in 45% of patients with a transplanted kidney.

The clinical presentation is the same as in all other patients with cardiac insufficiency. The following symptoms are reported: difficulty breathing, intolerance of physical activity, edema of the lower extremities and stomach.

Treatment: the first measure is to reduce physical activity and reduce salt intake. If this is not enough, medication therapy is started with a combination of diuretics, ACE inhibitors and digitalis.

### **3.3. Ischemic heart disease**

Ischemic heart disease (IHD) is the most common disease in the large group of all cardiovascular diseases. The prevalence of ischemic heart disease in patients with a transplanted kidney

is five times higher than in the general population. The main cause of ischemic heart disease is atherosclerosis of the coronary arteries, and in patients with transplanted kidney there are many risk factors that contribute to atherosclerosis: elevated arterial blood pressure, lipid metabolism disorder, microinflammation, hyperhomocysteinemia, oxidative stress and secondary hyperparathyroidism.

In patients with a transplanted kidney, there is a high risk of sudden cardiac death. The main causes are coronary arterial heart disease, left ventricular hypertrophy, and reduced coronary perfusion. In patients with a transplanted kidney, the prevalence of coronary heart disease is five times higher than the general population [6].

In all patients with ischemic heart disease, the following should be done: detailed anamnesis and physical examination, ECG at rest, blood biochemical analysis (lipids, glucose, creatinine, urea, hepatogram, complete blood count, uric acid, fibrinogen, hsCRP, etc.) echocardiographic examination, ergometric testing. In patients with transplanted kidney, the risk factors for the development of atherosclerosis should be controlled in the primary prevention and prevention of coronary artery disease development. In clinical practice, patients with acute myocardial infarction with elevation of ST connectors are using modern reperfusion therapy (thrombolysis or percutaneous coronary intervention). Medical treatment implies the use of anti-aging therapy, statins and beta blockers.

### **3.4. Valvular heart disease, heart rhythm disorders, and pericardial disease**

Valvular heart disease is common in patients with chronic dialysis. Current knowledge of heart valve disease (the evolution of pre-dialysis disease or the emergence of de novo diseases of the heart valve) in patients following kidney transplantation is scarce. In the literature, there are few data about heart rhythm disorders in patients with transplanted kidney. In a study by Sever and associates on the frequency of pericarditis in patients following kidney transplantation, an incidence of 2.4% was observed [50].

The development of pericarditis in patients with a transplanted kidney may contribute to the use of immunosuppressive therapy as it increases the risk of infection [51].

## **4. Assessment of the risk of cardiovascular disease in asymptomatic patients with a transplanted kidney**

Cardiovascular diseases are the main cause of morbidity and mortality in post-transplant patients [52]. The risk assessment of cardiovascular disease in asymptomatic patients with a transplanted kidney is of great practical importance because it allows the identification of patients at high risk for cardiovascular events, which further allows timely intervention before the disease develops. To assess the risk of cardiovascular disease in asymptomatic patients with a transplanted kidney, we can apply the scores used for assessment of cardiovascular risk in general population. The scores for the general population are the Systematic Coronary Risk

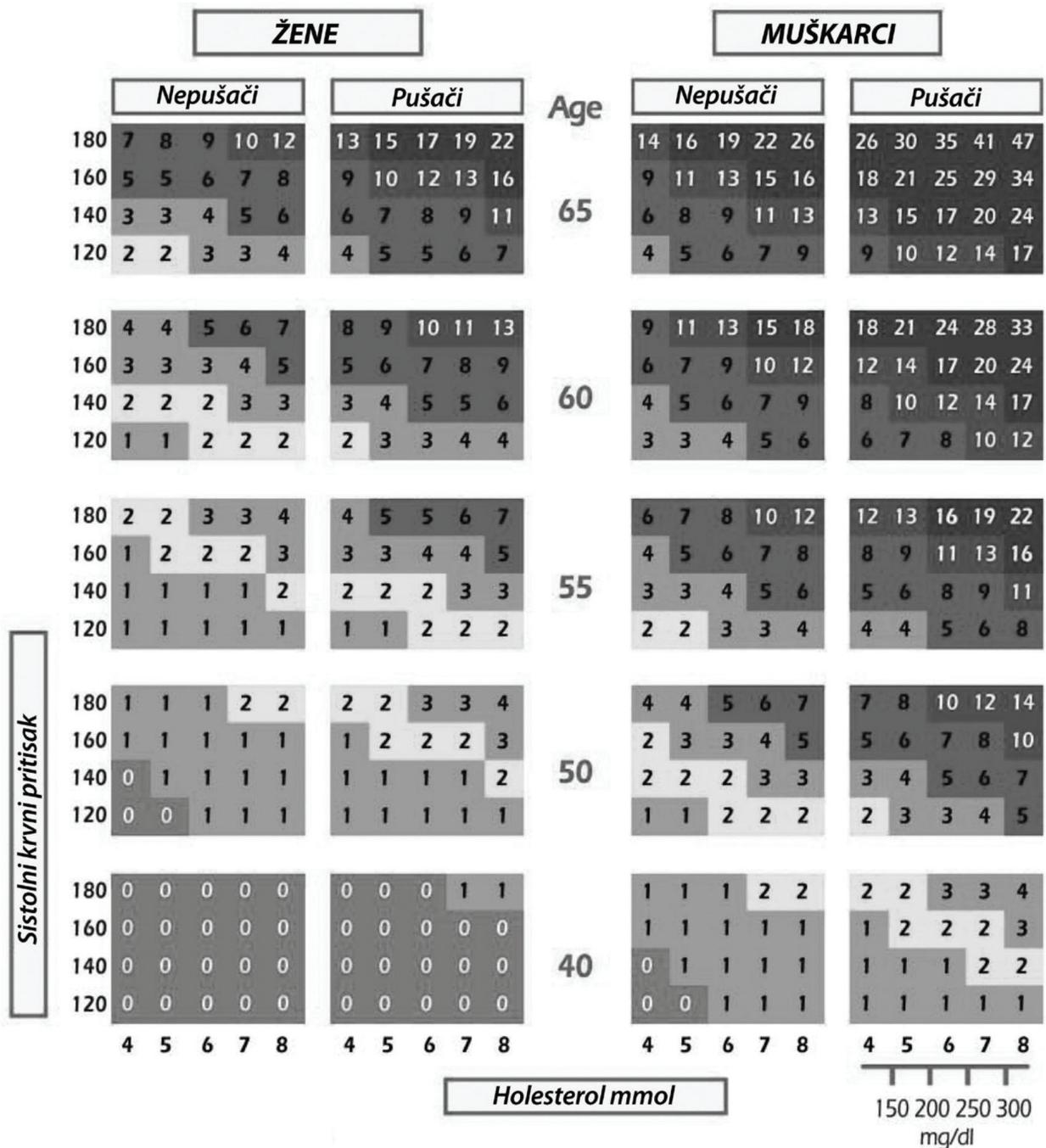


Table 1. Heart score high risk map.

Evaluation SCORE system, the Prospective Cardiovascular Munster PROAM score system, and the National Cholesterol Education Program Adult Treatment Panel III NTEP ATP III [53].

The new risk assessment model is based on the Heart Score system (Systematic Coronary Risk Evaluation). The Heart Score Risk Card has been developed on the basis of large prospective studies in Europe and predicts the fatal outcomes of cardiovascular disease for 10 years. The

assessment is based on the following risk factors: age, sex, smoking, systolic blood pressure, total cholesterol, or cholesterol/HDL ratio. A high risk threshold based on a fatal cardiovascular outcome is defined as more than or equal to 5%.

Early detection of high-risk patients for the development of cardiovascular diseases allows timely application of an appropriate therapeutic strategy that ensures high survival rates for patients with a transplanted kidney (**Table 1**).

Assessing the patient's risk of developing cardiovascular disease enables the identification of patients at high risk for the development of cardiovascular events, which allow the intervention before the disease develops. In asymptomatic patients, cardiovascular risk assessment should be carried out and preventive activities should be performed accordingly. Patients with established multifactorial risk should be subjected to preventive activities, and, if necessary to medication therapy.

Several studies have shown that the use of standard scores in the assessment of the degree of risk of cardiovascular disease in patients with renal disease is insufficient [54]. In these scores, we use the following data: age, gender, blood pressure, lipid level, without taking into account nontraditional risk factors for occurrence of cardiovascular diseases.

Nontraditional risk factors that are not included in these scores can play an important role in the insufficient assessment of the risk of cardiovascular disease in patients with a transplanted kidney. All these points should be considered by creating a new risk score that would include both traditional and nontraditional risk factors for cardiovascular disease. It is recommended that standard risk factors be enhanced with additional risk factors (e.g., homocystein, C-reactive protein). Additional risk factors are recommended for increasing the precision of risk assessment.

## 5. Conclusion

Cardiovascular disease is the leading cause of death in patients with a transplanted kidney. The incidence of cardiovascular disease in patients with a transplanted kidney is 3–5 times higher than in the general population. Risk factors for the development of cardiovascular diseases in patients with a transplanted kidney are divided into traditional and nontraditional. Traditional risk factors: immutable (age, gender, inheritance), variable (smoking, hyperlipidemia, hypertension, obesity, diabetes mellitus, physical activity, stress). Nontraditional risk factors: risk factors related to the status of transplantation and its treatment (immunosuppressive agents, graft rejection, viral infection - cytomegalovirus) and risk factors associated with chronic regression in allograft function (anemia, volume load, hyperhomocysteinemia, oxidative stress, secondary hyperparathyroidism, microinflammation). The most common cardiovascular diseases in patients after kidney transplantation are as follows: ischemic heart disease, congestive heart failure and left ventricular hypertrophy. Of all cardiovascular complications, ischemic heart disease is by far the most common cause of mortality (more than 50%) in patients with a transplanted kidney. Frequency of left ventricular hypertrophy ranges from 50 to 70% in patients with a transplanted kidney. The incidence of congestive heart failure in patients with a transplanted kidney is 2–5 times higher than the incidence in the general

population. The incidence of congestive heart failure in patients with a transplanted kidney was 10.2% 12 months after transplantation and 18.3% 36 months after transplantation. The risk assessment of cardiovascular disease in asymptomatic patients with a transplanted kidney is of great practical importance because it allows the identification of patients at high risk for cardiovascular events, which further allows timely intervention before the disease develops. To assess the risk of cardiovascular disease in asymptomatic patients with a transplanted kidney, we can apply the scores used for assessment of cardiovascular risk in general population. Several studies have shown that the use of standard scores in the assessment of the degree of risk of cardiovascular disease in patients with renal disease is insufficient. It is recommended that standard risk factors be enhanced with additional risk factors (e.g., homocystein, C-reactive protein). Additional risk factors are recommended for increasing the precision of risk assessment. Assessing the patient's risk of developing cardiovascular disease enables the identification of patients at high risk for the development of cardiovascular events, which allow the intervention before the disease develops.

## Author details

Daniela Loncar and Selma Hodzic\*

\*Address all correspondence to: [hodzic\\_selma@live.com](mailto:hodzic_selma@live.com)

Clinic for Internal Disease, University Clinical Center Tuzla, Bosnia and Herzegovina

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