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Cardiovascular disease in patients qualified to kidney transplantation**

Choroby układu sercowo-naczyniowego u chorych zgłaszanych do przeszczepienia nerki

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Keywords

kidney transplantation, waiting list, cardiovascular diseases, atrial fibrillation

Słowa kluczowe

przeszczepienie nerki, lista oczekujących, choroby układu sercowo-naczyniowego, migotanie przedsionków

Summary

Cardiovascular diseases are the leading causes of mortality in patients with chronic kidney diseases, including kidney transplant recipients. Thus, proper cardiological evaluation is crucial to yield the best possible outcomes. Anamnesis, physical examination, electrocardiography, chest x-ray, serum lipids, fasting glucose, then stress and echocardiography is performed in potential kidney transplant recipients. Coronary angiography should be considered in patients with positive stress test after acute coronary syndrome, with unstable angina and high cardiovascular risk. The other problem in this group are rhythm disturbances, with atrial fibrillation being the most common. Patients with atrial fibrillation and impaired kidney function are at the significantly higher risk of thrombotic complications, in particular ischemic stroke on one hand, and bleeding complications on the other hand (linearly to the stage of kidney diseases). Kidney transplant recipients treated with novel oral anticoagulants should be monitored in regard to kidney function and potential interactions with immunosuppressive therapy should be taken into account.

Streszczenie

Choroby sercowo-naczyniowe są główną przyczyną zgonu chorych z przewlekłą chorobą nerek, w tym pacjentów po transplantacji nerki. Zatem istotną częścią kwalifikacji pacjenta do zbiegu transplantacji nerki jest ocena kardiologiczna. Dodatkowym utrudnieniem jest brak ogólnie przyjętych zaleceń. W procesie kwalifikacji kardiologicznej bierze się pod uwagę: wywiad, badanie przedmiotowe, elektrokardiografię, zdjęcie rentgenowskie klatki piersiowej, ocenę profilu lipidowego, glikemię na czczo, następnie test wysiłkowy oraz badanie echokardiograficzne. Angiografię tętnic wieńcowych należy rozważyć u pacjentów z dodatnim testem wysiłkowym po przebytym ostrym zespole wieńcowym, z niestabilną chorobą niedokrwienną serca, wysokim ryzykiem sercowo-naczyniowym. Innym problemem w tej grupie chorych są zaburzenia rytmu, w tym migotanie przedsionków, które jest najczęstszą patologią. Chorzy z migotaniem przedsionków i upośledzoną funkcją nerek mają znacznie większe ryzyko powikłań zakrzepowych, szczególnie udaru niedokrwiennego mózgu, a jednocześnie większe zagrożenie krwawieniami. Ze względu na nowe możliwości terapeutyczne należy zwracać szczególną uwagę na funkcję nerek, co warunkuje możliwości zastosowania nowych leków przeciwkrzepliwych oraz ich potencjalne interakcje z lekami immunosupresyjnymi.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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Following the progress in kidney transplantation and post-transplantation care the mortality rate among kidney transplant recipients was significantly reduced in the 60's and 80's of last century. It was the result of reduced number of deaths caused by infectious complications (1). On the other hand, the increase of car-

**This work is dedicated to Professor Franciszek Kokot with the best wishes live a healthy and happy life and to thank for longterm research support.

diovascular (CV) mortality (1) resulted that the number of deaths remained constant in subsequent years. Currently, death among patients with functioning graft is the leading cause of graft loss and CV diseases are the major cause of death in that population (2, 3). It refers to approximately 50-60% of deaths, including 47% of deaths in the first 30 days after the transplantation by the incidence of coronary artery disease estimated on 1 per 100 patient-years of risk (2-5).

It should be noticed, that successfully completed kidney transplantation improves renal function and causes patient transfer from stage 5 in the KDIGO classification (eGFR < 15 ml/min) to stage 3, rarely to stage 1 or 2. It has been proven, that the risk of cardiovascular diseases increases with the stage of chronic kidney disease and is the highest in the population of dialysis patients (6). Cardiovascular diseases cause from 40 to over 60% of all deaths in this population (7, 8) as also in the population of kidney transplant recipients. The risk of death from cardiovascular diseases is higher among younger patients if compared to general population. Mortality among hemodialysis patients aged 25-44 years is comparable to those over 75 years old with normal renal function (8). It is associated with the occurrence of classic risk factors in the general population (Framingham Heart Study) such as: older age, male gender, hypertension, diabetes mellitus, hypercholesterolemia, smoking, no physical activity, charged family history of cardiovascular diseases (9, 10). There are also additional, specific for chronic kidney disease risk factors, predisposing to the development of cardiovascular diseases. They include: deterioration of renal function, resulting the recurrence of the primary disease, genetic predisposition to progression of chronic renal disease or abnormalities occurring secondary to renal disease, such as hypoalbuminemia, fluid overload, anemia, malnutrition, lipid disorders, chronic inflammation, calcium – phosphate hemostasis disorders (11-14).

They become very important by beginning chronic graft dysfunction, which causes progression of chronic kidney disease, leading to end-stage renal disease and dialysis. Moreover, the majority of kidney transplant recipients was dialyzed for many months or years before transplantation, that was associated with accelerated atherosclerosis progress in those population (15). Cardiovascular diseases diagnosed before transplantation were the strongest predictor of cardiovascular complications after transplantation (15, 16). On the other hand, the presence of blood vessels calcifications before transplantation correlated with higher mortality after transplantation – although no direct relationship was observed (17, 18).

Therefore classic, as also non-classic risk factors of cardiovascular diseases influence directly or indirectly the progression of chronic kidney disease (19). Among kidney transplant recipients there are also factors related to the transplantation, such as: graft loss, obesity, acute kidney rejection, delayed function of the graft, proteinuria, viral infections (e.g.: Cytomegalovirus) or side effects of immunosuppressive therapy (e.g. post-transplantational diabetes mellitus, hypertriglyceridemia, hypercholesterolemia).

Coronary artery disease (CAD) in patients with end-stage renal disease (ESRD) occurs more often than in the general population. Mortality in dialysis patients is extremely high; nearly every fourth patient dies during the annual observation. Most deaths occur from cardiovascular causes (20-22). The most important prognostic factor in patients with CAD is the evaluation of myocardial ischemia. However, the determination of the ischemia in dialysis patients is complicated. Non-invasive diagnostic is extremely difficult, because additional tests are characterized by low sensitivity and specificity. The sensitivity of non-invasive tests according to various sources were assessed from 52 to 95% and specificity of 71 to 94% (23, 24).

The symptoms of coronary artery disease in dialysis patients are often atypical. Atypical clinical symptoms, constantly increased levels of myocardial necrosis markers in patients with chronic kidney disease, including dialysis patients as also difficulties in ECG interpretation make the proper diagnosis difficult (24).

ECG often contains many abnormalities, that correspond with complex of CKD. This variety and nonspecific changes in ECG cause problems in interpretation and correct diagnosis. In our study, we often observed in dialysis patients, negative T wave and ST-segment changes such as non-specific, horizontal, oblique downward ST depressions. ST segment changes are not always associated with ischemia. However, even small ST-T segment changes require clinical verification. Left ventricular hypertrophy was observed in 58% of patients from the study population. There were no statistically significant differences in electrocardiographic parameters between the groups with and without diabetes mellitus. The value of non-invasive diagnostic (exercise stress test) in those patients is limited (2) because of the lack of proper physical efforts as also not reached heart rate limit. Limitations are associated with general weakness, poor exercise tolerance, poor mobility and advanced age (23). Angina pectoris occurs only in 24% of CKD patients with significant stenosis in coronary arteries (25). 62% of patients starting dialysis have significant coronary artery stenosis (26). A huge group of patients remains asymptomatic. On the other hand, exercise angina pectoris may be caused by anaemia or left ventricle hypertrophy. Atypical stenocardial pain makes the cardiac diagnostic in dialysis patients difficult.

The dobutamine stress echocardiography may be a better tool in cardiac diagnostic. It is the most sensitive and specific non-invasive method. Its sensitivity is estimated at 52-95%, and specificity at 71-94%, according to different authors (27-29). What should be mentioned, the results of this method depend on the experience and technical conditions of the center (30).

Stress echocardiography let to determine, who from the candidates to kidney transplantation need coronary angiography. However, large percentage of false positive stress echocardiography test results are observed. It causes temporary withdrawal of the patient from the transplantation list as also unnecessary coronary angiography.

The aim of the coronary artery disease diagnostic is to find out patients requiring revascularisation. There are two groups of patients: those who not on the list for a transplantation and candidates for renal transplantation. Kidney transplantation in dialysis patients do not only improves the quality of life, but also improve the prognosis (31). A screening among potential kidney transplant recipients must be conducted in order to avoid perioperative complications.

There is not much data concerning on the long-term survival in a population of patients after kidney transplantation and revascularization procedures. Herzog et al. (32) identified in a database of renal transplant recipients in United States (US Renal System Database) the number of 2,661 patients, who were hospitalized in 1995-1999 and who underwent coronary artery revascularization. The relative risk of death from any causes and from cardiovascular diseases in patients treated with percutaneous coronary interventions (PCI) with/without stent implantation as also after coronary artery bypass grafting (CABG) was similar. The estimated two-year survival after revascularization procedures (except vein grafts) was about 82% (57% after CABG and 53% after PCI) in dialysis patients (32). This is probably the result of "healthier" patients qualified to kidney transplantation. Herzog et al. (32) suggested, that the best survival in kidney transplant recipients requiring revascularization is observed after CABG (taking into account other comorbidities). However, CABG is associated with higher mortality in the perioperative period, but it has better long-term prognosis if compared to percutaneous coronary intervention (including better follow-up in group of patients treated with DES than with BMS) (33).

The guidelines of the American Heart Association and the American College of Cardiology Foundation published in 2012 in collaboration with the American Society of Transplant Surgeons, American Society of Transplantation and the National Kidney Foundation discuss the qualification of cardiac patients for the kidney and liver transplantation as well as the treatment of cardiovascular disease in this population (34).

Non-invasive diagnostic of cardiovascular diseases in potential kidney transplant recipients, who do not present any symptoms of CVD should be performed based on presence of risk factors, regardless of the presence of symptoms. The risk factors include: diabetes mellitus, history of CVD, dialysis period over one year, left ventricular hypertrophy, smoking, age over 60 years, hypertension, dyslipidemia. According to these recommendations, non-invasive diagnostic should be considered if the number of risk factors is 3 or more (IIb; C).

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population. The burden of AF is even greater in patients with concomitant kidney disease. Published studies in the last few years have highlighted the often under-recognized, yet highly prevalent relation between kidney disease and AF. Furthermore, evidence has suggested that the burden of AF will likely rise in this high-risk population, making the intersection of kidney disease and AF a highly relevant clinical problem.

Atrial fibrillation is frequent in patients with CKD with prevalence between 19 to 24% (35, 36). In the Framingham Heart Study, the prevalence of AF in CKD patients was 15 times higher than in general population (37) while in the Chronic Renal Insufficiency Cohort study (CRIC) of 3,267 patients with CKD, AF was present in 18%. It was associated with older age, female sex, smoking and history of heart failure (38). The frequency of AF was reported to be the highest in patients with stage 4 or 5 CKD, even after multivariable adjustment (39). In ESRD patients the prevalence of AF ranged between 7 and 27% (37, 40, 41). Transplant candidates undergo cardiovascular assessment, usually echocardiography and exercise stress testing, and require formal cardiology consultation. However, data on AF prevalence in waitlisted patients and kidney transplant recipients are very scarce. Among over 62,000 first kidney transplant recipients, 6.4% were diagnosed with AF prior to kidney transplant (42). According to USRDS, ~7% of all cardiovascular hospitalizations are attributed primarily due to AF in the first 2 years after kidney transplantation (43). The same figures were reported in Italian population of 304 kidney transplant recipients at a single center (43).

Oral anticoagulation is an effective therapy to reduce the risk for stroke related to AF. According to ESC guidelines, CHA_2DS_2-VASc and HAS-BLED score is obligatory to assess stroke risk and bleeding risk respectively (44). ESC guidelines recommends to introduce anticoagulation in patients with AF at high risk of stroke – CHA_2DS_2-VASc score ≥ 2, and considers this if there is a score of 1. Oral anticoagulation can be achieved through either vitamin K antagonist (VKA), which blocks the formation of multiple active vitamin K-dependent coagulation factors or a non-vitamin K oral anticoagulant (NOACs) – the direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban). However, the efficacy and safety of anti-coagulation for AF in the ESRD population with a functioning kidney transplant, another population at high cardiovascular risk, remains largely understudied. In a contemporary cohort of US kidney transplant recipients with newly diagnosed AF, warfarin use was associated with a small non-significant reduction in the composite outcome of death, stroke or gastrointestinal bleed. So far there is no data available on NOACs in kidney transplant recipients. According to EHRA guidelines from 2015 (45) dabigatran is not recommended because of interactions with cyclospo-

rine, in the case of other NOACs interactions are unknown. All NOACs are partially eliminated via the kidneys. Vast majority of kidney transplant recipients have CKD stage 3 or more. For patients with moderate renal impairment (eGFR 30-50 ml/min) the recommended dose of dabigatran is 220 mg taken as one 110 mg capsule twice daily, and rivaroxaban 15 mg taken once daily (44). Treatment with NOACs in patients with severe renal impairment (eGFR < 30 ml/min) is approved in Europe but it is not recommended according to the European Guidelines because there is no effectiveness and safety data in this population (44). NOACs offer new therapeutic approach in AF, however, we need to perform more studies also in high-risk, but so far understudied populations as CKD and kidney transplant recipients to choose and use wisely NOACs with the most possible benefit for our vulnerable patients as we presented in the recent review (45).

According to E. Braunwald: "decision-making process is deductive, based often on incomplete and uncertain data. Medical reasoning is complex and not always well understood. Medical decisions often carry a high risk of error. Paradoxically tremendous progress in medical science has increased diagnostic and therapeutic possibilities, but I made that decision making has become even more complex and difficult" (personal communication). Every patient has a right to properly conducted diagnostic and proper treatment, in particular vulnerable patient with ESRD evaluating for kidney transplantation.

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received/otrzymano: 04.08.2016
accepted/zaakceptowano: 25.08.2016