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TREATMENT OF ISCHEMIC HEART DISEASE IN END-STAGE KIDNEY DISEASE PATIENTS ON RENAL REPLACEMENT THERAPY

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This review paper aims to analyze the problem of diagnosis and treatment of coronary heart disease (CHD), also called ischemic heart disease (IHD), in patients with end-stage renal disease (ESRD). The analysis is based on current literature data. The issues of CHD risk stratification before patient listing for kidney transplantation (KT) and possible difficulties of diagnosing CHD using non-invasive examination methods in ESRD patients are considered. The effectiveness of myocardial revascularization and drug therapy, endovascular and surgical myocardial revascularization, is compared. The paper also discusses the peculiarities of drug therapy, particularly antiplatelet and antihyperlipidemic therapy in the treatment of CHD in dialysis-dependent patients and kidney recipients.

Keywords: end-stage renal disease, kidney transplantation, coronary heart disease, ischemic heart disease, myocardial revascularization, coronary stenting, coronary artery bypass surgery, drug therapy.

INTRODUCTION

In the last decade, there has been a rapid rise in chronic kidney disease (CKD) cases, associated with the aging population, spread of obesity, diabetes, and high blood pressure. CKD patients at all stages of the disease are characterized by a high level of cardiovascular pathology, accompanied by adverse outcomes [1]. Reports indicate that the risk of CHD is high in the early stages of CKD [2]. Renal replacement therapy (RRT) aimed at treating ESRD patients includes chronic (long-term) hemodialysis, peritoneal dialysis, and KT. KT is the gold standard treatment for ESRD. Compared to continuous RRT, successful KT offers better survival and a higher quality of life. According to the European Renal Association Registry Annual Report 2021, the life expectancy of kidney recipients is almost twice that of patients on long-term dialysis [3]. Nevertheless, cardiovascular diseases (CVD) remain one of the leading causes of mortality in kidney recipients with a functioning transplant [4].

This paper is devoted to analyzing the problems of diagnosis and treatment of CHD in patients with ESRD before and after KT, based on current literature data.

CHD RISK STRATIFICATION IN DIALYSIS-DEPENDENT PATIENTS

The goals of pre-transplant cardiovascular risk stratification are to identify asymptomatic coronary heart disease and silent ischemia, to identify surgically and anesthesiologically suitable potential kidney recipients, and to exclude patients with significant cardiovascular conditions that may lead to life-threatening perioperative complications [5]. Cardiovascular screening includes a combination of medical history, physical examination, assessment of functional status and the outcomes of non-invasive and invasive examination methods [6].

According to the 2020 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation, KT candidates with symptomatic cardiac disease (e.g., angina, arrhythmia, heart failure, valvular heart disease) should be treated by a cardiologist based on current cardiac clinical guidelines. Asymptomatic kidney transplant candidates at high risk for CHD (family history of diabetes, previous coronary artery disease) or low exercise tolerance, and patients on RRT for longer than 2 years, should undergo non-invasive coronary artery disease (CAD) screening to rule out CHD. The guidelines suggest that asymptomatic patients with severe triple vessel CAD should be excluded from the KT waiting list, unless the patient has a high expected likelihood of survival after surgery [7].

Karthikeyan et al. proposed an algorithm for cardiovascular risk stratification for KT candidates. According to the algorithm, coronary angiography (CAG) is recommended for patients who have clinical signs of angina, signs of heart failure, ventricular arrhythmias, and significant pathology of the heart valve apparatus. In their absence, the authors recommended assessment of cardiovascular risk criteria: major (age ≥50 years, history of CHD and previous myocardial infarction (MI), smoking, diabetes, pulmonary embolism, hypertension, and dyslipidemia) and minor (high-density lipoprotein <0.91 mmol/L and electrocardiographic signs of left ventricular hypertrophy). If more than one major risk criterion is present, stress myocardial perfusion scinti-

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graphy (MPS) is indicated to decide whether CAG would be required. In the absence of major criteria, the presence of less than 2 minor criteria and good exercise tolerance (>4 Mets), patients are listed for KT, and in the case of low exercise tolerance (<4 Mets), stress MPS is performed with further decision on whether to initiate CAG [8].

Hakeem et al. proposed their coronary screening and risk stratification algorithm for ESRD patients. In their proposal, the presence and severity of clinical symptoms and echocardiographic changes (primarily impaired contractility) are assessed first, and having a history of diabetes and CHD is taken into account. Then, depending on the results, either blood troponin T levels and coronary calcium levels are assessed, or a stress test is performed. Based on the results of this test, the need to conduct CAG is decided [9].

Nimmo et al. studied 2,572 kidney recipients who received either a stress test or CAG as pre-transplant screening and compared the association of these test results with major adverse cardiac events (MACE) within 5 years after transplantation. The incidence of MACE at 90 days, 1 year, and 5 years after KT was 0.9%, 2.1%, and 9.4% respectively. There was no statistically significant association between pre-transplant screening method (stress test or CAG) and MACE at all follow-up stages. Age, male sex and history of CHD were associated with MACE [10].

Over 50% of cardiovascular mortality in ESRD patients is associated with life-threatening cardiac arrhythmias due to systolic and diastolic dysfunction, left ventricular hypertrophy, myocardial fibrosis and electric myocardial inhomogeneity, coronary calcinosis, electrolyte imbalance and hypervolemia [11]. Thus, pre-transplant screening should be aimed not only at detecting coronary atherosclerosis, but also at assessing cardiovascular risk comprehensively prior to placing patients on the KT waitlist.

In their recent study, Vadala et al. compared pre-KT cardiovascular screening algorithms proposed by major scientific societies [12]: the European Renal Best Practice Transplantation Guideline Development Group (ERBP) [13], the American Heart Association (AHA) [14, 15], and the European Society of Cardiology (ESC) [16] (Table 1).

Table 1

Algorithm for cardiovascular screening before kidney transplantation [12] according to ERBP [13], ACC 2012 [14], 2022 [15], ESC [16]

<table>
<tr><td colspan="2">Criteria for high cardiovascular risk</td><td colspan="5">• Diabetes [13–16]
• Age >60–65 years [13–16]
• Smoking [14–16]
• History of CVD [13, 14]
• Duration of dialysis >1 year [14] to 5 years [15]
• Hypertension [14, 16]
• Dyslipidemia [14, 16]
• Left ventricular hypertrophy [14]
• History of cerebrovascular disease [15]
• Peripheral atherosclerosis [15]
• History of kidney transplantation (performed >5 years ago) [15]
• Family history of CVD [16]</td></tr>
<tr><td colspan="7">Pre- kidney transplant screening</td></tr>
<tr><td colspan="2">For low-risk patients</td><td colspan="3">For high-risk patients</td><td colspan="2">For patients with a history of CHD</td></tr>
<tr><td colspan="2" rowspan="2">• Medical history [16]
• Physical examination [16]
• Standard laboratory diagnosis [16]
• Electrocardiography (ECG) [13–15]
• Echocardiography (Echo) [14, 15]
• Chest X-ray [13]</td><td colspan="3" rowspan="2">• Medical history [16]
• Physical examination [16]
• Standard laboratory diagnosis [16]
• ECG [13–16]
• Echo [13–16]
• Chest X-ray [13]
• Stress test [13–16]
• Biomarkers (troponins I, T, NT-proBNP) [16]</td><td colspan="2">Examination same as for high-risk patients</td></tr>
<tr><td>• Last CAG was >2 years ago
• Revascularization [15]</td><td>• Last CAG was <2 years ago
• No revascularization [15]</td></tr>
<tr><td colspan="2" rowspan="2">No pathology detected</td><td colspan="2">Pathology detected</td><td colspan="2" rowspan="2">Stress Echo or noninvasive assessment of myocardial perfusion [15]</td><td rowspan="4">No additional examination required [15]</td></tr>
<tr><td colspan="2">No pathology detected</td></tr>
<tr><td rowspan="2">No pathology detected</td><td rowspan="2">Pathology detected</td><td colspan="2" rowspan="2">No additional examination required [13–16]</td><td colspan="2">Stress Echo or noninvasive assessment of myocardial perfusion [13, 16]</td><td rowspan="2">No pathology detected</td><td rowspan="2">Pathology detected by examination or by previous CAG [15]</td></tr>
<tr><td>No pathology detected</td><td>Pathology detected</td></tr>
<tr><td>No additional examination required [13–16]</td><td>Stress test or CAG [13–16]</td><td>No additional examination required [13, 16]</td><td>CAG [13–16]</td><td>No additional examination required [15]</td><td>CAG [15]</td></tr>
</table>

It should be taken into account that CHD diagnosis in ESRD patients is often difficult due to insufficient information content of some tests in this category of patients, which may lead to underestimation of cardiovascular risk. Table 2 presents possible reasons for the reduced informativity of some noninvasive CHD diagnosis methods for ESRD patients [17].

TREATMENT TACTICS FOR CHD IN DIALYSIS-DEPENDENT PATIENTS

Comparison of myocardial revascularization and medical treatment

The 2020 KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation do not recommend MR for asymptomatic kidney transplant candidates solely for the purpose of reducing perioperative risk of cardiovascular events [7].

According to various sources, there are differences of opinion regarding the optimal treatment for CHD in KT candidates, either conservative therapy or MR.

A recent meta-analysis of 8 studies comprising 945 patients demonstrates that revascularization is not superior to optimal medical therapy (MT) in reducing all-cause mortality (RR, 1.16, 95% CI 0.63–2.12) and cardiovascular mortality (RR, 0.75, 95% CI 0.29–1.89) or MACE (RR, 0.78, 95% CI 0.30–2.07) in patients waitlisted for KT [18].

A meta-analysis of 6 studies comprising 260 kidney transplant candidates receiving medical treatment for CHD and 338 patients undergoing coronary revascularization demonstrated similar results. The analysis showed no significant differences in cardiovascular disease outcomes between the two groups (RR, 1.415, 95% CI 0.885–2.263) [19].

At the same time, several studies have shown coronary revascularization to have better outcomes than a selection of optimal MT in ESRD patients.

In 2022, a meta-analysis of 13 studies comprising 20,688 CKD patients, including dialysis-dependent patients, and patients with severe stenotic CAD was conducted. CHD was treated with either conservative therapy or MR by coronary artery stenting (CAS) or coronary artery bypass graft (CABG). The revascularization group showed lower long-term mortality (with at least a 1-year follow-up) than the conservative therapy group: both after CAS (RR 0.66, CI 0.60–0.72) and after CABG (RR 0.62, CI 0.46–0.84), including in the dialysis-dependent patient group (RR 0.68, CI 0.59–0.79) [20].

A meta-analysis of 8 studies with 1,685 dialysis-dependent patients with CAD, of whom 739 patients underwent coronary revascularization and 946 received optimal MT, showed that revascularization (RR, 0.72, 95% CI 0.62–0.84) demonstrated a significantly lower long-term all-cause mortality compared to MT. Surgical revascularization showed no significant advantage over MT in reducing all-cause mortality (RR, 0.91, 95% CI 0.57–1.46) [21].

Comparison of endovascular and surgical myocardial revascularization

Due to the development of multivessel diffuse CAD in patients with CKD, together with severe calcinosis, many authors are wondering what the optimal surgical treatment method for coronary pathology in this patient cohort could be.

A 2021 meta-analysis of 32 studies with 84,498 patients demonstrated a comparison between 3 types of CHD treatment in patients with stage 4–5 CKD: MT, CAS, and CABG. The analysis revealed that all-cause mortality was lower in the CAS group than in the MT group at different follow-up periods: ≤1 month, 1 month

Table 2

Possible reasons for the reduced informativeness of some non-invasive CHD diagnosing methods in patients with ESRD [17]

Screening tests	Limitations of study
Exercise stress test	• Baseline ECG changes • Low exercise tolerance • Hypertensive response to exercise • Insufficient chronotropic response due to autonomic dysfunction
Stress echocardiography	• Operator dependent • Narrow ultrasound window in 20% of cases • Low exercise tolerance • Hypertensive response to exercise
Myocardial perfusion scintigraphy	Low sensitivity due to: • Uniform diffuse decrease in coronary blood flow (“balanced ischemia”) • Impaired vasoreactive response
CT coronary calcium scan	• Only low coronary calcium level is of value in predicting a negative outcome
Contrast-enhanced multislice coronary CT scan	• Low specificity due to severe coronary calcification

to 3 years, and >3 years. CABG compared with conservative therapy showed no significant advantage in reducing total mortality at any of the follow-up periods. Compared to CAS, CABG demonstrated a higher risk of mortality in early postoperative periods (≤1 month) and better outcomes in long-term follow-up (1 month to 3 years and more than 3 years) due to a lower risk of cardiovascular mortality and MACEs, as well as repeat revascularization [22].

Another study featuring 112 dialysis-dependent patients who underwent CAS (n = 86) or CABG (n = 26) between 2007 and 2017, also showed a higher risk of death in patients in the CABG group in the early postoperative period (within 1 month after surgery). However, long-term outcomes (overall mortality, MACE, repeat revascularizations) did not differ between the groups [23].

Medical treatment

According to the KDIGO guidelines, kidney recipients should take aspirin, beta-blockers and statins in accordance with cardiac clinical guidelines both while on the KT waiting list and postoperatively [7].

Antiplatelet therapy has been shown to reduce cardiovascular risk in CHD patients, but the prognostic effect of this group of drugs is not so obvious in ESRD patients. A number of studies have claimed that antiplatelet agents have no significant effect when used as both primary and secondary prophylaxis of cardiovascular events and on overall mortality in dialysis-dependent patients [24, 25].

As for the management of dialysis-dependent patients after coronary stenting, according to the literature, clopidogrel is preferred as the second antiplatelet drug (from the group of P2Y12 inhibitors) in addition to aspirin because of its greater safety in this category of patients compared to newer antiplatelet agents from this group (ticagrelor, prasugrel) [26]. The use of new P2Y12 inhibitors is acceptable only in cases of high ischemic and moderate hemorrhagic risk in ESRD patients [26] or in patients with clopidogrel resistance [27].

There is controversy regarding the appropriate duration of dual antiplatelet therapy (DAPT) in dialysis patients after coronary stenting.

Some reports argue that not all ESRD patients need 12 months of DAPT after stenting – a shorter dosage regimen is acceptable for some patients [28]. The 2019 EOC Guidelines for the diagnosis and management of chronic coronary syndromes suggested a 6-month DAPT regimen with aspirin and clopidogrel after intervention, with a possible shortening of the DAPT duration to 1–3 months for patients at high hemorrhagic risk [29]. Other studies have supported the use of a 6-month DAPT in the management of ESRD patients after coronary artery stenting [30, 31].

Other authors argue for the need to use prolonged DAPT in dialysis-dependent patients – longer than the established 12 months after intervention (15, 18 months) – due to lower cardiovascular risk without a significant increase in hemorrhagic risk [32].

The European Society of Cardiology proposed the use of prolonged DAPT for secondary prophylaxis in patients at high and very high risk of ischemic events (diffuse multivessel CAD, diabetes, recurrent MI, multifocal atherosclerosis, decreased left ventricular contractility, CKD with an estimated glomerular filtration rate (eGFR) of 15–59 ml/min/1.73 m^2) and low risk of hemorrhagic events (no history of ischemic or hemorrhagic stroke, gastrointestinal bleeding, gastrointestinal pathology associated with increased bleeding risk, liver failure, coagulopathy, extreme old age or frailty, ESRD with eGFR <15 ml/min/1.73 m^2) [29].

Other studies have suggested that the size and complexity of the coronary intervention procedure itself should be considered when deciding on DAPT duration. The following factors have been proposed, in which prolonged DAPT was associated with a reduced risk of cardiovascular events: 3 coronary arteries treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, recanalization of chronic occlusion, stent diameter <3 mm [33]. Coronary artery stenting in ESRD patients for acute MI was also mentioned among the indications for prolonged DAPT [34].

The effect of lipid-lowering therapy on cardiovascular risk depends on the CKD stage. Studies analyzing the effect of statin and ezetimibe therapy on cardiovascular outcomes in CKD patients, including dialysis-dependent patients, have shown that the effect of antihyperlipidemic drugs on outcomes is lower in patients with reduced eGFR and limited or absent in ESRD patients receiving dialysis treatment [35, 36]. Regarding statin dosage, it is recommended to use standard doses for CKD stages 1–2, and to reduce the dosage in advanced stages of the disease. Atorvastatin, which is practically not excreted by the kidneys but is mainly excreted by bile, is proposed as the drug of choice [36].

Hypertriglyceridemia can be managed through lifestyle modifications, including dietary adjustments, weight loss, increased physical activity, adequate glycemic control, and limitation of alcohol consumption [37].

Clinical guidelines for the management of patients with CKD K/DOQI and KDIGO do not recommend routine statins and a statins/ezetimibe combination in dialysis-dependent patients and children with CKD. However, statin or statin/ezetimibe therapy is recommended for primary and secondary prophylaxis of CVD in CKD patients not receiving RRT, as well as in patients after KT [37, 38].

The EOC and AHA guidelines recommend that statins or a statins/ezetimibe combination should be prescribed for patients with CKD stages 3–5, who are not receiving RRT, as well as for patients who, at the time of RRT initiation, were already receiving statins, ezetimibe,

or a combination of both, especially for patients with confirmed CAD. Statin therapy is not recommended in dialysis-dependent patients without confirmed coronary pathology [39, 40].

TREATMENT TACTICS FOR CHD IN KIDNEY RECIPIENTS

Comparison between myocardial revascularization and medical therapy

According to the available literature, studies comparing the treatment of CHD by coronary revascularization and selection of optimal drug therapy among post-kidney transplant patients have been less frequent than among kidney transplant candidates. The number of published reports on CABG in post-kidney transplant patients is limited [41].

A study including 1,460 kidney recipients found that correction of significant stenotic coronary lesion by coronary artery stenting (RR, 3.792, 95% CI 1.320–10.895) or CABG (RR, 6.691, 95% CI 1.200–37.323) was associated with better long-term (5-year) survival than medical therapy and was not associated with graft dysfunction and rejection [42].

Comparison of endovascular and surgical myocardial revascularization

MR techniques were compared among kidney recipients with coronary artery disease.

A recently published systematic review of 4 studies, in which 6,674 patients underwent CAS after KT and 4,402 patients underwent CABG, showed, that CAS compared with CABG was significantly associated with lower in-hospital mortality (OR 0.62, 95% CI 0.51–0.75) and 1-year postoperative mortality (OR 0.81, 95% CI 0.68–0.97), and lower acute kidney injury (AKI) prevalence (OR 0.33, 95% CI 0.13–0.84). Long-term outcomes (2–4 years of follow-up according to different studies included in the meta-analysis) were not significantly different between patients in the two groups (OR 1.05, 95%DI 0.93–1.18) [43].

A small retrospective study of kidney recipients with CHD who underwent MR by CAS (n = 27) or CABG (n = 24) showed better outcomes in the CAS group, but no significant difference between the groups was obtained: in-hospital mortality was 11.1% in the CAS group and 20.8% in the CABG group ($p = 0.45$), 1-year survival was 85.2% in the CAS group and 75% in the CABG group ($p = 0.97$), 4-year survival was 66.5% in the CAS group and 70% in the CABG group ($p = 0.97$). AKI after surgery was significantly more frequent after CABG (58.3% vs. 18.5%, $p < 0.01$). Graft survival at 1 year (95.7% in the CAS group and 94.1% in the CABG group) and at 4 years (76.8% in the CAS group and 77% in the CABG group) after revascularization was comparable between the groups ($p = 0.78$) [44].

Russian studies have confirmed the efficacy of MR by CAS after KT and its safety, manifested, among other things, by the absence of a significant negative effect of X-ray contrast agent on kidney graft function [45].

Medical treatment

The KDIGO clinical guidelines recommend diagnosing and treating CHD in post-KT patients according to the standards for the management of CHD in the general population [46].

Treatment of dyslipidemia in post-KT patients is similar to that in patients with CKD. The 2018 AHA guidelines [40] and 2019 EOC guidelines [39] recommend that kidney transplant recipients be categorized as high or very high cardiovascular risk, especially when low-density lipoprotein (LDL) levels >1.8 mmol/L, and that statins and ezetimibe should be used as first and second choice drugs for antihyperlipidemic therapy, respectively.

Statins have no proven protective effect on graft and patient survival. Nevertheless, a multicenter double-blind ALERT study, which analyzed 2,102 kidney recipients, showed a 32% reduction in LDL levels, as well as a decrease in the incidence of cardiovascular mortality and non-fatal MI in the group of patients treated with fluvastatin. At the same time, no significant difference in total mortality in the main and control groups was observed [47]. The best effect of CVD risk reduction was demonstrated when statin treatment is initiated within the first 2 years after KT [48]. Thus, a number of studies have shown that statin therapy should be recommended for kidney recipients with a well-functioning graft and an increased risk of CVD [37, 39].

Drug interactions are a common problem for post-transplant patients due to polypharmacy. Statins are metabolized in the liver by cytochrome P450, predominantly the CYP3A4 subtype. Fluvastatin, pravastatin, pitavastatin, and rosuvastatin are metabolized involving other cytochromes and are less likely to enter into drug interactions. Most statins are lipophilic except for the hydrophilic pravastatin and rosuvastatin, and therefore their use is considered safer [49]. According to the 2019 EOC guidelines [39] and 2013 KDIGO guidelines [37], it is recommended to start statin therapy at low doses with careful titration to avoid severe myopathy, rhabdomyolysis due to possible drug interactions, especially for patients receiving cyclosporine [39]. Drug interactions with tacrolimus are less frequent and dangerous compared to cyclosporine [50].

Ezetimibe is the drug of second choice for the treatment of dyslipidemia and is able to reduce LDL levels by 13–20% [49]. The American and European Societies of Cardiology recommend the use of ezetimibe in combination with statins for patients at high and very high risk of CVD or as secondary prevention to achieve target LDL cholesterol values [39, 40]. Ezetimibe can also be

prescribed as an alternative to statins in case of intolerance to statins. The use of ezetimibe with maximally tolerated statin doses has been shown to reduce dyslipidemia severity in kidney recipients without significant adverse effects on creatine phosphokinase levels and graft function [51].

The use of antihyperlipidemic drugs from other groups is limited in post-KT patients [49].

The use of aspirin in post-KT patients was analyzed in a FAVORIT trial, which showed no benefit of aspirin as primary prevention of cardiovascular events in kidney transplant recipients [52]. KDIGO clinical guidelines recommend the use of aspirin in kidney recipients with diabetes or as secondary prophylaxis in patients with confirmed CHD [46].

CONCLUSION

Pre-transplant screening for CHD in ESRD patients should not only focus on detection of coronary atherosclerosis, but also on assessing cardiovascular risk comprehensively before deciding whether to place patients on the KT waiting list.

Based on reports, endovascular MR has shown no worse, but in many cases better outcomes compared to both medical treatment and surgical revascularization for both dialysis-dependent patients and kidney recipients.

Drug treatment of CHD in dialysis-dependent patients and kidney recipients is generally consistent with drug treatment of CHD in the general population, but the specifics of antiplatelet agents and statins in these patients should be considered.

The authors declare no conflict of interest.

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