ORIGINAL ARTICLE

Aortic root dilation in kidney transplant recipients

Marta Obremska[1,2], Maria Boratyńska[3,4], Maciej Szymczak[3], Dorota Zyśko[5], Tomasz Płonek[1] Anna Goździk[1], Marian Klinger[3]

1 Department and Clinic of Cardiac Surgery, Wroclaw Medical University, Wroclaw, Poland
2 Department of Medical Emergency Service, Wroclaw Medical University, Wroclaw, Poland
3 Department and Clinic of Nephrology and Transplantation Medicine, Wroclaw Medical University, Wroclaw, Poland
4 Faculty of Natural Sciences and Technology, Karkonosze College in Jelenia Góra, Jelenia Góra, Poland
5 Department of Emergency Medicine, Wroclaw Medical University, Wroclaw, Poland

KEY WORDS

aortic root, dilation, kidney transplant

ABSTRACT

INTRODUCTION Aortic root (AoR) dilation is associated with cardiac damage and higher cardiovascular risk. Cardiovascular disease is the most common cause of death in patients after kidney transplantation (KTx).

OBJECTIVES The aim of this study was to assess the prevalence of enlarged AoR diameter in KTx recipients. Patients with bicuspid aortic valve, significant valvular disease, or evidence of connective tissue disorder were excluded.

PATIENTS AND METHODS A total of 87 KTx recipients were divided into 2 groups depending on immunosuppressive regimen: 41 patients receiving mammalian target of rapamycin inhibitors (mTORi) and 46 patients treated with calcineurin inhibitors (CNIs). In all patients, echocardiography was performed, laboratory and clinical markers of cardiovascular risk were assessed, and the AoR diameter was calculated.

RESULTS There were no differences between groups in age, sex, body surface area, body mass index, frequency of diabetes, hypertension, dyslipidemia, time after replacement therapy, creatinine levels, and estimated glomerular filtration rate. In the CNI group, the observed and calculated AoR diameters were similar ($P = 0.8$). In the mTORi group, the observed AoR diameter was higher than the calculated one ($P = 0.002$). The concentric and eccentric left ventricular hypertrophy was similar in both groups ($P = 0.12$ and $P = 0.69$, respectively). In the stepwise regression analysis, the AoR diameter was associated with body surface area and mTORi treatment.

CONCLUSIONS KTx recipients have a high prevalence of AoR dilation. Immunosuppressive regimen based on mTORi increases the incidence of AoR enlargement.

INTRODUCTION An aortic root (AoR) enlargement, measured at the sinuses of Valsalva, is mainly associated with inherited aortic diseases, such as Marfan syndrome or bicuspid aortic valve, and is a rare condition diagnosed in healthy individuals. In general population, AoR dilation has been associated with age, male sex, and anthropometric parameters such as weight, height, and body surface area (BSA).[1-3] The frequency of detection of AoR dilation varies between studies.[4-7] The differences result from a lack of a uniform definition of AoR dilation with respect to sex, age, and BSA, as well as from a high heterogeneity of study populations.

In recent years, sex-specific upper limits of normal AoR diameter indexed to BSA and height have been identified,[8-10] and an empirical equation to predict AoR diameter has been calculated.[11]

AoR dilation is asymptomatic and is found incidentally on imaging tests such as echocardiography, computed tomography, or magnetic resonance. Recent studies suggested that AoR dilation may be caused by the same risk factors as those for cardiovascular disease (CVD) and that an enlarged AoR diameter may predict cardiovascular events.[12-14]

During routine echocardiographic examinations, we noted an enlarged AoR diameter in kidney transplant (KTx) recipients. There are multiple risk factors, including immunosuppressive treatment, that contribute to cardiac and arterial

Correspondence to:
Marta Obremska, PhD,
Klinika Chirurgii Serca,
ul. Borowska 213, 50-556 Wrocław,
Poland, phone: +48 71 736 41 00,
email: mobremska@gmail.com
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TABLE 1 Anthropometric and clinical data of kidney transplant recipients depending on immunosuppressive therapy

Parameter	mTORi group	CNI group	*P* value
Female sex, n (%)	15 (37)	25 (54)	0.09
Age, y	59.3 (8.3)	60.9 (11.2)	0.5
BSA, m^2	1.87(0.20)	1.85 (0.18)	0.3
BMI, kg/m^2	26.2 (3.4)	26 (5.4)	0.9
Diabetes, n (%)	6 (14)	16 (34)	0.03
Hypertension, n (%)	37 (90)	42 (91)	0.9
Duration of kidney replacement therapy, mo	153.7 (63.7)	131.8 (57.7)	0.1
Duration of hemodialysis, mo	27.4 (27.7)	29.3 (24.3)	0.7
Time after KTx, mo	126.3 (59.2)	102.5 (51.9)	0.049
Total cholesterol, mmol/l	6.03 (1.5)	5.4 (1.2)	0.03
Triglycerides, mmol/l	2.5 (1.2)	1.9 (1.0)	0.03
Creatinine, µmol/l	147.6 (61.8)	164.4 (90.2)	0.3
eGFR, ml/s	0.77 (0.28)	0.69 (0.28)	0.2
Proteinuria, g/l	0.3 (0.3)	0.4 (0.4)	0.3
SBP, mm Hg	134.88 (11.37)	136.30 (13.14)	0.6
DBP, mm Hg	78.79 (7.23)	79.46 (8.77)	0.7

Data are presented as mean (SD) unless stated otherwise.

Abbreviations: BMI, body mass index; BSA, body surface area, CNI, calcineurin inhibitor; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate KTx, kidney transplantation; mTORi, mammalian target of rapamycin inhibitors; SBP, systolic blood pressure

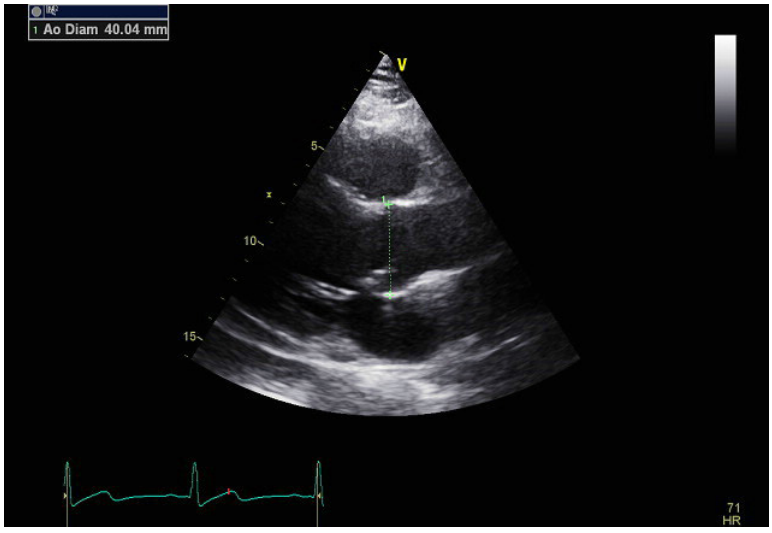

FIGURE 1 Measurement of aortic root diameter in the parasternal long-axis view

damage.[15,16] Premature development of CVD is the main cause of death in renal transplant recipients with a functioning allograft. Hence, there is an ongoing search for cardioprotective immunosuppressive therapy.

Ischemic heart disease, left ventricular (LV) structure and function, and arterial stiffness have been extensively studied in patients after KTx. However, abnormalities in the AoR diameter have not been documented in this population. Therefore, the aim of this study was to assess the prevalence of an enlarged AoR diameter and compare the effect of immunosuppressive regimens based on either mammalian target of rapamycin inhibitors (mTORi) or calcineurin inhibitors (CNIs) on the risk of AoR dilation in KTx recipients.

PATIENTS AND METHODS This study comprised 87 patients (47 men and 40 women; mean [SD] age, 60.1 [9.9] years, who received Ktx between 1987 and 2013. Data were collected over a mean (SD) period of 103 (56) months after KTx. Patients with bicuspid aortic valve, significant valvular disease, or evidence of connective tissue disorder were excluded. In all patients, demographic data, clinical history, and biochemical parameters before and after KTx were collected (**TABLE 1**). Additionally, information on immunosuppressive treatment, systolic and diastolic blood pressure (BP), development of diabetes, lipid concentrations, kidney graft function, and echocardiography after transplantation was obtained.

KTx recipients were divided into 2 groups depending on the type of immunosuppressive therapy. The first group received mTORi and the second received CNIs. The mTORi group included 41 patients (47%) at a mean age of 59 years, who received sirolimus (15 patients) or everolimus (26 patients) in combination with steroids and mycophenolate mofetil (15 patients) or only with steroids (8 patients). In 14 patients, low doses of the CNI tacrolimus or cyclosporine were administered. In 18 patients, mTORi was administered de novo after KTx as a protocol drug. In 22 patients, mTORi was introduced at a mean (SD) of 60 (59) months after transplantation due to neoplastic disease or signs of CNI nephrotoxicity. Patients received mTORi for a mean (SD) of 75.5 (39) months. The CNI group included 46 patients (53%) at a mean age of 60.9 years, who were treated with tacrolimus (22 patients) or cyclosporine (24 patients) with mycophenolate mofetil (32 patients) or azathioprine (4 patients) and prednisone. In this group, the immunosuppressive regimen remained unchanged from the time of KTx. The patients received CNIs for a mean (SD) of 103.3 (51) months.

The incidence of AoR dilation and its association with demographic, anthropometric, clinical, and laboratory data were evaluated and compared between groups. All these parameters were assessed at the same time as the cardiac examination by echocardiography. Laboratory test results and data on comorbidities at baseline were collected from the patients' medical records. Moreover, the following follow-up data were obtained: echocardiography and laboratory test results, as well as data on comorbidities diagnosed during the follow-up.

All patients provided written informed consent to participate in the study.

Echocardiography All patients underwent transthoracic echocardiography using a high-resolution ultrasound machine (GE Vivid E 9, Horten, Norway). The parasternal long-axis views

were used for the measurements of the aorta and left ventricle. The AoR diameter was measured in 2-dimensional view at the maximum diameter of the sinuses of Valsalva perpendicular to the long axis of the proximal aorta during the end--diastolic phase, following the leading edge-to--leading edge convention (FIGURE 1). The tubular part of the ascending aorta (TAo) was measured 3 cm above the aortic valve in 2-dimensional view using the same convention. The AoR diameter for each patient was calculated according to the equation for adults, based on sex, age, and BSA, as published by Devereux et al[11]: 2.423 + (age [y]*0.009) + (BSA [m^2]*0.461) – (sex [1=M. 2=F]*0.267), and referred to as $AoR_{Devereux}$. The calculated values of the AoR were compared with the observed measurement. Two classifications of AoR dilation were used. The first one included an AoR diameter larger than the calculated value. The second classification was based on the observed measurement of the AoR indexed for BSA (AoR/BSA). According to the latter definition based on the 2015 American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines,[8] a value larger then 1.9 cm/m^2 for men and 2.0 cm/m^2 for women indicated an AoR dilation. The measure of TAo was also indexed for BSA (TAo/BSA), and enlargement was defined as a value larger than 1.7 cm/m^2 for men and 1.9 cm/m^2 for women, based on the same guidelines.[8] The AoR index was calculated by dividing the observed AoR diameter by the $AoR_{Devereux}$ diameter for each patient.[8]

The linear measurements of the left ventricle, such as end-diastolic LV diameter (LVEDd), end--diastolic septal wall thickness, and end-diastolic posterior wall thickness (PWTd) obtained by M-mode were performed. The LV mass (LVM) was estimated according to the American Society of Echocardiography and was indexed to the BSA. The upper limit of the LV mass index (LVMI) was 115 g/m^2 for men and 95 g/m^2 for women. The relative wall thickness (RWT) was calculated for classified LV geometry, using the following formula: RWT = (2PWTd)/LVEDd. The concentric hypertrophy was diagnosed in the presence of the following factors: increased LVMI, normal cavity size of the left ventricle, and RWT >0.42. The eccentric hypertrophy was diagnosed in the presence of an increased LVMI, increased cavity size of the left ventricle, and RWT ≤0.42. The LV ejection fraction was measured using the modified Simson's rule. All echocardiographic examinations were performed by a cardiologist with 15 years of experience in echocardiography and certification of the Section of Echocardiography of the Polish Cardiac Society.

Statistical analysis Quantitative variables were presented as mean (SD) and qualitative variables, as numbers and percentages. The significance of the differences between variables was assessed using the *t* test. A multiple stepwise regression analysis was performed to assess the associations between the AoR diameter as the dependent variable and anthropometric, demographic, echocardiographic, biochemical, and clinical parameters (BSA, age, sex, time after KTx, cholesterol, triglyceride, and serum creatinine levels, estimated glomerular filtration rate, LVM, presence of diabetes, systolic and diastolic BP as an average of 3 measurements, and type of immunosuppressive therapy). *P* values of less than 0.05 were considered significant.

RESULTS Patients in the mTORi group did not differ from those in the CNI group with respect to age, sex, the cause of end-stage renal disease, and duration of hemodialysis before KTx. Prior to KTx, both groups had a similar frequency of diabetes (7% and 17% in the mTORi and CNI groups, respectively, $P = 0.16$), dyslipidemia (43.7% and 37% in the mTORi and CNI groups, respectively, $P = 0.08$), and comparable serum concentrations of total cholesterol and triglycerides. Hypertension was more common in the mTORi group (93% vs 70%, $P = 0.01$) before KTx.

Following KTx, anthropometric parameters such as BSA and BMI, the incidence of hypertension, systolic and diastolic BP, and kidney allograft function were similar in both groups. Anthropometric and clinical data in both groups at the time of the study (during the echocardiography examination) are shown in TABLE 1.

Diabetes was more frequent in the CNI group ($P = 0.03$). The time following KTx was longer in the mTORi group ($P = 0.049$), but there were no differences in the total duration of renal replacement therapy (the total duration of hemodialysis and the time after KTx) between the groups. The mTORi group had higher total cholesterol levels and triglycerides compared with the CNI group ($P = 0.03$). All patients from both groups received statins.

Echocardiographic parameters of the ascending aorta and left ventricle in both groups are shown in TABLE 2. The calculated $AoR_{Devereux}$ diameter was similar in both groups ($P = 0.2$). In the mTORi group, patients had a significantly higher AoR diameter than the CNI group ($P = 0.005$). In the CNI group, the observed and $AoR_{Devereux}$ diameters were similar ($P = 0.8$). In the mTORi group, the observed AoR diameter was significantly higher than the calculated values ($P = 0.002$). The AoR index was significantly higher in the mTORi group. The observed AoR diameter and $AoR_{Devereux}$ with the empirical equation in patients treated with mTORi and CNIs are shown in FIGURE 2.

In 59 patients (67.8%), the observed diameter was larger than the reference $AoR_{Devereux}$ value (31 patients [75.6%] in the mTORi group and 28 patients [60.9%] in the CNI group, $P = 0.14$). The mean (SD) difference of the AoR diameter between groups was 1.4 (4.2) mm: in the mTORi group, 2.4 (4.6) mm, and in the CNI group, 0.4 (3.7) mm ($P = 0.03$).

The enlargement of the AoR was more common in men (19 men [67.9%] in the mTORi group and

TABLE 2 Echocardiographic parameters of the aortic root, tubular part of the ascending aorta, and left ventricle in kidney transplant recipients depending on immunosuppressive therapy

Parameter	mTORi group	CNI group	*P* value
$AoR_{Devereux}$, mm	34.7 (2.1)	34.1 (2.1)	0.2
Observed AoR, mm	37.1 (4.9)	34.5 (3.5)	0.01
Aortic root index	1.1 (0.1)	1.02 (0.1)	0.03
TAo diameter, mm	36.8 (5.1)	34.4 (3.1)	0.03
LVEDd, mm	53.5 (7.02)	50.5 (5.3)	0.02
LVESd, mm	33.6 (7.3)	30.4 (5.6)	0.02
SWTd, mm	14.7 (3.1)	13.9 (1.9)	0.1
PWTd, mm	11.8 (0.9)	11.67 (1.21)	0.6
RWT	0.45 (0.08)	0.47 (0.06)	0.2
LVMI, g/m^2	159.4 (36.3)	143.03 (36.6)	0.04
LV hypertrophy, n (%)	40 (87)	38 (92.7)	0.4
Concentric LV hypertrophy, n (%)	21(51.2)	31 (67.4)	0.1
Eccentric LV hypertrophy, n (%)	8 (19.5)	3 (6.5)	0.7
LVEF, %	60.1 (6.9)	61 (5.7)	0.5

Data are presented as mean (SD) unless stated otherwise.

Abbreviations: $AoR_{Devereux}$, expected diameter of the aortic root; observed AoR, measured diameter of the aortic root; LV, left ventricle; LVEDd, left ventricular end-diastolic diameter; LVEDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass indexed for body surface area; PWTd, posterior wall end-diastolic diameter; SWTd, septum wall thickness at end diastole; RWT, relative wall thickness; TAo, tubular part of the ascending aorta

7 men [36.8%] in the CNI group, $P = 0.03$) than in women (12 women [38.7%] in the mTORi group and 3 women [33.3%] in the CNI group, $P = 0.77$).

The AoR/BSA ratio larger than the recommended upper limit was observed in 40 patients (46%) from both groups: in 21 patients (51.2%) in the mTORi group and 19 patients (41.3%) in the CNI group ($P = 0.35$).

The diameter of TAo was larger in the mTORi group compared with the CNI group ($P = 0.03$). The TAo/BSA ratio was larger than the recommended upper limit in 59 KTx recipients (67.8%) (32 patients [78.1%] from the mTORi group and 27 patients [58.7%] from the CNI group, $P = 0.05$).

In the mTORi group, patients had larger left ventricle measured in the end-diastolic and end-systolic phases ($P = 0.02$), as well as a higher LVMI ($P = 0.04$). Nine patients (1 woman and 8 men) did not have LV hypertrophy. Three of those patients (7%) were from the mTORi group, and six patients (13%) were from the CNI group ($P = 0.07$). The concentric and eccentric LV hypertrophy was similar in the mTORi and CNI groups ($P = 0.12$ and $P = 0.69$, respectively).

In the multiple regression analysis, none of the examined factors were related to the AoR diameter (TABLE 3). In the stepwise regression analysis, the AoR diameter was related to the BSA and mTORi treatment (TABLE 4).

DISCUSSION The present study showed a high prevalence of AoR dilation in patients after KTx, regardless of the assessment method. In previous studies on large general populations, such as the Framingham Heart Study, the Hypertension Genetic Epidemiology Network Study, the Cardiovascular Health Study, The Strong Heart Study, the prevalence of AoR dilation was low and differed between men (12.7%) and women (4.6%–10%) in both normotensive and hypertensive patients.[4,12,17,18]

To date, there have been no studies on the AoR size in renal transplant recipients. Thus, we compared the results of our patients to those with chronic kidney disease (CKD). Patients with CKD also showed a high prevalence of AoR dilation. Mulé et al[19] found a relationship between the AoR size and glomerular filtration rate in 379 CKD patients, most of whom had hypertension. The receiver operating characteristic curve analysis revealed that a glomerular filtration rate of less than 50 ml/min (estimated by the CKD-EPI equation) is the threshold value that can be used to distinguish patients with an enlarged AoR. The prevalence of AoR dilation increased with the stage of CKD and was the highest in stages 4 and 5. Depending on the method, AoR dilation in stage 5 was found in 39% of the patients, when using absolute measurements of the AoR, in 31% of the patients when the AoR was indexed for height, or in 18% of the patients, when using AoR normalized to BSA.[19]

In another study, Kaddorauch et al[20] evaluated the effect of impaired renal function on the aortic diameter in 97 pediatric patients (mean age, 11.2 years), including patients on chronic hemodialysis or peritoneal dialysis, and in 19 KTx recipients, who were not analyzed separately. More than 80% of the pediatric patients had hypertension. The authors found aortic dilation in 31% of the patients compared with 2.3% in healthy children and 2.8% in hypertensive children. Patients with aortic dilation often had poor control of BP and glomerular diseases.[20]

In the search for the underlying mechanisms of the high incidence of AoR dilation in KTx patients, we considered anthropometric parameters, BP, metabolic disorders, allograft function, duration of renal replacement therapy, and type and duration of immunosuppressive treatment. Apart from a relationship between the BSA and mTORi treatment, we did not find any correlations between these factors and AoR dilation. In our study, most patients from both groups had hypertension after KTx and its incidence did not differ between groups. The results of studies on the general population were ambiguous, although hypertension was associated with aortic dissection and rupture in patients with AoR dilation.[21] In some studies, the prevalence of AoR dilation was similar in hypertensive and normotensive individuals,[4] but other authors suggested a higher prevalence of AoR dilation in the hypertensive population, with differences between men and women.[5,8] However, those studies did not consider the duration of hypertension. A meta-analysis by Covella et al[6] on a pooled population of more

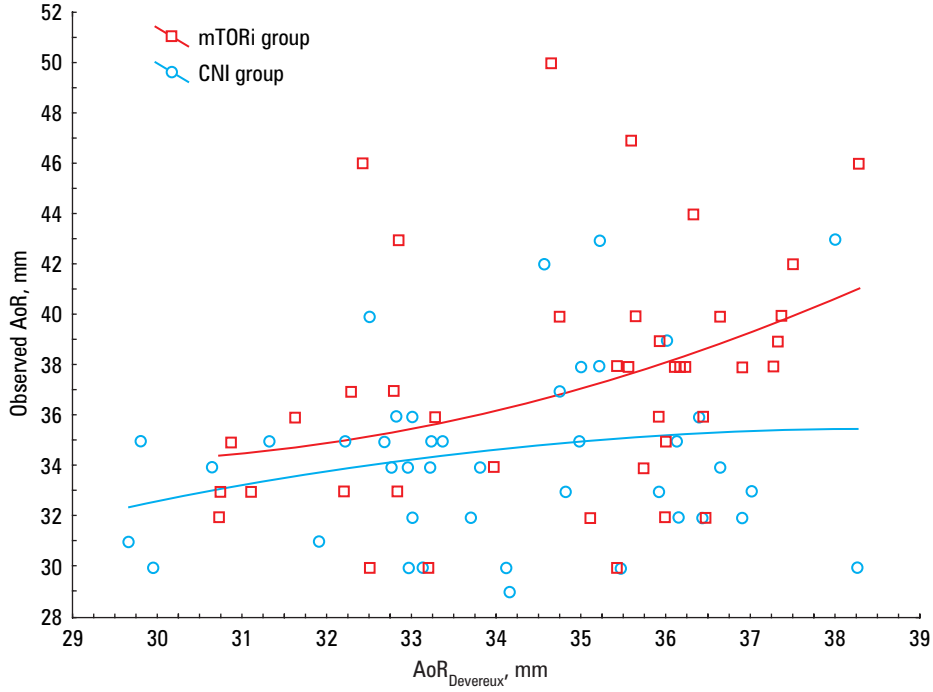

FIGURE 2 Plot of the observed aortic root (AoR) diameter and the expected diameter from the empirical equation ($AoR_{Devereux}$) in kidney transplant recipients receiving the mammalian target of rapamycin inhibitors (mTORi) and calcineurin inhibitors (CNIs)

TABLE 3 Multiple regression analysis for aortic root diameter in kidney transplant recipients

Parameter	β	SE of β	β	SE of β	*P* value
Age	–0.02	0.11	–0.01	0.05	0.9
BSA	0.23	0.13	5.28	3.08	0.1
Female sex	–0.14	0.14	–1.18	1.23	0.3
mTORi treatment	0.19	0.11	1.73	0.98	0.1
Time after KTx	0.16	0.12	0.01	0.01	0.2
Diabetes	0.001	0.10	0.01	1.04	0.9
Total cholesterol	0.14	0.12	0.01	0.01	0.3
Triglycerides	–0.20	0.12	–0.01	0.01	0.1
SBP	–0.12	0.11	0.04	0.04	0.3
DBP	–0.09	0.12	–0.05	0.07	0.4

$R^2 = 0.5125$, adjusted $R^2 = 0.1545$

Abbreviations: see TABLE 1

TABLE 4 Stepwise regression analysis for aortic root diameter in kidney transplant recipients

Parameter	β	SE of β	β	SE of β	*P* value
BSA	0.30	0.09	7.06	2.27	0.002
mTORi treatment	0.26	0.09	2.25	0.87	0.01

$R^2 = 0.4263$, adjusted $R^2 = 0.1628$

Abbreviations: see TABLE 1

than 10 000 patients showed that AoR dilation was more frequent in hypertensive patients (nearly 10%), particularly in men (12.7%).[6] An association between diastolic BP, the average night-time diastolic BP, mean arterial pressure, and AoR dilation was shown in the Framingham Heart Study and in the Cardiovascular Health Study.[3,12] LVM was a strong predictor of AoR dilation among hypertensive patients.[22]

In a study of patients with essential hypertension, Milan et al[5] showed a strong correlation between an enlargement of the AoR and the parameters of aortic stiffness, such as the aortic augmentation index and central pulse pressure. Aortic stiffness is commonly found in CKD, and similarly to AoR dilation, it correlates with renal function.[23] Aortic stiffness improved after KTx, but this improvement was sometimes intermittent or depended on immunosuppressive treatment.[24,25] It was also found that aortic stiffness is an independent predictor of cardiovascular events in the general population and in patients with end-stage renal disease, including KTx recipients.[26-28] Arterial stiffness is a result of accelerated vascular aging, which derives from the remodeling of large vessels and circumferential wall stress. The destructive effect of arterial stiffness arises from transmission of high flow pressure in the aorta into the capillary flow, which injures microcirculation particularly in high-flow organs such as the heart, brain, and kidneys.

In a recent study, Sahlen et al[29] found that a larger AoR influenced arterial elastance and stroke volume in patients with coronary artery disease. Patients with AoR dilation had lower effective arterial elastance (LV afterload), larger LV end-diastolic volume (LV preload), and larger stroke volume than patients with a normal AoR size. A positive association between the stroke volume and AoR size was observed in the general population.[4] The authors suggested that dilation of the AoR in elderly and hypertensive patients may be favorable, possibly by mitigating the adverse impact of concomitant aortic wall stiffening.[29] Thus, simultaneous studies of AoR dilation and arterial stiffness in transplant patients are justified.

We assessed the clinical relevance of AoR dilation in patients after KTx. There was no

association between the AoR diameter and CVD risk factors or LV function and structure. However, in the mTORi group (where the incidence of the AoR diameter was higher), the left ventricle was larger in the end-diastolic and end-systolic phases and LVMI was higher. LV hypertrophy in our study was found in most of the KTx recipients, both in the mTORi and CNI groups. The multiple stepwise regression analysis did not reveal a relationship between AoR enlargement and echocardiographic parameters of the left ventricle.

Numerous studies have shown an association between the AoR diameter and the risk of cardiovascular events. Gardin et al[12] studied a general population of 3993 individuals (>65 years of age) and found that a high AoR diameter at baseline was associated with an increased risk of congestive heart failure, stroke, and cardiovascular and all-cause mortality during a 10-year follow-up. Lam et al[13] showed a relationship between the AoR dilation and heart failure in the Framingham Heart Study, which included 6483 individuals followed for over 8 years. Cuspidi et al[22] reported that the AoR diameter indexed to height was predictive of incidental nonfatal and fatal CVD events among 1860 middle-aged individuals from the general population, who were followed for over 148 months. They found that the overall risk of cardiovascular events was significantly increased when the changes in the LV structure occurred simultaneously with AoR dilation. Such a combination was a stronger predictor of cardiovascular prognosis than LV hypertrophy alone. Masugata et al[14] reported that the AoR diameter may be a useful marker of subclinical LV diastolic dysfunction in patients with at least one cardiovascular risk factor such as hypertension, diabetes, or dyslipidemia.

We found an association between AoR enlargement and immunosuppressive regimen based on mTORi in KTx recipients. Patients treated with mTORi demonstrated a higher incidence of AoR dilation and a lager AoR diameter than those treated with CNIs. Therefore, patients treated with mTORi should undergo echocardiographic monitoring to reduce the risk of aortic complications, which increases with the degree of AoR enlargement.

The differences in the incidence of AoR dilation in the studied groups led us to consider dyslipidemia, which is a common side effect of mTORi treatment, as a possible cause. Serum cholesterol and triglyceride levels were significantly higher in patients treated with mTORi than those treated with CNIs, but there was no association between the lipid levels and AoR dilation. Cholesterol is involved in endothelial dysfunction and remodeling of the vascular wall through apoptosis and inflammation including the secretion of metalloproteinases. A deposition of cholesterol and triglycerides with an accompanying high tumor necrosis factor-α expression in the aortic wall was reported in guinea pigs treated with rapamycin.[30] Epidemiological studies have linked higher cholesterol levels with an increased risk of abdominal aorta dilation in contrast to thoracic aorta dilation. An aneurysm of the abdominal aorta is a result of inflammatory processes linked to atheromatosis, which is involved in extracellular matrix degeneration. Recently, Alegret et al[31] identified low-density lipoprotein cholesterol and apolipoprotein B as independent factors predicting an enlargement of the AoR diameter in 80 patients with bicuspid aortic valve (a common congenital cardiac malformation), suggesting that lipids may be involved in the pathomechanism of AoR dilation.

The effect of mTORi on the AoR dilation seems multifactorial. Experimental studies showed that 7-day exposure of rat aortae and hearts to sirolimus led to impaired endothelium-dependent and -independent vascular relaxation, a reduced formation of vascular nitric oxide, and an increased production of transmural radical oxygen species.[32] Disturbing the balance between radical oxygen species and antioxidant enzymes may increase the activity of matrix metalloproteinase and promote elastin fiber fragmentation. Moreover, rapamycin is a powerful inhibitor of the platelet-derived growth factor and enhances the expression of interstitial metalloproteinases through this mechanism.

The inhibition of endothelial cell proliferation and arterial smooth muscle cell proliferation and migration is another mechanism by which mTORi contribute to AoR dilation.[33,34] This effect may damage aortic wall repair and regeneration but is useful in the prevention of accelerated vasculopathy in transplanted hearts, chronic graft vascular disease, and restenosis after percutaneous transluminal coronary angioplasty.[35,36] The cardioprotective effect of mTORi observed in heart transplant recipients is contrary to recent reports of increased mortality of renal transplant recipients treated with mTORi.[37,38]

The limitations of our study include a small number of patients and the lack of a comparison of the AoR sizes measured before immunosuppressive treatment to the ones obtained after the treatment. Moreover, many patients (30%) had been treated with CNIs before they switched to the treatment protocol based on mTORi, and some patients received both CNIs and mTORi.

Studies on a large population of renal transplant recipients, with a simultaneous examination of arterial stiffness and AoR size together with cardiac assessment, may help explain whether AoR dilation is a compensatory mechanism of aortic stiffness or a predictive factor of cardiovascular events.

In conclusion, renal transplant recipients have a high prevalence of AoR dilation. Patients following the immunosuppressive regimen based on mTORi have larger diameters of the AoR compared with those treated with CNIs. KTx recipients should be monitored due to the potential risk of aortic complications, especially when treated with mTORi.

SUPPLEMENTARY MATERIAL Supplementary material is available with the article at www.pamw.pl.

CONTRIBUTION STATEMENT OM conceived the concept of the study. OM and BM contributed to the design of the research. All authors were involved in data collection. OM, BM, and ZD analyzed the data. All authors edited and approved the final version of the manuscript.

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