Long-Term Impact of Different Immunosuppressive Drugs on QT and PR Intervals in Renal Transplant Patients

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Background: Sudden cardiac deaths due to arrhythmias are thought to be an important cause of mortality in patients with renal transplants. Exposure to immunosuppressive drugs may lead to QT or PR interval abnormalities which may consequently cause arrhythmias. Our study investigated the long term impact of four different immunosuppressive drugs on PR and corrected QT intervals (QTc) in renal transplant patients

Methods: The study population consisted of 98 kidney transplant recipients. Study patients were receiving immunosuppressive management with tacrolimus, cyclosporine A, everolimus or azathioprine according to the local protocols. QTc and PR intervals obtained from the most recent post-transplant electrocardiograms were compared with the pre-transplant intervals dated before the transplantation procedure.

Results: Post-transplant QTc intervals had prolonged significantly in comparison to the pre-transplant QTc intervals in all groups. However, there were no significant differences between the immunosuppressive agents with regard to post-transplant QTc interval prolongation ($p > 0.05$). There were no significant differences between the groups with regard to the pre and post-transplant PR interval changes ($p > 0.05$).

Conclusions: QT interval prolongation, a marker of risk for arrhythmias and sudden death, is highly prevalent among kidney transplant patients receiving different classes of immunosuppressive drugs.

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ventricular tachycardia/fibrillation; basic; pharmacology; pharmacokinetics/dynamics; clinical

Kidney transplantation is the treatment of choice for end-stage renal disease and has been shown to be associated with improved quality of life and reduced morbidity and mortality rates.¹ Renal transplantation improves cardiac function and eventually confers a survival benefit in patients with renal disease. However, kidney transplant recipients continue to die prematurely despite the improvements in surgery and immunosuppressive therapies. Mortality from cardiovascular diseases is the leading cause of death after

renal transplantation and sudden cardiac death accounts for a significant proportion of deaths.² Cardiovascular events in renal transplant patients may be associated with the pretransplant disease process, coexistence of several cardiovascular risk factors or direct effect of immunosuppressant medications.³

The mechanisms responsible for the increased risk of sudden deaths in renal transplant patients are not yet fully understood, but complex ventricular arrhythmias have been documented to

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be common among kidney transplant recipients with functioning grafts.⁴ Arrhythmias are thought to be an important cause of sudden death, which is responsible for 15% of the mortality in this population.^{5,6} Cardiovascular diseases in the form of coronary artery disease, left ventricular hypertrophy and congestive heart failure are common in patients with renal disease. These syndromes are associated with strong remodeling of cardiac ion channels resulting in the acquired cardiac channelopathies with an increased risk of sudden cardiac death. Therefore, administration of any drug that is capable of modulating ion channels may result in electrocardiographic QT and PR interval changes and subsequently an elevated risk of life-threatening arrhythmias.⁷ In this context, long-term exposure to immunosuppressive drugs may be an important contributor to the QT or PR interval abnormalities which may consequently be leading to arrhythmias.

ECG parameters, such as PR, QTc, and QRS durations, have been shown to predict mortality and cardiovascular events in the general population especially in patients at high risk.⁸⁻¹² These abnormalities have been linked to occurrence of malignant arrhythmias in different cardiac diseases.¹³ Several studies also suggested that end-stage renal disease patients have prolonged QTc duration and that this may be linked to the occurrence of ventricular arrhythmias.¹⁴⁻¹⁶ Electrocardiographic abnormalities, particularly related with the QTc interval, are significantly greater in patients on hemodialysis in comparison to healthy individuals.¹⁷ These abnormalities are also suggested as indicators of subsequent arrhythmia risk in patients on hemodialysis.¹⁸

Although abnormalities of QT and PR intervals are considered to be arrhythmia predictors, ECG abnormalities have not been extensively assessed in the long-term follow-up of patients with kidney transplantation. High rate of sudden cardiac death in transplant patients may be associated with the arrhythmogenic potential of immunosuppressive agents, but the information regarding the impact of long-term exposure to immunosuppressive drugs on ECG parameters of patients with renal transplantation is also lacking. Therefore, the primary aim of our study was to investigate the long-term impact of four different immunosuppressive drugs on PR and QTc intervals in patients with renal transplantation. Our secondary aim was to document temporal PR and QTc interval changes

in the long-term follow-up of patients with renal transplantation.

PATIENTS AND METHODS

The study population consisted of 98 kidney transplant recipients (55 men, 43 women) under immunosuppressive treatment with functioning grafts. Study patients were receiving immunosuppressive management with tacrolimus, cyclosporine A, everolimus, or azathioprine according to the local protocols. All patients were recruited from the outpatient transplant unit of Istanbul University Cerrahpasa School of Medicine.

Renal transplant patients satisfying the following inclusion criteria were enrolled; patients >18 years of age who underwent successful kidney transplantation and having functional grafts, creatinine level <2 mg/dL. The exclusion criteria were; clinical evidence of coronary artery disease and heart failure, hepatic failure, neoplastic or infectious diseases, patients receiving class I or class III antiarrhythmic drugs, patients using β -blockers and/or nondihydropyridine group calcium channel blockers (verapamil and diltiazem), ECG findings of bundle branch block, atrial fibrillation or atrial flutter. Patients with a history of renal transplantation less than 6 months of duration or who experienced a $\geq 20\%$ increment in plasma creatinine levels at any time during the preceding 3 months were also excluded from the study. Congestive heart failure and coronary artery disease were screened by symptoms, physical examination, ECG and transthoracic echocardiography. Complete bundle branch block was diagnosed when the duration of the QRS complex on the ECG was ≥ 120 ms.

Conventional 12-lead ECG was obtained from patients with functional grafts receiving immunosuppressive medication. The latest available pretransplant ECGs were obtained from the patient charts and analyzed accordingly. The most recent posttransplant ECGs were compared with the pretransplant ECGs dated before the transplantation procedure. The corrected QT intervals (QTc) and PR intervals obtained from the most recent posttransplant ECGs were compared with the pretransplant intervals dated before the transplantation procedure. All ECGs were recorded at a paper speed of 25 mm/s. The measurement of QTc and PR intervals for each lead were performed manually with calipers by a single observer. The

Table 1. Baseline Demographic and Laboratory Characteristics of the Patients

	Tacrolimus (n = 51)	Cyclosporine (n = 23)	Everolimus (n = 15)	Azathioprine (n = 9)	P
Age (years)	39.12 ± 9.61	39.76 ± 9.36	39.43 ± 9.23	38.50 ± 8.28	>0.05
BUN (mg/dL)	45.71 ± 17.78	47.00 ± 15.68	50.21 ± 14.38	42.75 ± 11.52	>0.05
Creatinine (mg/dL)	1.417 ± 0.433	1.610 ± 0.375*	1.649 ± 0.469*	1.113 ± 0.304	<0.05*
GFR (mL/min/1.73 m ²)	54.49 ± 21.31	48.19 ± 16.73	42.93 ± 14.37	63.38 ± 15.10	>0.05

BUN = blood urea nitrogen; GFR = glomerular filtration rate.

*Statistically significant (P < 0.05) compared to tacrolimus and azathioprine groups.

QT interval was measured from the earliest onset of the QRS complex to the point of the T-wave offset, defined by a return of the terminal T wave to the isoelectric TP baseline. In the presence of U wave interrupting the T wave, the terminal portion of the visible T wave was extrapolated to the TP baseline to define the point of the T-wave offset. If the end of T wave could not be reliably determined, the lead was not included in the analysis. Each QT interval was corrected for the patient's heart rate using the Fridericia's formula ($QT_{Fc} = QT/RR^{1/3}$), where QTc is the corrected QT interval. PR interval is measured from the beginning of the P wave to the beginning of the QRS complex.

The laboratory tests included blood urea nitrogen, creatinine, glucose, total cholesterol, and triglycerides. Patients with a history of established diabetes mellitus and patients with fasting glucose levels ≥ 126 mg/dL or with a glycated hemoglobin of (Hb A1C) $\geq 6.5\%$ were considered as diabetics. Hypercholesterolemia was defined as fasting blood total cholesterol levels >240 mg/dL and triglyceride levels >150 mg/dL or previous diagnosis of hyperlipidemia and current use of antihyperlipidemic medication. Hypertension was defined as blood pressure $\geq 140/90$ mmHg or previous diagnosis of arterial hypertension and current use of antihypertensive drugs. Patients with a body mass index (BMI) ≥ 30 were classified as obese. Estimated GFR (eGFR) was calculated with Cockcroft–Gault formula.

Statistics

Statistical analyses were performed using the SPSS software version 17 (SPSS, Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov) to determine whether or not they were normally distributed. Descriptive analyses were presented mean $\pm$ standard deviation (SD) and categorical variables were expressed as percentages. Groups were compared with the one-way ANOVA and chi-square tests. When an overall significance was observed, pairwise post hoc tests were performed using Tukey's test. Multivariate analysis was used to investigate the association between the baseline demographic and laboratory characteristics of the patients. Paired samples *t*-test was used for comparison of pre- and posttransplant heart rates, RR intervals and QRS intervals as appropriate. Paired samples *t*-test was used to compare the measurements at two time points (pre- and posttransplantation) for PR and QTc intervals. An overall P value of less than 0.05 was considered to be statistically significant.

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RESULTS

All patients (n = 98) were receiving immunosuppressive treatment in addition to steroids with the following drugs according to the local protocols: 51 patients were being treated with tacrolimus + MPA (mycophenolic acid derivatives) (52%, 31 male, 21 female, mean age 39.12 $\pm$ 9.61), 23 patients with cyclosporine A + MPA (23.5%, 12 male, mean age 39.76 $\pm$ 9.36), 15 patients with everolimus + MPA (15.3%, 9 male, mean age 39.43 $\pm$ 9.23) and finally nine patients with azathioprine alone (9.2%, 4 male, mean age 38.50 $\pm$ 8.28). The mean duration from transplantation was 4.12 $\pm$ 2.82 years in tacrolimus group, 4.88 $\pm$ 3.12 years in cyclosporine A group, 7.28 $\pm$ 4.42 years in everolimus group and 8.57 $\pm$ 7.27 in azathioprine group.

The demographic, laboratory and clinical characteristics of the four groups are demonstrated in Tables 1 and 2. There were no statistically significant differences between the groups with respect to age, urea, GFR, hypertension, hyperlipidemia, obesity, and diabetes mellitus. However, creatinine levels were significantly higher in patients

Table 2. Clinical Characteristics of the Patient Groups

	Tacrolimus (n = 51)		Cyclosporine (n = 23)		Everolimus (n = 15)		Azathioprine (n = 9)		P
	n	%	n	%	n	%	n	%	
HTN	27	64.3	15	71.4	6	42.9	5	62.5	>0.05
DM	10	23.8	4	19.0	5	35.7	2	25.0	>0.05
HLP	8	19.0	3	14.3	4	28.6	2	25.0	>0.05
Obesity ^a	7	16.7	4	19.0	4	28.6	2	25.0	>0.05

HTN = hypertension; DM = diabetes mellitus; HPL = hyperlipidemia.

^aBMI ≥ 30 kg/m².

receiving cyclosporine and everolimus in comparison to patients receiving tacrolimus and azathioprine ($P = 0.013$). Multivariate analysis of the data revealed that increased age and presence of obesity were significantly associated with DM ($P = 0.003$), increased age and creatinine were associated with reduced GFR ($P = 0.026$) and increased age and presence of DM were significantly associated with obesity ($P = 0.038$).

There were no significant differences between the four groups with regard to the pretransplantation QTc intervals ($P > 0.05$). Electrocardiographic analysis revealed that posttransplant QTc intervals had prolonged significantly in comparison to the pretransplant QTc intervals in all immunosuppressive drug groups (Table 3). However, statistical analysis of four groups demonstrated that there were no significant differences between the immunosuppressive agents with regard to the pre- and posttransplant QTc interval changes ($P > 0.05$).

There were no significant differences between the 4 groups with regard to the pretransplantation PR intervals ($P > 0.05$). The posttransplant PR intervals were significantly shortened in patients receiving tacrolimus and everolimus ($P < 0.05$) (Table 3). On the other hand, there were no statistically significant changes in PR intervals of patients receiving azathioprine and cyclosporine ($P > 0.05$). However, comparison of patients receiving tacrolimus and everolimus demonstrated that there were no significant differences between the groups with regard to the pre- and posttransplant PR interval changes ($P = 0.626$).

The statistical analysis of all study patients surprisingly showed a statistically significant posttransplant increase in heart rates and consequently posttransplant reductions in RR intervals ($P = 0.001$ and $P < 0.50$, respectively) (Table 4). There was no statistically significant difference between pretransplant and posttransplant QRS intervals duration.

DISCUSSION

Renal transplantation is the preeminent treatment for end-stage renal disease patients. A number of reports have demonstrated that kidney transplant recipients have less comorbidities, improved quality of life and better survival in relation to patients on long-term dialysis therapy.¹⁹ Posttransplant life expectancy is significantly increased, therefore nonimmune complications related to the transplant and posttransplant course have emerged as important factors in defining long-term outcomes.²⁰ However, the high incidence of cardiovascular death is a significant barrier to improve long-term outcomes in patients with renal transplants.²¹ Increased awareness of cardiovascular disease has resulted in a reduction in cardiovascular disease-related deaths over time yet cardiovascular disease remains the major cause of death in transplant recipients. The high incidence of cardiovascular disease in renal transplant patients can be attributed to three categories of risk factors. First, the conventional risk factors such as age, gender, family history, smoking, and hypertension may be more heavily represented, at least to some extent, in the transplant population. Second, there may be additional risk factors associated with deterioration of renal function or to abnormalities occurring secondary to renal dysfunction such as anemia and hypertension. Third, there are cardiovascular risk factors specifically related to transplantation, most notably those occurring secondary to adverse effects of immunosuppressive therapy.²²

A remarkable proportion of cardiovascular deaths in renal transplant patients are thought to be associated with sudden cardiac deaths.^{5,23,24} The mechanisms and risk factors responsible for the increased risk of sudden deaths in these patients are not fully understood yet, but complex ventricular arrhythmias have been documented to

Table 3. Changes in PR and QTc Intervals in Transplant Patients Receiving Different Immunosuppressive Agents

	Pretransplant PR (ms)	Posttransplant PR (ms)	P
Tacrolimus (n = 51)	143.43 ± 29.68	127.38 ± 25.67	<0.05*
Cyclosporine (n = 23)	138.00 ± 27.78	128.10 ± 25.22	>0.05
Everolimus (n = 15)	142.14 ± 37.86	120.00 ± 23.86	<0.05*
Azathioprin (n = 9)	131.25 ± 15.75	118.75 ± 18.85	>0.05
	Pretransplant QTc (ms)	Posttransplant QTc (ms)	P
Tacrolimus (n = 51)	417.99 ± 27.72	436.47 ± 35.26	<0.05*
Cyclosporine (n = 23)	421.74 ± 27.28	450.96 ± 31.63	<0.05*
Everolimus (n = 15)	421.14 ± 30.86	454.60 ± 19.82	<0.05*
Azathioprin (n = 9)	425.21 ± 23.32	449.15 ± 31.85	<0.05*

*Statistically significant (P < 0.05).

ms = milliseconds.

Table 4. Comparison of Pretransplant and Posttransplant Heart Rates, RR, and QRS Intervals (n = 98)

	Pretransplant	Posttransplant	P
Heart rate (bpm)	80.41 ± 15.58	85.26 ± 14.09	0.001*
RR interval (ms)	774.13 ± 150.49	713.01 ± 128.36	<0.05*
QRS interval (ms)	78.53 ± 18.13	81.33 ± 17.15	>0.05

*Statistically significant (P < 0.05).

bpm = beat per minute; ms = milliseconds.

be common among kidney transplant recipients with functioning grafts⁴ and pointed as one of the etiologies of sudden death, which is responsible for 15% of the mortality in this population.^{5,6}

A number of studies have reported that immunosuppressive agents may potentially contribute to the risk of cardiovascular events through the development of new-onset diabetes mellitus, hypertension and hyperlipidemia in renal transplant patients.²⁵ However, the contribution of these immunosuppressive agents to increased cardiovascular mortality may not solely be related to worsening of the conventional risk factors. This increase in mortality may also be associated with their potential arrhythmogenic potential. Several workgroups reported life threatening arrhythmias including sinus arrests, and ventricular arrhythmias as well as QT abnormalities related to the administration of some immunosuppressive agents which are also commonly being used in renal transplant patients.^{26–28} Despite major differences in chemical structures, both cyclosporine A and tacrolimus inhibit the calcineurin pathway. This inhibition may contribute not only to the immunosuppressant effects of both drugs but also the sympathetic excitation and other unwelcome effects. However, the mechanisms responsible for the increased QT changes under calcineurin inhibitors remain unclear.

Electrocardiographic findings, particularly PR, QTc, and QRS durations, have been shown to predict mortality and cardiovascular events in the general population especially in patients at high risk.^{8–12} Preclinical evaluation of delayed ventricular repolarization, manifested as a prolonged QT interval, reflects the electrical instability of the myocardium and is routinely used as an indicator of potential risk or proarrhythmia such as torsades de pointes, ventricular fibrillation and sudden death.²⁹ Therefore, a prolonged QT interval and abnormalities in QT dispersion may also provide prognostic information in renal transplant patients.

QT abnormalities are already commonly encountered in chronic renal patients, particularly in patients undergoing dialysis, and possess an increased risk of cardiovascular mortality.³⁰ Renal transplantation improves cardiac function and eventually confers a survival benefit in patients with renal disease. Electrolyte abnormalities normalize, left ventricular hypertrophy tend to decrease and the autonomic dysfunction improves following renal transplantation.^{31,32} Correction of these pathologic conditions by renal transplantation is expected to be associated with the improvement of the QT abnormalities in patients undergoing hemodialysis. However, our study revealed that in the long-term follow-up, posttransplant QTc intervals have been significantly prolonged in comparison to the

pretransplant QTc intervals in patients with renal transplants. Given the association of QT abnormalities with ventricular arrhythmias, a prolonged QT interval and abnormalities in QT dispersion may also provide prognostic information in renal transplant patients. To the best of our knowledge, a limited number of small scale studies have investigated the QT interval changes in renal transplant patients shortly after the transplantation. A small study reported normalization in QT intervals in patients with successful renal transplantations (n = 26) in comparison to a group of patients on hemodialysis (n = 26). However, these measurements have been performed just weeks (2–8 weeks) after transplantation and therefore do not reflect the impact of immunosuppressive drugs on QT intervals in the long-term management. Moreover, pretransplant QT was not known in transplant group and comparison with the posttransplant values was not performed.³³ Another study compared QT dispersion of 34 renal transplant patients (mean time after transplantation was 51.8 ± 40.4 months) with 34 healthy control subjects and found that QT dispersion was not statistically different in patients with transplantation with respect to healthy control subjects. Although the mean time after transplantation was reasonably long, this study did not compare the pretransplant and posttransplant QTc intervals in renal transplant patients.³⁴ Finally, Monfared et al., compared pretransplant and posttransplant QTc intervals in 34 patients with renal transplantation. They showed reduction of QTc interval after successful renal transplantation. However, the posttransplant QTc intervals were measured only 2 weeks after the transplantation and obviously this finding do not reflect the potential impact of long-term exposure to immunosuppressive drugs on QTc intervals.³⁰ In contrary to those findings, our study revealed that the QT interval prolongation is highly prevalent in the long-term follow up of kidney transplant patients. A limited number of studies have compared QT prolongation in patients using tacrolimus or CyA, however comparison of four different immunosuppressive drugs with regard to their long-term impact on ECG parameters in renal transplant patients has not been carried out.^{35, 36}

Preexisting QT interval abnormalities in renal transplant patients may be induced by electrophysiological remodeling of the heart due to concomitant cardiovascular disease such as coronary

artery disease, left ventricular hypertrophy and heart failure. Inevitably, exposure to multiple potentially proarrhythmic medications (including immunosuppressive agents), and their abnormal excretion and metabolism may also contribute to the electrocardiographic changes and eventually the risk of arrhythmia in renal transplant patients. We believe that the duration and extent of drug exposure is also important in determination of arrhythmogenic risk and therefore our results revealing QT and PR changes in long-term follow-up is important. Therefore, in contrary to some small studies reporting improvement in QT intervals shortly after transplantation, we have documented QT prolongation in the late posttransplant measurements. The ECG analysis also surprisingly showed a statistically significant posttransplant increase in heart rates and consequent reductions in RR intervals. Despite this increase in heart rates and reductions the RR intervals of posttransplant patients, QTc was documented to be increased significantly, which further supports our findings. To our knowledge, our study was the first study investigating the long-term impact of four different immunosuppressive drugs, namely tacrolimus, cyclosporine A, everolimus, and azathioprine, on PR and QTc intervals. However, lack of the data on the association of cardiovascular outcomes of the patients with the QTc prolongation could be considered as a limitation of our study.

A limited number of small scale studies reported normalization of QT intervals in renal transplant patients shortly after successful transplantation. In contrary to those findings, our study revealed that the QTc interval prolongation, a marker of risk for arrhythmias and sudden death, is highly prevalent among kidney transplant patients receiving different classes of immunosuppressive drugs. However, there were no significant differences between the immunosuppressive agents with regard to posttransplant QTc interval prolongation. Our study indicates that close follow-up of QT and PR intervals should be considered as an indispensable part of routine evaluation of renal transplant patients. Evidently, other drugs with QT prolongation potential should also be used cautiously in patients receiving immunosuppressive agents. Further dedicated studies focusing on the clinical importance of immunosuppressive agents on PR and QTc changes are needed in attempt to contribute in reducing the rate of sudden death in renal transplant patients.

REFERENCES

- Hashiani AA, Rajaeefard A, Hasanzadeh J, et al. Ten-year graft survival of deceased-donor kidney transplantation: A single-center experience. *Ren Fail* 2010;32(4):440-447.
- Bumgardner GL, Henry ML, Elkhammas E, et al. Obesity as a risk factor after combined pancreas/kidney transplantation. *Transplantation* 1995;60:1426-1430.
- Gill JS. Cardiovascular disease in transplant recipients: Current and future treatment strategies. *Clin J Am Soc Nephrol* 2008;3(Suppl 2):S29-S37.
- Marcassi AP, Yasbek DC, Pestana JO, et al. Ventricular arrhythmia in incident kidney transplant recipients: Prevalence and associated factors. *Transpl Int* 2011;24(1):67-72.
- West M, Sutherland DE, Matas AJ. Kidney transplant recipients who die with functioning grafts: Serum creatinine level and cause of death. *Transplantation* 1996;62(7):1029-1030.
- Jardine AG, Fellström B, Logan JO, et al. Cardiovascular risk and renal transplantation: Post hoc analyses of the Assessment of Lescol in Renal Transplantation (ALERT) Study. *Am J Kidney Dis* 2005;46(3):529-536.
- Gussak I, Gussak HM. Sudden cardiac death in nephrology: Focus on acquired long QT syndrome. *Nephrol Dial Transplant* 2007;22(1):12-14.
- Cheng S, Keyes MJ, Larson MG, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *J Am Med Acad* 2009;301:2571-2577.
- Oikarinen L, Nieminen MS, Viitasalo M, et al; for LIFE Study Investigators. QRS duration and QT interval predict mortality in hypertensive patients with left ventricular hypertrophy: The Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension* 2004;43:1029-1034.
- Vrtovec B, Delgado R, Zewail A, et al. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. *Circulation* 2003;107:1764-1769.
- Iuliano S, Fisher SG, Karasik PE, et al. QRS duration and mortality in patients with congestive heart failure. *Am Heart J* 2002;143:1085-1091.
- Elhendy A, Hammill SC, Mahoney DW, et al. Relation of QRS duration on the surface 12-lead electrocardiogram with mortality in patients with known or suspected coronary artery disease. *Am J Cardiol* 2005;96:1082-1088.
- Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000;36(6):1749-1766.
- Stewart GA, Gansevoort RT, Mark PB, et al. Electrocardiographic abnormalities and uremic cardiomyopathy. *Kidney Int* 2005;67:217-226.
- Suzuki R, Tsumura K, Inoue T, et al. QT interval prolongation in the patients receiving maintenance hemodialysis. *Clin Nephrol* 1998;49:240-244.
- Voiculescu M, Ionescu C, Ismail G. Frequency and prognostic significance of QT prolongation in chronic renal failure patients. *Rom J Intern Med* 2006;44:407-417.
- Cupisti A, Galetta F, Morelli E, et al. Effect of hemodialysis on the dispersion of the QTc interval. *Nephron* 1998;78(4):429-432.
- Buemi M, Aloisi E, Coppolino G, et al. The effect of two different protocols of potassium haemodiafiltration on QT dispersion. *Nephrol Dial Transplant* 2005;20(6):1148-1154.
- Collins AJ, Foley RN, Herzog C, et al. US renal data system 2012 annual data report. *Am J Kidney Dis* 2013;61(1 Suppl 1):A7, e1-476.
- Kuo CS, Atarashi H, Reddy CP, et al. Dispersion of ventricular repolarization and arrhythmia: Study of two consecutive ventricular premature complexes. *Circulation* 1985;72(2):370-376.
- Liu T, Brown BS, Wu Y, et al. Blinded validation of the isolated arterially perfused rabbit ventricular wedge in preclinical assessment of drug-induced proarrhythmias. *Heart Rhythm* 2006;3(8):948-956.
- Straus SM, Sturkenboom MC, Bleumink GS, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur Heart J* 2005;26(19):2007-2012.
- Morales JM, Marcén R, Andrés A, et al. Renal transplantation in the modern immunosuppressive era in Spain: Four-year results from a multicenter database focus on post-transplant cardiovascular disease. *Kidney Int Suppl* 2008;(111):S94-S99.
- Kasiske BL, Guijarro C, Massy ZA, et al. Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 1996;7(1):158-165.
- Jardine AG. Assessing the relative risk of cardiovascular disease among renal transplant patients receiving tacrolimus or cyclosporine. *Transpl Int* 2005;18(4):379-384.
- Hodak SP, Moubarak JB, Rodriguez I, et al. QT prolongation and near fatal cardiac arrhythmia after intravenous tacrolimus administration: A case report. *Transplantation* 1998;66(4):535-537.
- Calandra S. Sinus arrest during tacrolimus treatment: Was the QT interval prolonged? *Transplantation* 1998;66(3):402-404.
- Johnson MC, So S, Marsh JW, et al. QT prolongation and Torsades de Pointes after administration of FK506. *Transplantation* 1992;53(4):929-930.
- Foroughi M, Karkhaneh Yousefi Z, Majidi Tehrani M, et al. Prolonged QT interval and coronary artery bypass mortality due to heart failure. *Asian Cardiovasc Thorac Ann* 2009;17(6):604-607.
- Monfared A, Atrkar Roshan Z, Salari A, et al. QT intervals in patients receiving a renal transplant. *Exp Clin Transplant* 2012;10(2):105-109.
- Cashion AK, Hathaway DK, Milstead EJ, et al. Changes in patterns of 24-hr heart rate variability after kidney and kidney-pancreas transplant. *Transplantation* 1999;68:1846-1850.
- Yildiz A, Sever MS, Demirel S, et al. Improvement of uremic autonomic dysfunction after renal transplantation: A heart rate variability study. *Nephron* 1998;80:57-60.
- Monfared A, Ghods AJ. Improvement of maximum corrected QT and corrected QT dispersion in electrocardiography after kidney transplantation. *Iran J Kidney Dis* 2008;2(2):95-98.
- Koc M, Toprak A, Ozener IC, et al. QT dispersion in renal transplant recipients. *Nephron* 2002;91(2):250-254.
- Galiatsou E, Morris ST, Jardine AG, et al. Cardiac and vascular abnormalities in renal transplant patients: differential effects of cyclosporin and azathioprine. *J Nephrol* 2000;13(3):185-192.
- Gerhardt U, Suwelack B, Pawolka A, et al. High QT dispersion in tacrolimus-treated kidney transplant recipients. *Transplant Proc* 2001;33(3):2148-2150.