

OPEN ACCESS

Clinical Pharmacy

Research Article

Effects of esomeprazole and pantoprazole on renal function in stable kidney transplantation recipients: A randomized clinical trial

Doaa El Bohy^{a*}, Magdy El Sharkawy^b, Soheir Abo-Elazm^c, Sara Shahin^d, Waleed Bchari^b, Azza Mancy^e, Manal El Hamamsy^d

^aDepartment of Clinical Pharmacy; Future University in Egypt, Cairo, 11835, Egypt

^bDepartment of Internal Medicine & Nephrology; Faculty of Medicine, Ain Shams University, Cairo, 11566, Egypt

^cDepartment of Pharmacology; Faculty of Medicine, Cairo University, Cairo, 11562, Egypt

^dDepartment of Clinical Pharmacy; Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt

^eDepartment of Clinical Pharmacy; Faculty of Pharmacy, Fayoum University, Fayoum, 63514, Egypt

ABSTRACT

Renal allograft survival requires the administration of multiple immunosuppressive drugs. This strategy may lead to gastric complications that necessitate gastro-protective medications, notably, proton pump inhibitors (PPIs). This study aimed to compare the effects of pantoprazole and esomeprazole on renal function in stable renal transplant recipients. A prospective, parallel, open-label clinical trial was performed with forty-seven adult renal transplant recipients receiving immunosuppressive therapy with cyclosporine (CSA) doses adjusted to attain trough concentrations of 100-150 µg/L, mycophenolate mofetil (MMF) at 750 mg q12 h and prednisolone at 5 mg daily at Nasser Institute, Cairo, Egypt. The enrolled participants were randomized into two groups, which received either esomeprazole or pantoprazole at the same dose (40 mg once daily). Renal function was measured at baseline and monthly for 6 months. The study was conducted between January-September 2016. Main outcome measures clinical signs of rejection reflected by renal function decline, assessed by elevated levels of serum creatinine. The mean serum creatinine level was significantly lower in the sixth month than at baseline in esomeprazole group (p 0.004); interestingly there was a continuous decrease of serum creatinine levels in esomeprazole group and nearly constant values in pantoprazole group. There was no significant difference in serum creatinine levels between the two groups. From this study, it could be concluded that esomeprazole may be preferred over pantoprazole in renal transplant recipients because it decreased serum creatinine which is one of the markers of chronic allograft rejection in stable renal transplantation recipients.

Keywords: *Allograft rejection; serum creatinine; renal transplantation; proton-pump inhibitors; gastric complications.*

*Correspondence | Doaa El-Bohy; Department of Clinical Pharmacy; Future University in Egypt, Cairo, 11835, Egypt.

Email: delbohy@gmail.com

Citation | El Bohy D, El Sharkawy M, Abo-Elazm S, Shahin S, Bchari W, Mancy A, El Hamamsy M. 2019. Effects of esomeprazole and pantoprazole on renal function in stable kidney transplantation recipients: A randomized clinical trial. Arch Pharm Sci ASU 3(1): 106-115

DOI: [10.21608/aps.2019.10411.1003](https://doi.org/10.21608/aps.2019.10411.1003)

Online ISSN: 2356-8380. **Print ISSN:** 2356-8399.

Received 11 April 2019. **Accepted** 30 May 2019.

Copyright: ©2019 El Bohy et al. This is an open-access article licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited

Published by: Ain Shams University, Faculty of Pharmacy

1. INTRODUCTION

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). Although kidney transplantation improves the recipient's quality of life, a chronic illness remains in which patients require medication and monitoring of graft function [1, 2]. To minimize the risk of rejection, recipients are placed on maintenance regimens of immunosuppressive medications [3].

A maintenance regimen currently consists of two classes of immunosuppressive drugs in addition to a low dose of glucocorticoids. The four classes of immunosuppressive drugs are calcineurin inhibitors (tacrolimus or cyclosporine), an antimetabolite (mycophenolate mofetil; MMF), mechanistic target of rapamycin mTOR inhibitors (sirolimus or everolimus), and co-stimulation blockers (belatacept) [4]. However, multiple adverse effects of these immunosuppressive therapies have also been reported [5, 6]. These drugs are powerful immunosuppressants, where immunosuppressant-associated long-term renal toxicity is mediated by renal arteriolar vasoconstriction; the mechanism underlying the renal toxicity of these medications is accompanied by the production of reactive oxygen species in renal tubular and glomerular cells [7]. One of the major sources of intracellular reactive oxygen species in mitochondria. Thus, these organelles are linked to cyclosporin A (CSA) renal toxicity [8].

Numerous complications of immunosuppressive treatments occur in the gastrointestinal (GI) tract. The incidence of GI complications after kidney transplantation is as high as 12% for upper GI bleeding episodes [9-11].

Proton-pump inhibitors (PPIs), such as pantoprazole and esomeprazole, are used for the

treatment of symptoms of acid-related disorders and the primary prevention of gastroduodenal toxicity [12].

Long-term prophylaxis with PPIs is often utilized after kidney transplantation, regardless of the immunosuppression regimen [13]. However, concerns have been raised about adverse events, including hyponatremia, hypomagnesemia and calcineurin inhibitors (CNIs) drug interactions [14]. Exposure to PPIs may also be associated with an increased risk of incident chronic kidney disease (CKD) and CKD progression. The mechanisms by which PPIs may lead to CKD remain unknown. Reports have demonstrated an association between PPIs use and acute kidney injury (AKI) that is mainly mediated by interstitial nephritis [15].

Monitoring graft function is crucial in this population, and it is performed by measuring serum creatinine levels to evaluate kidney function [16].

This study aimed to compare the effects of pantoprazole and esomeprazole on renal function in stable renal transplant recipients on a triple immunosuppressive regimen consisting of CsA, MMF, and corticosteroids by measuring serum creatinine levels, which may reflect the rejection of the transplanted organ. To the best of our knowledge, this is the first comparative study to assess the effects of esomeprazole and pantoprazole on renal function in stable renal transplantation recipients.

2. PATIENTS AND METHODS

2.1. Study design and setting

A prospective, randomized, parallel, open-label clinical trial of renal transplant recipients with a follow-up duration of 6 months was conducted between January and September 2016; the study included an esomeprazole group and a pantoprazole group. The study was performed in

the renal transplantation unit of the Nasser Institute in Cairo, Egypt. Ethical approval was obtained from the Ain Shams University and Nasser Institute ethics committees, as well as the Egyptian Ministry of Health ethics committee (No: 7-2015/22). The Clinicaltrials.gov registration number is NCT03812419. Informed consent was obtained from all participants recruited for the study.

2.2. Patients

Eighty renal transplant recipients were screened for eligibility. The sample size was determined by a power calculation in G power software version 3.0.10, in which this sample size at $\alpha=0.05$ showed an effect size of 0.8 for the serum creatinine level. Eligible candidates for inclusion were adult stable renal transplant recipients; all participants continued the same maintenance triple immunosuppressive therapy, which had been taken for at least 3 years before the study and continued to be taken throughout the study period. All included patients had undergone transplantation 5 years before the initiation of the study. Pediatric patients, those > 65 years old, multi-organ transplant recipients, pregnant or lactating patients, those with malignancies, and those with active infections or inflammation and pre-transplant GI tract disorders were considered ineligible. Seventy candidates were eligible and recruited, out of which 47 completed the study (11 did not comply with treatment, and 12 were lost to follow-up). The study started in January 2016 and continued until September 2016.

2.3. Medications

Participants were randomly assigned to one of two groups by single randomization. Each group received 40 mg/day PPI therapy with either esomeprazole (Ezogast; Copad Pharma, Cairo, Egypt) in group I ($n=25$ at study completion) or pantoprazole (pantoprazole; Pharo Pharma,

Alexandria, Egypt) in group II ($n=22$ at study completion). Besides, participants continued to receive the immunosuppressant combination of CsA (Sandimmune; Novartis, East Hanover, NJ, USA), MMF (Cellcept; Roche, Basel, Switzerland) and the corticosteroid prednisolone (Solupred; Sanofi Aventis, Tours, France).

2.4. Administration

Cyclosporine was administered in two doses adjusted to achieve a trough concentration (C_0) of 100-150 $\mu\text{g/L}$ according to the transplantation center protocol for maintenance blood CsA levels. The morning dose was taken at least 15 minutes before or after the PPIs were taken; each patient received MMF 750 mg q12 hr and prednisolone 5 mg daily, and each group received 40 mg/day PPI therapy on an empty stomach. All medications were taken orally.

2.5. Measurements

Renal function was assessed monthly throughout the 6-month trial period. Three milliliters of blood was collected in a separator tube containing a gel that enhances coagulation and centrifuged at 147.9 g for 15 min; then, the serum was separated and used for the measurement of serum creatinine with a QuantiChrom creatinine assay kit [17]. Blood urea nitrogen was measured with a QuantiChrom urea assay kit [18], and serum uric acid was measured with a QuantiChrom uric acid assay kit [19].

2.6. Outcomes

The deterioration of renal function was defined as the doubling of the serum creatinine level, as that may indicate graft dysfunction and subsequent rejection.

2.7. Statistical analysis

SPSS version 24 (IBM, Armonk, NY, USA) was used for the data analysis. Quantitative variables are expressed as the means \pm SD, and

qualitative variables are expressed as numbers and percentages. Chi-square (χ^2) tests were used to assess the deviation of the observed distribution of qualitative variables from the expected distributions. For the quantitative variables, repeated measures analysis of variance (ANOVA) with a Bonferroni post hoc test was used for the comparison of means of related samples (within groups), and independent-sample t-tests were used for comparisons between the two groups. A *p*-value < 0.05 was considered to indicate a statistically significant test result.

3. RESULTS

3.1. Study population

Forty-seven recipients completed the study, which was conducted between January and September 2016. They were screened, randomized and allocated according to the consort 2010 guidelines, as shown in **Fig. 1**. Baseline demographics (age, sex, and weight) were not different between the two groups, as shown in **Table 1**.

Table 1. Demographic data comparison at the baseline between the esomeprazole and pantoprazole groups of renal transplant recipients on triple immunosuppressive maintenance regimen.

Demographic variables		Group (I) Esomeprazole 40 mg/day	Group (II) Pantoprazole 40 mg/day
Age (years)	<i>Mean ± SD</i>	39.9 ± 13.2	38.3 ± 10.1
	(range)	(20-65)	(20-60)
Sex	Female	32%	36.4%
	Male	68%	63.6%
Weight (kg)	<i>Mean ± SD</i>	74.0 ± 20.2	84.0 ± 19.1
	(range)	(37-117)	(55-125)

Group (I) n= 25

Group (II) n= 22

Age and weight are represented as the mean ± SD, while sex is presented as the percentage. The Chi-square (χ^2) test was used to assess the deviation of the observed distribution of qualitative variables from the expected distribution.

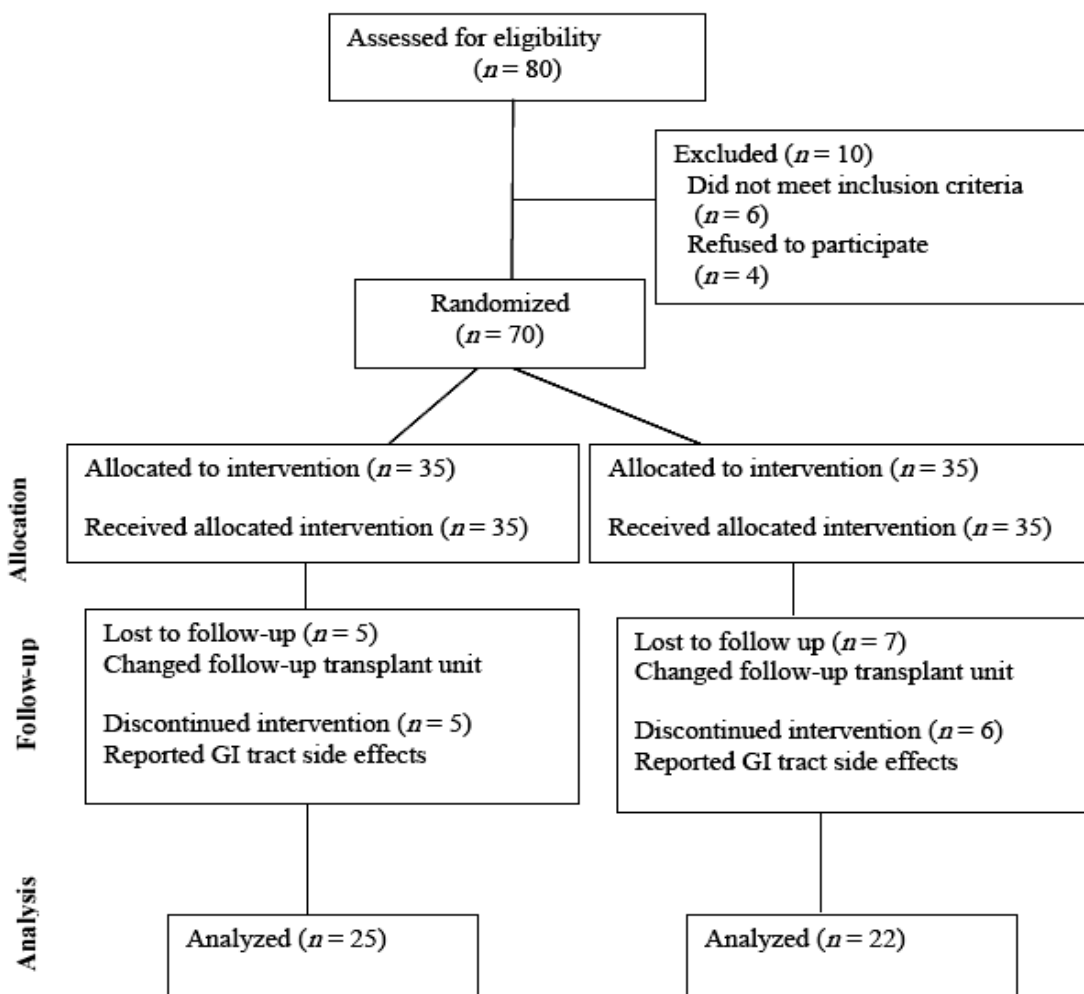


Fig. 1. Participant flow diagram

3.2. Renal function test

we compared renal function tests in the two study groups as a continuous monitoring parameter for the effect of the two studied PPIs (esomeprazole or pantoprazole) on the transplanted kidney where we found that serum creatinine was the only renal function test that showed a decrease in esomeprazole group ($p=0.004$) at month 6 (1.1 ± 0.4 mg/dL) than at baseline (1.4 ± 1.5 mg/dL) as shown in **Fig. 2**.

And no statistically detected change in esomeprazole group through the whole period of the study 6 months for (BUN and uric acid), pantoprazole group showed no statistical difference in all the assessed parameters for the study duration. Upon comparing the 3 assessed renal function test (Serum creatinine, BUN and serum uric acid) between the two groups no statistically significant difference was detected at any time point for any of the assessed parameter data illustrated in **Tables 2 and 3**.

Table 3. Serum uric acid comparison in the two study groups for 6 months in stable renal transplant recipients on triple immunosuppressive maintenance regimen.

Parameter	Group I							Group II							P- Value
	Esomeprazole group (40 mg/day)							Pantoprazole group (40 mg/day)							
	Months							Months							
Renal function															
	Baseline	1	2	3	4	5	6	Baseline	1	2	3	4	5	6	
Serum uric acid															0.57
Mean \pm SD	6.8	6.7	6.6	6.5	6.5	6.1	6.2	6.5	6.3	6.4	6.4	6.5	6.2	6.3	0.36
	\pm	\pm	\pm	\pm	\pm	\pm	\pm	\pm	\pm	\pm	\pm	\pm	\pm	\pm	0.65
	1.6	1.4	1.0	0.3	1.8	0.9	1.0	2.0	1.6	1.7	1.8	1.5	1.5	1.4	0.82
															0.59
															0.76
															0.67

Comparison of serum uric acid monthly for the study duration of 6 months both within group using repeated measures ANOVA and the Bonferroni post hoc test and between groups using an independent-samples t-test.

4. DISCUSSION

The current study is of practical clinical importance because it compared the nephrotoxic effects of the two studied PPIs used in renal transplantation recipients by assessing renal function at monthly intervals for 6 months. The present study showed a continuous decrease in serum creatinine levels in the esomeprazole group over the 6 months and near-constant levels of serum creatinine in the pantoprazole group. There were no differences between the two groups regarding serum creatinine levels or any other renal function test.

Different immunosuppressive drugs. CNI such as CsA, the anti-proliferative agent MMF and steroids are used as maintenance immunosuppressive regimens in renal transplant recipients [20]. PPIs are commonly prescribed for kidney transplant recipients [21]. CSA and PPIs

are metabolized by CYP3A4 in the liver, and an increase in CsA concentration has been recognized as being linked to PPI co-administration [22].

Chronic graft dysfunction is characterized by a progressive impairment in kidney function associated with the occurrence or worsening of arterial hypertension and proteinuria [23]. Graft failure is defined as either returning to dialysis or death with a functioning graft [24].

The long-term use of CNIs is a major contributing factor to the development of CKD. The nephrotoxic mechanism is thought to be related to alterations in the vascular tone at the level of the afferent arteriole [25].

The CsA dose in our study was adjusted according to the study centre protocols to avoid any elevation of CsA serum levels leading to

nephrotoxicity or any decreases below the effective concentration leading to allograft rejection, which is in line with the findings in relevant studies stating that nephrotoxicity due to CsA is dose-dependent, and it is reversible with a decrease in the dose or drug withdrawal [26]. Another supporting report stated that the nephrotoxic potential of CsA is clinically, histologically, and molecularly indistinct at all levels of detection [27].

Despite its well-known limitations, the serum creatinine concentration remains the most commonly used marker of the glomerular filtration rate (GFR) following kidney transplantation because of the convenience and low cost of its measurement. The nadir value of serum creatinine during the first weeks after transplantation is used as the benchmark for identifying subsequent graft dysfunction [28]. There is agreement among nephrology studies about the role of serum creatinine levels in indicating graft failure after renal transplantation [29].

As several PPIs are now available, it is important to compare their effectiveness and side effects, especially concerning the kidney. A very surprising finding showed a gradual decrease in serum creatinine levels in the esomeprazole group throughout the entire study period. There was no other significant finding in other renal function tests either within each of the study groups or in comparisons between the two groups. *Xie et al.* recently reported that AKI does not mediate the association between PPIs and the occurrence of CKD, which may explain the current study findings [30]. An alternative hypothesis suggests that PPIs may increase the CKD risk by promoting hypomagnesemia, which conflicts with our findings [31]. Another speculation is that enteric infections are known adverse effects of PPIs that are attributed to changes in the gut microbiome [32]. An altered

gut microbiome, as well as endotoxins entering circulation, may contribute to uremic toxicity and CKD progression [33].

In chronic graft dysfunction, a phenomenon known as creeping creatinine occurs, which is a gradual increase in creatinine levels over time [34]. Its diagnosis requires the demonstration of the existence of a negative slope in the creatinine level with a minimum of 6 measurements performed during the last months of follow-up (from 3 to 18 months) [35].

Furthermore, treatment with PPIs is associated with a significantly elevated risk of doubling serum creatinine levels and progression to ESRD, which contradicts the present findings [36].

This contradiction between the present study findings and those in previously published studies may stem from the fact that the exact nephrotoxic mechanisms of PPIs are not well established and currently remain merely speculations; in addition, previous studies focused on the group effect either in AKI or CKD patients, with no in-depth research into different members of the PPIs family, while the current study compared the effects of two members of the PPIs family (esomeprazole and pantoprazole) commonly used in renal transplantation recipients.

Limitations

As the study was performed in a single-center outpatient clinic, the sample size was relatively small, and the duration of follow-up was limited to 6 months.

Conclusion

In stable renal transplant recipients receiving immunosuppressive maintenance therapy, esomeprazole may be preferable to pantoprazole because it resulted in continuously decreasing serum creatinine levels, while the use of pantoprazole resulted in constant serum creatinine levels.

Recommendations

The effect of esomeprazole on renal function should be further investigated in a larger number of recipients, for longer duration and in multiple centers to detect its potential beneficial effect in this population.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding Statement

Not applicable

5. REFERENCES

- Theofilou P. Identifying risk factors associated with compliance to medication in elderly kidney transplant patients. *J Transplant Technol Res.* 2012; 2(2): 2–3
- McKay D, Steinberg S, eds. *Kidney transplantation: A Guide to the Care of Kidney Transplant Recipients.* New York, USA: Springer; 2010. ISBN 978-1-4419-1690-7. <https://www.springer.com/gp/book/9781441916891>
- Pinsky B, Takemoto S, Lentine K, Burroughs T, Schnitzler M, Salvalaggio P. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant.* 2009; 11 (9): 2597–2606.
- US Department of Health and Human Service. “2011 Annual Report of the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients”. *Am J Transplant.* 2013; 1:1-36. <https://onlinelibrary.wiley.com/toc/16006143/2013/13/s1>
- Masson P, Henderson L, Chapman S, Craig J, Webster A. Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev.* 2014; 11: 010699. doi:10.1002/14651858.
- Haller M, Royuela A, Nagler E, Pascual J, Webster A. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev.* 2016; 8: CD005632. doi:10.1002/14651858.CD005632.pub3.
- Lim S, Hyoung B, Piao S, Doh K, Chung B, Yang C. Chronic cyclosporine nephropathy is characterized by excessive autophagosome formation and decreased autophagic clearance. *Transplantation.* 2012; 94:218-25.
- El-Kashef D, El-Kenawi A, Suddek G, Salem H. Allicin ameliorates kidney function and urinary bladder sensitivity in cyclosporine A-treated rats. *Hum Exp Toxicol.* 2016. pii: 0960327116660864.
- Berardinelli L, Raiteri M, Beretta C, Pasciucco A, Giussani A, Carini M, et al. What has changed in more than 40 years of activity and 3000 kidney transplants at Policlinico University Hospital, Milan. *Clin Transpl.* 2011; 99-110.
- Lempinen M, Halme L, Sarkio S, Arola J, Honkanen E, Turunen U et al. CMV findings in the gastrointestinal tract in kidney transplantation patients, patients with end-stage kidney disease and immune-competent patients. *Nephrol Dial Transplant.* 2009; 24:533-3539.
- Telkes G, Peter A, Tulassay Z, Asderakis A. High frequency of ulcers, not associated with *Helicobacter pylori*, in the stomach in the first year after kidney transplantation. *Nephrol Dial Transplant.* 2011; 26 (2): 727-732.
- Procurement, Organ Network, Transplantation and Scientific Registry of Transplant Recipients (SRTR). *OPTN/SRTR 2010 Annual Data Report.* Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation. 2011; 12 (1): 1-156.
- Perazella M, Markowitz G. Drug-induced acute interstitial nephritis. *Nat Rev Nephrol.* 2010; 6(8): 461–470.
- Yan X, Benjamin B, Tingting L, Hong X, Yan Y, Ziyad Al-Aly. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. *BMJ.* 2017; 7(6): e015735. Doi: 10.1136/bmjopen-2016-015735.
- Lazarus B, Chen Y, Wilson F, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA. Intern Med* 2016; 176:238–246.
- Antoniou T, Macdonald E, Hollands S, et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-

- based cohort study. *CMAJ Open* 2015; 3:E166–E171.
17. Zhang S, Wang J, Lu K, Mott R, Longeras R, Ma J. Therapeutic potential of angiostatin in diabetic nephropathy. *Clin J Am Soc Nephrol*. 2006; 17: 475–486.
 18. Davalos-Misslitz A, Rieckenberg J, Willenzon S, Worbs T, Kremmer E, Bernhardt G et al. Generalized multi-organ autoimmunity in CCR7-deficient mice. *Eur. J. Immunol*. 2007; 37: 613–622.
 19. Viel E, Benkirane K, Javeshghani D, Touyz R, Schiffrin E. Xanthine oxidase and mitochondria contribute to vascular superoxide anion generation in DOCA-salt hypertensive rats. *Heart and Circ*. 2008; 295: H281-H288.
 20. Matas A, Smith J, Skeans M, Thompson B, Gustafson S, Stewart E et al. OPTN/SRTR 2013 Annual Data Report: kidney. *Am J Transplant*. 2015; 15:1-34.
 21. Courson A, Lee J, AullMJ, Lee J, Kapur S, McDermott J. Routine prophylaxis with proton pump inhibitors and post-transplant complications in kidney transplant recipients undergoing early corticosteroid withdrawal. *Clin Transplant*. 2016; 30:694–702.
 22. Ogawa, R, Echizen H. Drug-drug interaction profiles of proton pump inhibitors. *Clin Pharmacokinet*. 2010; 49(8): 509-533.
 23. Vadivel N, Tullius SG, Chandraker A. Chronic allograft nephropathy. *Semin Nephrol*. 2007; 27 (4): 414-29.
 24. Sales M, Rostami Z, Rahimi Froushani A, Mehrzmay A, Mohammadi J, Einollahi B et al. Chronic graft loss and death in patients with post-transplant malignancy in living kidney transplantation: a competing risk analysis. *Nephrourol Mon*. 2014; 6(2):14302.
 25. Van Buren D, Burke J, Lewis R. Renal function in patients receiving long-term cyclosporine therapy. *JASN*. 1994; 4(8):S17-22.
 26. Ponticelli C. Cyclosporine: from renal transplantation to autoimmune diseases. *Ann. N. Y. Acad. Sci*. 2005; 1051: 551–558.
 27. Roos van Groningen M, Scholten E, Lelieveld P et al. Molecular comparison of calcineurin inhibitor-induced fibrogenic responses in protocol renal transplant biopsies. *JASN*. 2006; 17: 881–888.
 28. Hawley C. Estimated donor glomerular filtration rate is the most important donor characteristic predicting graft function in recipients of kidneys from live donors. *Transpl Int*. 2007; 20: 64–72
 29. About A, Foucher Y, Trebern-Launay K, Legendre C, Kreis H, Mourad, et al. Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. *Kidney Int*. 2015; 87(2):343–9.
 30. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD. *JASN*. 2017; 27(10):3153-63.
 31. Park C, Kim E, Roh Y, et al. The associations between the uses of proton pump inhibitors and the risk of hypomagnesemia: a systematic review and meta-analysis. *PLoS One*. 2014; 9: e112558.
 32. Jackson M, Goodrich J, Maxan M, et al. Proton pump inhibitors alter the composition of the gut microbiota. *Gut* 2016; 65:749–756.
 33. Ramezani A, Raj D. The gut microbiome, kidney disease, and targeted interventions. *JASN*. 2014; 25:657–670.
 34. Paul L, Hayry P, Foegh M, Dennis M, Mihatsch M, Larsson E et al. Diagnostic criteria for chronic rejection/accelerated graft atherosclerosis in heart and kidney transplants: a joint proposal from the Fourth Alexis Carrel Conference on Chronic Rejection and Accelerated Arteriosclerosis in Transplanted Organs. *Transplant Proc*. 1993; 25 (2): 2022-3.
 35. Dudley C, Pohanka E, Riad H, Dedochova J, Wijngaard P, Sutter C et al. Mycophenolate mofetil substitution for cyclosporine in renal transplant recipients with chronic progressive allograft dysfunction: the «creeping creatinine» study. *Transplantation*. 2005; 79 (4): 466-75.
 36. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. *Kidney Int*. 2017; 91(6):1482- 94.