Original Article

Lipid Management in Kidney Transplant Recipients Per KDIGO and American Heart Association Guidelines: A Single-Center Experience

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Abstract

Background: The 2013 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommends statin treatment for all adult kidney transplant recipients (KTRs), except those aged <30 years of age and without prior cardiovascular risk factors (CVRF), but does not specify on-treatment low-density lipoprotein cholesterol (LDL) target levels. The 2018 American Heart Association (AHA) guidelines addressed the management of hyperlipidemia in the general population based on an individualized approach of the CVRF with a specific on-treatment LDL target.

Objective: To analyze dyslipidemia management according to the recommendations of the KDIGO and AHA guidelines.

Methods: This retrospective study included all KTRs who underwent transplantation between January 2017 and May 2020 at King Abdulaziz Medical Center, Riyadh, Saudi Arabia. The rate of statins prescription in general, rate of statins prescription among KTRs per their CVRF, and rate of achieving the proposed LDL goals, as defined by the AHA, were analyzed.

Results: A total of 287 KTRs were included. Of the 214 (74.6%) patients aged ≥30 years, 80% received a statin. Statins were prescribed in 93% and 96% of KTRs with diabetes or coronary artery disease, respectively. In patients aged ≥30 years, LDL targets, per AHA guidelines, were achieved in 62% with a target of 2.6 mmol/l, and in 19% with a target of 1.8 mmol/l. Statin therapy resulted in non-significant changes in the mean LDL values from baseline to 12 months after transplantation ($P = 0.607$), even when only patients prescribed statin after transplantation were included ($P = 0.34$).

Conclusion: By applying the KDIGO guidelines, a high rate of statin prescriptions was achieved among KTRs with multiple CVRF and KTRs in general. However, a significant proportion of these KTRs did not achieve the LDL targets proposed by the AHA guidelines, suggesting that higher-intensity statins would be required to achieve these targets.

Keywords: American Heart Association, cardiovascular risk factors, dyslipidemia, guidelines, Kidney Disease: Improving Global Outcomes, kidney transplantation, statins

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INTRODUCTION

Dyslipidemia, defined as elevated LDL target levels of ≥2.6 mmol/l (100 mg/dL), is very common after kidney transplantation (KTx).[1,2] Studies have reported that 45%–90% of kidney transplant recipients (KTRs) develop dyslipidemia.[3,4] Dyslipidemia is a major contributing factor to the increased risk of coronary events after KTx.[2,5-9]

Statins significantly reduce cardiac mortality in the general population when used for primary or secondary prevention.[10-12] In KTRs, the ALERT study (and its extension) is the only randomized controlled trial that has evaluated the effect of statin therapy on cardiovascular outcomes following KTx.[13] The study found that patients (aged ≥30 years) randomized to the experimental group (i.e., fluvastatin 80 mg) had a reduced risk of major adverse cardiac events by hazards ratio (HR) of 0.79 (95% CI: 0.63–0.99; $P = 0.036$), and a reduced risk of cardiac death or non-fatal myocardial infarction (MI) by HR of 0.71 (95% CI: 0.55–0.93; $P = 0.014$). However, despite the lower cardiac deaths and non-fatal MIs, fluvastatin did not lower the overall mortality, the rate of coronary interventions, or the graft loss.[13]

The Kidney Disease: Improving Global Outcomes (KDIGO) organization in 2013 recommended statin treatment for all adult KTRs,[2] but patients aged <30 years and without prior cardiovascular risk factors (CVRF) could choose not to receive statin therapy.[8,14] However, with only one randomized control trial (ALERT) with a lack of statistical significance in the primary analysis, this recommendation was graded by the KDIGO experts as weak (level/grade: 2A). Moreover, the KDIGO guidelines neither specified an LDL threshold to initiate statin therapy nor the on-treatment LDL target levels. There was also no recommendation regarding adjusting the statin regimen based on the LDL target levels.[2,15] Consequently, repeating a lipid profile during follow-up was not mandatory per the KDIGO guidelines.

On the other hand, the American Heart Association (AHA) guidelines of 2018 address the management of hyperlipidemia in the general population but are not specific for KTRs. These guidelines consider renal disease as a risk-enhancing factor.[16] In general, the risk of MI is approximately six-fold higher after KTx compared with the general population.[17] In addition, the rate of cardiovascular death or non-fatal MI is approximately 21.5 per 1000 patient years.[8] This risk places KTRs in the "high risk category" based on the scale of the AHA guidelines (i.e., >20% risk for cardiac events in 10 years).[18] The AHA guidelines recommend an individualized approach for the management of dyslipidemia based on the CVRFs of each patient with a specific on-treatment LDL target.[16]

It is yet unknown whether prescribing statins to KTRs per KDIGO will satisfy, in real practice, the AHA recommendations (i.e., the rate of statins prescription, particularly in those with multiple CVRFs, stain intensity, and LDL-lowering effects, and the rate of achieving the proposed LDL goals). Therefore, this study was conducted to analyze the achieved results of dyslipidemia management in KTRs at a single center according to the two guidelines (KDIGO versus AHA) in terms of rate of statins' prescription in KTRs in general, rate of prescription in KTRs according to their CVRF, change in lipid profile over the study period, and the rate of achieving the proposed LDL goals in KDIGO versus AHA.

MATERIALS AND METHODS

Study design, setting, and participants

This retrospective study included all KTRs who underwent KTx from January 01, 2017, to May 31, 2020, and had a minimum follow-up period of 12 months at King Abdulaziz Medical Center (KAMC), Riyadh, Saudi Arabia. KAMC is one of the largest kidney transplant centers in the Middle East.

All data were extracted from the electronic medical records. The study was conducted after receiving approval from the Institutional Review Board of KAMC.

Management of dyslipidemia in kidney transplant recipients

The medical management of dyslipidemia in KTRs at KAMC has been adopted from the 2013 KDIGO guidelines.[19] In addition to advising therapeutic lifestyle changes, all KTRs aged ≥30 years are initially prescribed atorvastatin (typically, 10 mg daily) before discharge after KTx. For patients who were already on statins prior to their transplantation, the statin regimen is maintained.[19] KTRs aged <30 years are typically not prescribed statins at the time of the KTx, unless they have multiple CVRFs such as diabetes mellitus (DM), hypertension, smoking, and a history of cardiovascular disease.

The immunosuppression protocol at our center is tacrolimus based. Although there is less interaction between tacrolimus and statins, in general, we avoid using simvastatin. We prescribe statins at dosages not exceeding half the maximum dose recommended for the general population. In addition, as the KDIGO recommendations are followed, there is no specific schedule for follow-up

testing of the lipid profile, and dosages are typically not titrated per the LDL target. Ezetimibe, fibric acid, bile acid sequestrants, omega-3 fatty acids, or niacin are not used due to potential drug interactions and as LDL is the main target of dyslipidemia management as per published guidelines.[2]

Variables

The collected data included the demographic information of patients and their traditional CVRF (i.e., coronary artery disease [CAD], cerebral vascular disease, peripheral vascular disease, diabetes, hypertension, and smoking). In addition, lipid profiles were collected at baseline (pre-transplant) and at 12 months after KTx.

According to the 2013 KDIGO guidelines, KTRs were divided into two age groups: <30 and ≥30 years. The CVRF between both groups were compared. In addition, the management of dyslipidemia was analyzed in terms of the number of CVRF in each group; the pattern of statins prescription at our center (i.e., the time of initiation, type, intensity, and discontinuation); the proportion of KTRs who received statins in both groups as per the KDIGO guidelines; the proportion of KTRs who reached their LDL targets based on their CVRF as per the AHA guidelines; and LDL changes from baseline pre-KTx level.

Statistical analysis

The analysis was performed using SPSS version 24 (Chicago, Illinois, USA). The mean, standard deviation, frequency, and percentage were calculated with descriptive statistics. The mean difference of the continuous variables was compared using a paired sample Student's *t*-test, and differences between groups using an unpaired Student's *t*-test. The categorical variables were compared using Fisher's exact test. All *P* values were two-sided, and $P \leq 0.05$ was considered significant.

RESULTS

A total of 287 KTRs were included and 2 were excluded: one died from disseminated infection 1 month after surgery, and the other lost his graft 2 days following the transplant surgery due to renal vein thrombosis that was thought to be due to technical complications. The majority of the KTRs were aged ≥30 years (214; 74.6%), male (58.2%), and received a living donor KTx (80.5%) [Table 1].

Table 1: Characteristics of the included kidney transplant recipients (*n*=287)

Parameters	*n* (%)
Age (years)	
≥30	214 (74.6)
<30	73 (25.4)
Gender	
Female	120 (41.8)
Male	167 (58.2)
Donor type	
Deceased	56 (19.5)
Living	231 (80.5)
HTN	218 (79.3)
Pretransplant DM	99 (34.5)
DM type I	25 (25.3)
DM type II	74 (74.7)
Smoking (current)	25 (8.7)
CAD	38 (13.2)
CVD	15 (5.2)
PVD	8 (2.8)
Pretransplant BMI category	
Obese stage 2 (BMI 35–39.9 kg/m^2)	12 (4.2)
Obese stage 1 (BMI: 30–34.9 kg/m^2)	58 (20.2)
Overweight (BMI 25–29.9 kg/m^2)	84 (29.3)
Normal	103 (35.9)
Underweight	29 (10.1)
Weight gain by 1-year post-KTx (kg)	6.0±8.3
Post-KTx weight increase >5%	171 (59.60)
PTDM	22 (7.7)
Creatinine at 1-year post-KTx (μmol/L), mean±SD	98.9±59.7
Rejection rate (in the 1st year post-KTx)	22 (7.7)

BMI – Body mass index; DM – Diabetes mellitus; PTDM – Posttransplant diabetes mellitus; HTN – Hypertension; CAD – Coronary artery diseases; CVD – Cerebrovascular diseases; PVD – Peripheral vascular diseases; HTN – Hypertension; KTx – Kidney transplantation; SD – Standard deviation

Cardiovascular risk factors in both groups

In the ≥30 years age group, 7% had no traditional CVRF, while 28%, 31%, 17%, and 17% had one, two, three, or more than three risk factors, respectively. In the <30 years age group, 19% had no traditional CVRF, while 52%, 25% and 5% had one, two, or three additional risk factors, respectively. DM or CAD and its equivalents were present in 44% and 22% of those aged ≥30 years and 5% and 5% of those aged <30 years, respectively [Figure 1].

Patterns of statin prescriptions

Eighty-one patients (28.2%) were on statins before KTx; all these patients had ≥3 CVRF or established CAD. In addition, 75 (26.1%) patients were initiated on statins prior to discharge after KTx, 39 patients (13.6%) were started on statins in the first year after KTx, and 92 patients (32.1%) did not receive statins during the study period. The most frequently used statin was atorvastatin 10 mg (60%) or 20 mg (23%). Statins were discontinued in 7 (2.5%) patients: in 4 due to elevated liver functions and in 3 for other causes.

Statin prescription according to age group and in compliance with the KDIGO guideline

In the ≥30 age group, 171 (80%) patients received statins, and thus compliance with the 2013 KDIGO guidelines was achieved in 80% of the group. In the <30 years age group, 24 (33%) patients received statins, and compliance with the 2013 KDIGO guidelines was achieved in 100% of the cases [Table 2].

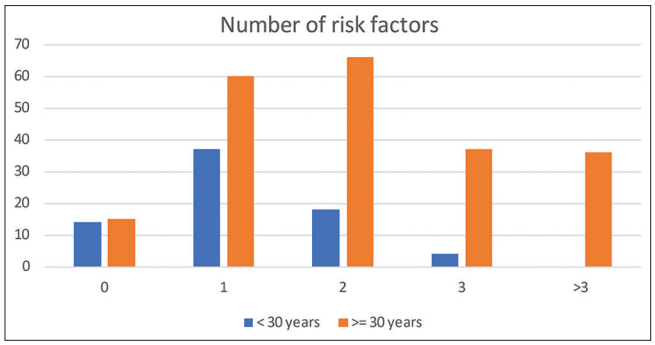

Figure 1: The frequency of cardiovascular risk factors in both age groups

Rate of achieving low-density lipoprotein targets based on cardiovascular risk factors (per the American Heart Association guidelines)

In the ≥30 years age group, statins were prescribed in 67%, 58%, 88%, 89% and 97% of the patients with zero, one, two, three, or more than three CVRFs, respectively. In the <30 years age group, statins were prescribed in 21%, 20%, 72%, or 50% of the patients with zero, one, two, or three CVRFs, respectively. However, of those with DM or CAD (or its equivalents), in the ≥30 years age group, statins were prescribed in 93% and 96% of the cases, while in the <30 years age group, they were prescribed in 44% or 22% of the cases.

The 2013 KDIGO guidelines do not specify a target for LDL but universally advise the use of moderate intensity statins for KTRs aged ≥30 years. The LDL targets of AHA were achieved in 62% of the patients aged ≥30 years with an LDL target of 2.6 mmol/l, or in 19% of the patients with an LDL target of 1.8 mmol/l. Of those with DM or CAD (or its equivalents), the LDL target was achieved in 67% and 74% of the patients, respectively, with and LDL target of 2.6 mmol/l, and in 21% and 17% of the patients with an LDL target of <1.8 mmol/l.

Changes in the mean low-density lipoprotein values

Statin therapy produced only mild and non-significant changes in the mean LDL values from baseline to 12 months (at baseline: 2.53 ± 0.90; after 12 months: 2.56 ± 0.85; $P = 0.607$). The findings were similar even when the analysis only included the 114 patients prescribed statin after transplantation (LDL change: −0.1; $P = 0.34$).

DISCUSSION

The current study demonstrates that the KTRs aged ≥30 years often have multiple CVRF, as only 7% did not have any traditional CVRF. The high burden of CVRF among KTRs aged ≥30 years makes the universal use of statins among such patients a reasonable approach.

Table 2: Rate of statin prescriptions in kidney transplant recipient age groups (*N* = 287)

Age group (years)	*n* (%)	On statin (*n*=195), *n* (%)	*P*
≥30	214 (74.60)	171 (80)	<0.001
<30	73 (25.40)	24 (33)	

The universal prescription of fluvastatin in the ALERT trial to the KTRs, aged 30–75 years, reduced the risk of cardiac death or definite non-fatal MI (HR: 0.65; 95% CI: 0.48–0.88).[13] The current study also found that most (81%) of KTRs aged <30 years have at least one CVRF, with about one-third having more than one risk factor.

The age threshold of initiating statin therapy among KTRs remains uncertain, as the ALERT study did not enroll participants <30 years old, despite them being at an increased cardiovascular risk. A study by Pilmore *et al*. estimated that the rate of cardiovascular death in young KTR, aged 25–44 years, is approximately 5 per 1000 patient-years.[14] Accordingly, the KDIGO guidelines suggested the use of statins in KTRs aged <30 years based on their individualized risk factors.

The target LDL among KTRs is also unknown. In the ALERT trial, LDL was lowered by an average of 38% to 2.5 mmol/l (98 mg/dL) at the last follow-up.[13] In the general population, multiple studies support the aggressive lowering of LDL, especially in high-risk patients. A meta-analysis of 26 randomized trials with >170,000 participants showed that each 1.0 mmol/l reduction in LDL target level reduced the annual rate of major cardiovascular events by just over one-fifth.[20] There was no evidence of a specific threshold within the cholesterol range studied. If the AHA guidelines are applied to individualized KTRs, the LDL levels target can be <2.6 mmol/l or <1.8 mmol/l based on the CVRF. In this study, statins were prescribed mainly at moderate intensity (atorvastatin at 10 mg or 20 mg in 60% and 23% of the cases, respectively). However, statin therapy produced only mild and non-significant changes of the mean LDL values in the first year post-KTx. Statins were also prescribed to most KTRs aged ≥30 years; however, one-third of the KTRs with risk factors and two-thirds of the KTRs with DM and CAD or equivalents did not achieve the LDL targets proposed by the AHA guidelines. Although this observation may not have been earlier reported in the KTx literature, it is well-reported in multiple cardiac studies, where the LDL goals were attained in only 36% to 52% of patients treated with statins after myocardial infarction or percutaneous coronary intervention. [21,22] The same issue is likely common in real life practice of KTx as well.

Fluvastatin and pravastatin are considered the safest statins to use in KTRs because they are not metabolized by cytochrome P450 3A4.[23] However, these statins are less potent. Simvastatin has more potential drug–drug interactions and its maximum dose should not exceed 40 mg daily. Rosuvastatin can be associated with proteinuria and should be used at the lowest dose (5 mg) and possibly avoided in KTRs.[23] Atorvastatin is potent and is well tolerated in KTRs. The findings of the current study suggest using higher doses of atorvastatin (i.e., 20 mg or 40 mg) when managing dyslipidemia of KTRs to achieve the desired LDL reduction [Table 3].[15,24]

Like the non-KTx (cardiac) population, the compliance rate with statin prescription is variable.[4,24] This current study showed a relatively high compliance rate with the statin prescription protocol (80% in the ≥30 years age group). The relatively higher compliance rate is likely driven by our protocol, which recommends initiating statins prior to discharge from KTx. To our knowledge, there have been no prior recommendations in this regard in KTRs, although a similar approach has been advised by multiple cardiac studies.[25,26] Therefore, a protocolized approach of statin prescription, preferably prior to patients' discharge, can facilitate a higher statin prescription for KTRs.

Table 3: Low-density lipoprotein cholesterol-lowering efficacy of different statins and the respective conversion doses[15,24]

High intensity (≥50%)	Moderate intensity (30%–49%)	Low intensity (<30%)
Atorvastatin 40 mg (or 80 mg) Rosuvastatin 10 mg	Atorvastatin 10 mg (or 20 mg) Rosuvastatin 5 mg Simvastatin 20–40 mg Fluvastatin 80 mg XL or 40 mg BID Lovastatin 40 mg (or 80 mg) Pravastatin 40 mg (or 80 mg)	Simvastatin 10 mg Fluvastatin 20–40 mg Lovastatin 20 mg Pravastatin 20 mg

LDL – Low-density lipoprotein; BID – Two times a day; XL – Extended release

This study showed that despite a high rate of compliance with statin prescriptions, based on the protocolized approach by KDIGO guidelines, more than one-third of KTRs with risk factors, and two-thirds of KTRs with DM and CAD (or its equivalents), did not achieve their LDL targets, based on the AHA guidelines of dyslipidemia management. The current application of KDIGO 2013 and AHA 2018 guidelines in the management of dyslipidemia in KTRs have their strengths and limitations.

Although KDIGO guidelines for the management of dyslipidemia is specific for KTRs population, these recommendations were graded as weak and conditional, as they were based only on the ALERT trial. On the other hand, the algorithm used by the AHA was designed for use in the general population;[18] however, it does not account for nontraditional risk factors such as the status of KTx which may markedly increase the CV risk along with the traditional CVRF.[8,9] In addition, the 10-year risk calculator of atherosclerotic cardiovascular disease used by AHA has other limitations as a result of insufficient data about patients younger than 40 years or older than 79 years and patients from other ethnic origins.[18] Table 4 outlines the differences between the KDIGO 2013 and AHA 2018 guidelines in the management of dyslipidemia in KTRs.

For the above reasons, this study supports a change in our management approach of dyslipidemia in KTRs and

Table 4: The differences between the 2013 Kidney Disease: Improving Global Outcomes and the 2018 American Heart Association guidelines of dyslipidemia management in kidney transplant recipients

Parameters	KDIGO 2013	AHA 2018
Dyslipidemia management approach	Protocolized management of dyslipidemia	Individualized management of dyslipidemia
Target of the guidelines	Renal transplant recipients	General population. Kidney disease is considered as a risk modifier
Primary prevention		
Age	Suggests universal statin use for all adult kidney recipients, and targeted therapy based on risk factors for patients <30 years	Complex algorithm based on age and risk factors For example, patients (40–75) without DM: To use risk calculator and to consider renal disease as risk modifier
LDL target	Not specified	Specific LDL target (<2.6 or 1.8 mmol/l) based on risk factors
Dosing	Moderate intensity	Moderate or high intensity based on risk
Special conditions such DM	No specific recommendation	Moderate or high intensity based on risk (age 40–75)
Follow up and monitoring	No specific recommendation	To ensure compliance and target achievement
Advantage	Ensure more universal use of statins More practical in a busy transplant practice	Achieving tighter LDL target (extrapolated from general population)
Outcomes studies/RCT	ALERT study	Data are extrapolated from general population. Not intended for specific subgroups such renal transplant recipients
Strength and grade of recommendations	Weak and conditional (2A)	

LDL – Low-density lipoprotein cholesterol; DM – Diabetes mellitus; KDIGO – Kidney Disease: Improving Global Outcomes; AHA – American Heart Association; RCT – Randomized controlled trial

Table 5: A recommended new approach to statin prescriptions in kidney transplant recipients

To universally prescribe statins to KTRs aged ≥30 years
To individually prescribe statins to KTRs aged <30 years based on their CVRF
To use higher-intensity statins such as atorvastatin 20 or 40 mg daily
To initiate statins prior to discharge after KTx
To periodically monitor lipid profile to ensure compliance, check for adverse effects, and to titrate treatment, if required

KTRs: Kidney transplant recipients; KTx – Kidney transplantation; CVRF – Cardiovascular risk factor

to combine the protocolized approach of KDIGO and the LDL-targeted approach of the AHA, as outlined in Table 5. This new approach aims to achieve a higher rate of statins prescriptions and to reach lower LDL targets in this high-risk population.

Strengths and limitations

To the authors' knowledge, this is the first study to analyze dyslipidemia management according to the recommendations of two international guidelines and to evaluate the real-world experience in one of the largest renal transplant centers in the Middle East region. However, this study has several limitations. First, it is a single-center study, which limits its generalizability. Second, its observational retrospective nature and the short duration of follow-up limit its ability to assess the risk and benefit of statin therapy, particularly a more intense therapy. Well-controlled prospective studies are needed to approximate these gaps, particularly the hard cardiovascular outcomes in relation to the LDL targets.

CONCLUSION

This study showed that following the KDIGO guideline resulted in a relatively high rate of statin prescriptions; however, more than one-third of the KTRs with risk factors, and two-thirds of the KTRs with DM and CAD (or its equivalents), did not achieve the LDL target levels proposed by the AHA guidelines. Higher-intensity statins or LDL-targeted approach would be required to achieve these AHA target levels. There is a need for further studies to determine the best approach to manage dyslipidemia in KTRs and to examine the target LDL level in kidney transplant population.

Ethical considerations

The study was approved by the Institutional Review Board of KAMC (Ref no.: RC20.382. R; date: November 16, 2020), Riyadh, Saudi Arabia. Requirement for informed consent was waived owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: ZA; Methodology: ZA; Data collection: AA, AN; Data analysis: ZA; Writing–original draft preparation: ZA, MT; Writing – review and editing: ZA, MT; Supervision: ZA.

All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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