

ORIGINAL ARTICLE

Impact of sirolimus on long-term adverse cardiovascular outcomes in kidney transplant recipients: A nationwide cohort study

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Abstract

Background: Kidney transplant recipients (KTRs) are at high risk for cardiovascular disease due to the long-term use of immunosuppressive therapy. This study aims to evaluate the long-term impact of sirolimus on cardiovascular outcomes in Korean KTRs.

Methods: From a cohort of 7180 eligible KTRs identified from 2010 to 2021, 387 KTRs who received sirolimus were included. To control for confounding variables, propensity score matching was applied, and the landmark method was used to address immortal time bias. The primary outcome was major adverse cardiovascular events (MACE), defined as a composite of myocardial infarction, coronary revascularization, ischaemic stroke and all-cause mortality.

Results: The analysis showed no significant difference in MACE between the sirolimus-treated and untreated groups (hazard ratio, 1.40; 95% confidence interval, .77–2.55), despite a higher incidence of dyslipidaemia in the sirolimus-treated group. However, subgroup analysis revealed an increased MACE risk in KTRs with pre-transplant congestive heart failure (CHF) who were treated with sirolimus (hazard ratio, 6.22; 95% confidence interval, 1.78–21.74), while no significant differences were found in other subgroups.

Conclusions: These findings suggest that while sirolimus can be a viable option for immunosuppression, it should be used cautiously in those with pre-existing CHF.

KEYWORDS

adverse cardiovascular outcomes, kidney transplantation, mTOR inhibitors, Sirolimus

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1 | INTRODUCTION

Patients with end-stage kidney disease (ESKD) exhibit high rates of cardiovascular mortality.¹ The risk of death associated with cardiovascular disease (CVD) events in patients undergoing dialysis is 10–20 times greater than that in the general population.² While transplantation can mitigate this risk, CVD remains the leading cause of mortality in kidney transplant recipients (KTRs).³ KTRs have both traditional and transplant-specific risk factors for CVD. Traditional factors, such as hypertension, diabetes and dyslipidaemia, are well-known risk factors for CVD. Transplant-specific risk factors include adverse metabolic effects of immunosuppressive medications and kidney allograft rejection. Induction and maintenance of immunosuppression are essential for preventing acute kidney allograft loss due to acute and chronic rejection. However, the long-term use of immunosuppressive medications can increase the risk of CVD in KTRs owing to metabolic derangements such as hypertension, obesity, hyperglycaemia, and dyslipidaemia.^{4,5}

Recent research has increasingly focused on addressing the long-term complications associated with sustained immunosuppression in KTRs, particularly nephrotoxicity induced by calcineurin inhibitors (CNI) and increased susceptibility to infection and malignancy.⁶ Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, are used as a component of immunosuppressive therapy in kidney transplant (KT) for their potent immunosuppressive effects and various advantages, such as anti-tumour and antiviral effects, and their relatively low nephrotoxicity.⁷ The mTOR inhibitors exert both positive and negative cardiovascular effects. mTOR inhibitors can reduce cardiac hypertrophy⁸ but induce hyperglycaemia and dyslipidaemia,^{4,9} which may cause major adverse cardiovascular events (MACEs) including cardiac death, non-fatal myocardial infarction, cardiac intervention procedures and stroke.¹⁰

Additionally, racial differences have been identified in the impact of sirolimus on kidney allograft outcomes and the incidence of new-onset diabetes, which can influence cardiovascular disease.¹¹ Furthermore, racial differences in cardiovascular risk among KTRs have been documented,^{12,13} with Asian individuals showing a relatively low cardiovascular risk.^{14,15} Despite the ethnic differences in cardiovascular risk, evidence on the cardiovascular outcomes of mTOR inhibitors in Asian KTRs is limited. Because everolimus was not covered by insurance for KTRs in Korea until 1 May 2022, sirolimus has been the primary choice for mTOR inhibitor therapy in most Korean KTRs.¹⁶ Hence, the aim of this study was to assess the cardiovascular outcomes of sirolimus in KTRs using a nationwide claims database in Korea.

2 | PARTICIPANTS AND METHODS

2.1 | Study design and data source

We emulated a hypothetical target trial in which KTRs received or did not receive sirolimus within the first year after kidney transplantation.¹⁷ Further details on the protocol of the emulated target trial are described in [Table S1](#). This study was conducted using nationwide insurance reimbursement claims data from 2010 to 2021, obtained from the Health Insurance Review and Assessment Service of Korea. The data set included demographic information, diagnoses, procedures and prescriptions, with each participant anonymized by a unique identifier code. This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University (IRB no. CUIRB-2022-E009, May 24, 2022), which waived the requirement for informed consent because all patient data were anonymized and de-identified using a randomized identification number prior to the retrospective analysis.

2.2 | Study population

We included all KTRs from 2011 to 2019 who were identified by procedure code for KT and hospitalization code.¹⁰ The exclusion criteria for the study are as follows: (1) KTRs younger than 20 years on the KT date; (2) deceased on the KT date; (3) with a history of transplantation before the KT date; (4) received non-kidney transplants on the KT date or subsequently; (5) diagnosed with cancer (International Classification of Diseases, 10th Revision [ICD-10] codes: C00–C99) during the study period; (6) with a history of being diagnosed with ischaemic heart disease (ICD-10 codes: I20–I25), valve disorders (ICD-10 codes: I34–I36), stroke (ICD-10 codes: I60–I69) or MACEs within 1 year prior to the KT date; (7) have used mTOR inhibitors within 1 year prior to the KT date; (8) have used everolimus during the study period; (9) experienced MACEs before the landmark point; and (10) with treatment switching before the landmark point.

2.3 | Treatment

The landmark point was set at 1 year after the KT date. KTRs treated with sirolimus before the landmark point were classified as the sirolimus-treated group, whereas those treated with sirolimus after the landmark point were included in the sirolimus-untreated group.

After the landmark point, treatment during the follow-up period was determined using the initiation date

of each prescription and cumulative days of administration obtained from the claims data. The type of treatment was defined by the inclusion of sirolimus in the immunosuppressive therapy regimen. Additionally, follow-up was censored in cases where immunosuppressive therapy assigned to each group was discontinued for >30 days, death-censored graft failure (DCGF) occurred, or the study period was terminated.

2.4 | Study outcomes

The primary outcome was MACEs, defined using ICD-10 codes as a composite of myocardial infarction, coronary revascularization, ischaemic stroke and all-cause death. Myocardial infarction was identified using ICD-10 codes I21–I22 during hospitalization. Coronary revascularization procedures were identified using the procedure codes for angioplasty or bypass surgery (procedure codes: M6551–M6554, M6561–M6567, M6571, M6572, M6620, M6634, M6638, O1640–O1642, O1647–O1649, OA640–OA642 and OA647–OA649). Ischaemic stroke was defined using ICD-10 code I63 with hospitalization. All-cause death was determined based on claims related to death as a medical result. The date of the first occurrence of any of these four components was considered the date of composite cardiovascular outcomes.

The secondary outcomes included each component of MACEs and DCGF. DCGF was defined as successive dialysis sessions beyond 90 days after transplantation, allograft nephrectomy (procedure code: R3275) or retransplantation. The DCGF date was determined by the first successive dialysis session or procedure date.

2.5 | Covariates

Prior to the index date, the following baseline characteristics, which were considered to be potentially associated with the study outcomes, were assessed: age at the KT date, sex, KT year, type of insurance, dialysis duration, dialysis modality, donor type, desensitization, induction therapy, acute rejection episode, Charlson comorbidity index (CCI) score, comorbidities, medications for CVD, and other immunosuppressive medications (shown in [Figure S1](#)). The dialysis duration was measured from the initial dialysis date until KT. If the dialysis duration was <3 months, it was considered pre-emptive.¹⁰ Haemodialysis was defined by procedure codes O7020, O9992, O9993, and OH011, while peritoneal dialysis was defined by procedure codes O7061, O7062, and O7071–7 and a history of receiving peritoneal dialysis solution. The Organ Transplantation

Law of South Korea mandates that recipients bear the cost of donor nephrectomy in the case of living-donor KT, while the government covers the primary expenses for organ donation in the case of a deceased donor. Therefore, the donor type was classified as a living donor when the procedure code for donor nephrectomy (R3272) was charged to a recipient.¹⁸ To assess the immunologic risk in KTRs, data on desensitization therapy and induction therapy were collected. Desensitization was defined as the use of rituximab, IVIG, or plasmapheresis (procedure code X2505),¹⁹ and the induction regimens such as basiliximab and rabbit anti-thymocyte globulin (rATG) were extracted. The features of the Korea National Health Insurance Service (KNHIS) claims data complicate the specification of the exact time of kidney allograft rejection. Therefore, acute rejection was defined as any case in which a diagnosis of kidney allograft rejection, identified by ICD-10 codes T86, T86.1 or both, was recorded within 3 months after KT.¹⁸ The Charlson Comorbidity Index was defined using ICD-10 codes over a 1-year period prior to KT.

2.6 | Statistical analysis

Baseline characteristics are presented as frequencies and percentages for categorical variables and medians and ranges for continuous variables. Fisher's exact test and the chi-squared test were used to compare categorical data, whereas the unpaired *t*-test and Mann–Whitney *U*-test were used to compare continuous data. The crude incidence rates were calculated as the number of events by the total person-time. Propensity score matching (PSM) was performed to control for the influence of confounding variables between the sirolimus-treated and sirolimus-untreated groups. Propensity scores were estimated using logistic regression, incorporating factors such as sex, age, KT year, type of insurance, dialysis duration, donor type, presence of desensitization, type of induction therapy, occurrence of acute rejection episodes, CCI score, comorbidities and concomitant medications on the index date. Sirolimus-treated KTRs were matched to sirolimus-untreated KTRs at a 1:4 ratio using the nearest-neighbour matching method without replacement. The balance of covariates before and after matching was assessed using standardized mean differences (SMD), where a value >.1 signified an imbalance.²⁰ We assessed the effect of sirolimus use on outcomes using Cox proportional hazards analysis. The proportional hazard assumption was evaluated using statistical tests and graphical diagnostics based on the Schoenfeld residuals. Cumulative incidence curves were plotted and compared using log-rank tests. All statistical

analyses were performed using SAS Enterprise Guide 7.1 (The SAS Institute, Cary, NC, USA) or R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>) software. Statistical significance was set at a two-sided p -value $< .05$.

2.7 | Subgroup analysis

To identify factors associated with the effect of sirolimus on MACE, we performed a series of multivariate Cox regression analyses, each including sirolimus, a covariate, and the interaction term between sirolimus and the corresponding covariate. A subgroup analysis was conducted based on baseline characteristics with an SMD $> .1$ after PSM and covariates with significant interaction terms.

2.8 | Sensitivity analysis

To validate the robustness of our findings, we conducted sensitivity analyses. First, KTRs were followed through to the end of the study without censoring for changes in treatment status after the landmark point, similar to an intention-to-treat (ITT) analysis. Second, we employed a negative control design to address uncontrolled confounding and other potential biases, defining chronic obstructive pulmonary disease (COPD, ICD-10 code: J44), non-alcoholic fatty liver disease (NAFLD, ICD-10 code: K760), and osteoarthritis (ICD-10 codes: M15–17) as negative control outcomes.²¹ Third, we applied the clone-censor-weight method to assess selection bias.²² The detailed methods are presented in the Methods S1 and Figure S2.

3 | RESULTS

3.1 | Baseline characteristics

Among 22,860 KTRs between 2010 and 2021, 15,680 were excluded based on predefined criteria. Of the remaining 7180 eligible recipients, 387 received sirolimus (shown in Figure 1).

Before PSM, the sirolimus-treated and -untreated groups showed several significant differences. The sirolimus-treated group had a higher proportion of males (62.79% vs. 57.34%) and showed notable differences in kidney transplant years, particularly in 2011 (4.13% vs. 10.01%). The use of CNIs and antimetabolites was significantly lower in the sirolimus-treated group (73.39% vs. 99.32% and 23.26% vs. 88.30%, respectively). Additionally, the sirolimus-treated group had a higher incidence of acute rejection (9.04% vs. 6.11%), a higher use of rATG

(22.22% vs. 17.83%) and a higher cumulative dose of corticosteroids (60.72% vs. 49.57%). Post-KT, the prevalence of dyslipidaemia (78.55% vs. 71.10%) and statin use (52.20% vs. 41.93%) was higher in the sirolimus-treated group. The detailed baseline characteristics are presented in Table S2.

The baseline characteristics of KTRs after a 1:4 propensity score matching are shown in Table 1. In total, 387 sirolimus-treated KTRs were matched with 1548 sirolimus-untreated KTRs. Among these, 64.91% were males, and the mean age was 46.74 ± 11.03 years. Regarding insurance type, 88.79% of KTRs were covered by health insurance. In terms of dialysis duration prior to transplantation, 31.73% were pre-emptive, 17.78% had been on dialysis for .25–1.5 years, 16.23% for 1.5–3 years and 34.26% for more than 3 years. Donor types were categorized as deceased (22.38%) or living (77.62%) donors. Desensitization treatments were employed in 22.27% of the KTRs. Basiliximab was administered to 84.50% of the KTRs, while rATG was administered to 17.62% of the KTRs as induction therapy.

As of the index date, the distribution of CCI scores among KTRs showed that 14.01% had a score of 2, and 25.99% had a score of 6 or higher. The majority of KTRs had hypertension (93.07%) and dyslipidaemia (77.47%). Regarding concomitant medications for CVD, 52.20% of the KTRs used statins, 10.39% were on anticoagulants, and 1.76% were taking antiplatelet agents. Acute rejection occurred in 8.63% of KTRs. Moreover, 92.30% of KTRs were on calcineurin inhibitors, and 43.88% used antimetabolites. Cumulative steroid use was classified as low in 39.74% and high in 60.26% of the KTRs.

The baseline characteristics (SMD $> .1$ between the sirolimus-treated and untreated groups) were observed in the KT year, type of induction therapy and other immunosuppressive medications. Basiliximab was administered less frequently in the sirolimus-treated group (79.84% vs. 85.66%), whereas rATG was administered more frequently (22.22% vs. 16.47%). Additionally, the use of CNI and antimetabolites was lower in the sirolimus-treated group (73.39% vs. 97.03% and 23.26% vs. 49.03%, respectively).

3.2 | MACE associated with sirolimus treatment

The incidence rates and hazard ratios of the outcomes in the sirolimus-treated and -untreated groups are shown in Table S3. During the 6159 person-years of the sirolimus-untreated group, 65 MACEs were diagnosed, with an incidence rate of 10.55 cases per 1000 person-years. During the 850 person-years of the sirolimus-treated group, 13 MACEs were diagnosed, with an incidence rate of 15.30 cases per 1000 person-years.

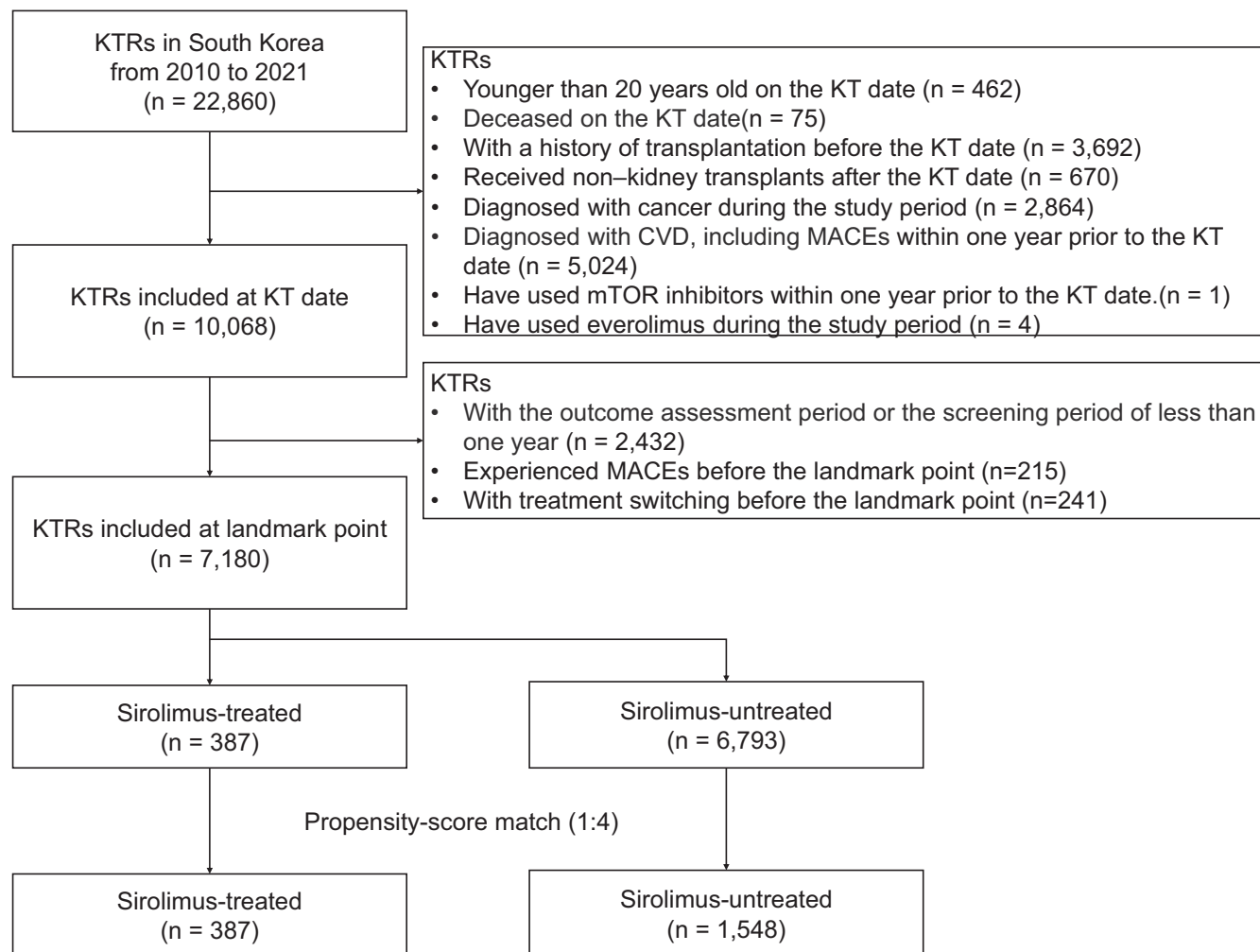


FIGURE 1 Study cohort selection process. CVD, cardiovascular disease; KTRs, kidney transplant recipients; MACE, major adverse cardiovascular events; mTOR, mammalian target of rapamycin.

In unadjusted analyses, the hazard ratio for MACE appeared higher in the sirolimus-treated group than in the sirolimus-untreated group, although this difference was not statistically significant (HR: 1.40, 95% CI: .77–2.55). The estimated HRs for myocardial infarction, ischaemic stroke, coronary revascularization, all-cause death and DCGF were 1.83, .77, 2.62, 2.09 and .30, respectively; however, these differences were not statistically significant. The cumulative incidence of MACE in KTRs treated and untreated with sirolimus, with a 1-year landmark point, is illustrated in [Figure 2](#). The log-rank test comparing the cumulative incidence between the two groups yielded a *p*-value of .27, indicating no significant difference. Consistent with the primary outcomes, no significant differences were observed in the secondary outcomes. The detailed results are presented in [Figure S3](#).

After setting the landmark, we validated the proportional hazards assumption shown in [Figures S4, S5](#). We generated plots of the log of the negative log of survival

functions, which showed parallel trends. The Schoenfeld test results were not statistically significant.

3.3 | Subgroup analysis

In the multivariate Cox analysis evaluating the interaction between sirolimus treatment and each baseline characteristic, a significant interaction was observed between congestive heart failure (CHF) and sirolimus treatment (*p* = .0097). No significant interactions were found between imbalanced baseline characteristics (KT year, induction therapy or other immunosuppressants). The corresponding *p*-values and hazard ratios are presented in [Table S4](#).

[Figure 3](#) shows a summary of the results of the subgroup analyses according to induction therapy, use of immunosuppressive medications and presence of CHF at the index date. There were no significant differences in the risk of MACE between the sirolimus-treated and

TABLE 1 Baseline characteristics after 1:4 propensity-score matching.

Characteristics	Total (n = 1935)	Sirolimus treated (n = 387)	Sirolimus untreated (n = 1548)	SMD
Age (years, mean $\pm$ SD)	46.74 $\pm$ 11.03	46.62 $\pm$ 11.43	46.77 $\pm$ 10.93	.013
<40	499 (25.79)	99 (25.58)	400 (25.84)	.006
40–49	583 (30.13)	114 (29.46)	469 (30.30)	.018
50–59	622 (32.14)	126 (32.56)	496 (32.04)	–.011
$\geq$ 60	231 (11.94)	48 (12.40)	183 (11.82)	–.018
Sex				
Male	1256 (64.91)	243 (62.79)	1013 (65.44)	.055
Female	679 (35.09)	144 (37.21)	535 (34.56)	–.055
Kidney transplant year				
2011	112 (5.79)	16 (4.13)	96 (6.20)	.094
2012	157 (8.11)	40 (10.34)	117 (7.56)	–.098
2013	238 (12.30)	52 (13.44)	186 (12.02)	–.043
2014	265 (13.70)	52 (13.44)	213 (13.76)	.009
2015	140 (7.24)	32 (8.27)	108 (6.98)	–.049
2016	281 (14.52)	45 (11.63)	236 (15.25)	.106
2017	212 (10.96)	50 (12.92)	162 (10.47)	–.076
2018	213 (11.01)	48 (12.40)	165 (10.66)	–.055
2019	317 (16.38)	52 (13.44)	265 (17.12)	.102
Type of insurance				
Health insurance	1718 (88.79)	346 (1718)	1372 (88.63)	–.025
Medical aid	217 (11.21)	41 (217)	176 (11.37)	.025
Dialysis duration (years)				
Pre-emptive (<0.25)	614 (31.73)	137 (614)	477 (30.81)	–.098
0.25–1.5	344 (17.78)	61 (344)	283 (18.28)	.067
1.5–3.0	314 (16.23)	58 (314)	256 (16.54)	.043
$\geq$ 3	663 (34.26)	131 (663)	532 (34.37)	.011
Donor type				
Deceased donor	433 (22.38)	78 (20.16)	355 (22.93)	.067
Living donor	1502 (77.62)	309 (79.84)	1193 (77.07)	–.067
Desensitization	431 (22.27)	85 (21.96)	346 (22.35)	.009
Induction therapy				
Basiliximab	1635 (84.50)	309 (79.84)	1326 (85.66)	.155
rATG	341 (17.62)	86 (22.22)	255 (16.47)	–.146
Acute rejection	167 (8.63)	35 (9.04)	132 (8.53)	–.018
CCI score				
2	271 (14.01)	56 (14.47)	215 (13.89)	–.017
3	462 (23.88)	95 (24.55)	367 (23.71)	–.020
4	438 (22.64)	78 (20.16)	360 (23.26)	.075
5	261 (13.49)	51 (13.18)	210 (13.57)	.011
$\geq$ 6	503 (25.99)	107 (27.65)	396 (25.58)	–.047
Underlying disease				
Hypertension	1801 (93.07)	357 (92.25)	1444 (93.28)	.040
Diabetes	1137 (58.76)	227 (58.66)	910 (58.79)	.003

TABLE 1 (Continued)

Characteristics	Total (n = 1935)	Sirolimus treated (n = 387)	Sirolimus untreated (n = 1548)	SMD
Dyslipidaemia	1499 (77.47)	304 (78.55)	1195 (77.20)	-.033
Congestive heart failure	252 (13.02)	55 (14.21)	197 (12.73)	-.043
Arterial fibrillation	48 (2.48)	11 (2.84)	37 (2.39)	-.028
Co-medication				
Statin	1010 (52.20)	202 (52.20)	808 (52.20)	.000
Anticoagulant	201 (10.39)	39 (10.08)	162 (10.47)	.013
Antiplatelet agent	34 (1.76)	6 (1.55)	28 (1.81)	.020
Immunosuppressants				
Calcineurin Inhibitor	1786 (92.30)	284 (73.39)	1502 (97.03)	.706
Antimetabolite	849 (43.88)	90 (23.26)	759 (49.03)	.557
Corticosteroid, cumulative dose ^a				
Low	769 (39.74)	152 (39.28)	617 (39.86)	.012
High	1166 (60.26)	235 (60.72)	931 (60.14)	-.012

Note: Data are shown as number of kidney transplant recipients (percentage).

^aUsing the prednisolone equivalent dose, the cumulative dose was calculated and transformed into a categorical variable based on the median value (69.75 mg).

-untreated groups for the subgroups defined by induction therapy and the use of immunosuppressive medications. However, in KTRs with pretransplant CHF, sirolimus increased the risk of MACEs (HR: 6.22, 95% CI: 1.78–21.74).

3.4 | Sensitivity analysis

The outcomes in the intention-to-treat (ITT) analysis did not differ from those in the main analysis. The HRs for MACE, myocardial infarction, ischaemic stroke, coronary revascularization, all-cause death and DCGF were 1.16, 1.02, .95, 1.09, 1.85 and 1.39, respectively, with no significant differences observed (Table S5). The analysis of negative control outcomes also yielded consistent findings, with HRs of .31 (95% CI, .08–1.30) for COPD, 1.01 (.53–1.91) for NAFLD and .98 (.71–1.36) for osteoarthritis. Similarly, using the clone-censor-weight method, the HR was 1.08 (95% CI, .86–1.35), indicating no significant difference (Table S6, Figures S6, S7).

4 | DISCUSSION

To the best of our knowledge, this is the first nationwide study to observe the long-term effects of sirolimus on MACE in KTRs. In de novo KTRs in Korea, sirolimus, compared to other immunosuppressants, was not associated with the risk of MACEs in this real-world setting with HR (95% CI) of 1.40 (.77–2.55).

The evaluation of sirolimus has been conducted in multiple studies with various regimens, but mostly

within fixed regimens for up to 24 months. A study evaluating the effect of everolimus over 24 months found no impact on MACE in various subgroups, including KTRs without pretransplant dyslipidaemia and diabetes, KTRs with pretransplant dyslipidaemia, and KTRs with pretransplant diabetes. The risk ratios for these groups were .91, .95 and .86, respectively.²³ In another 24-month study of everolimus, MACEs occurred in 2.3% of KTRs treated with everolimus compared to 4.5% of those treated with CNIs by month 24 ($p = .145$).²⁴ Additionally, in a study of 178 KTRs, the sirolimus group did not show a significant increase in the risk of any cardiovascular event compared to the control group (hazard ratio 1.94; 95% CI .83–4.52).²⁵

To minimize the impact of factors other than sirolimus in this study cohort, KTRs with a cancer diagnosis or a history of MACE were excluded. Consequently, vulnerable individuals were omitted, leading to a younger cohort. The proportion of living-donor transplants was high, a characteristic of Korean KTRs, with other baseline characteristics similarly representative of this population.²⁶

Despite performing PSM, SMD for immunosuppressive agents remained above .1. This discrepancy is likely because sirolimus was used as a secondary agent, leading to lower rates of CNI and AM use in KTRs on sirolimus than those on standard triple therapy. Additionally, the higher rate of rATG over basiliximab use in the sirolimus-treated group suggests that rATG was administered to immunologically high-risk patients, who are more prone to nephrotoxicity, resulting in the use of sirolimus for these KTRs. Furthermore, subgroup analysis showed that the impact of sirolimus on MACE does not change depending

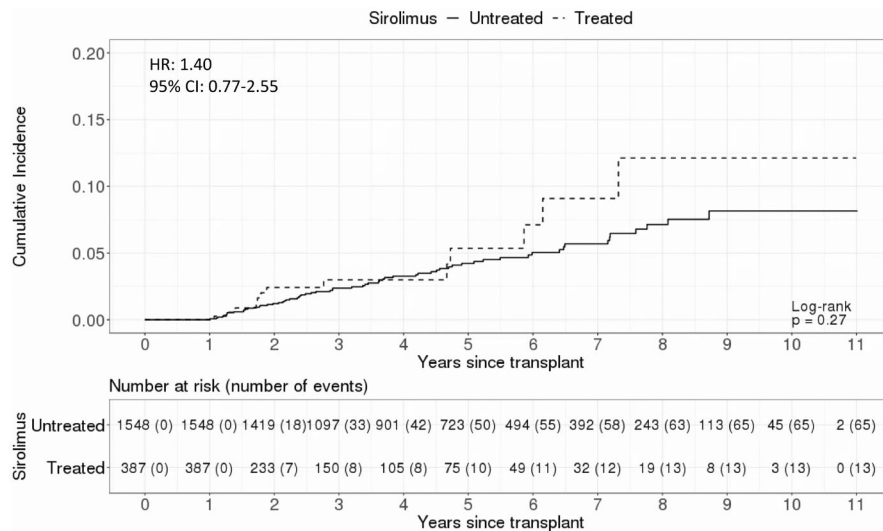


FIGURE 2 Cumulative incidence of major adverse cardiovascular events in sirolimus-treated and untreated kidney transplant recipients with a 1-year landmark point. CI, confidence interval; HR, hazard ratio.

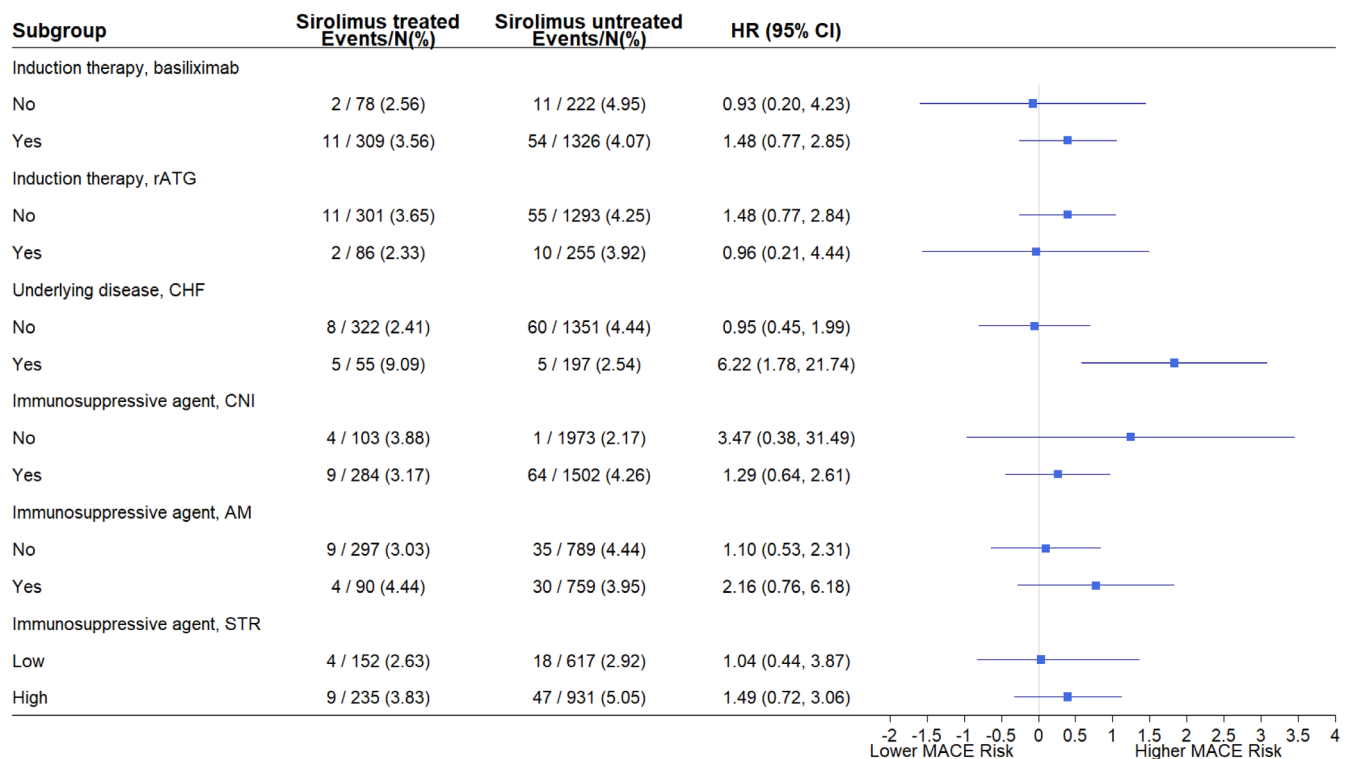


FIGURE 3 Subgroup analysis of major adverse cardiovascular events associated with sirolimus treatment. Forest plot illustrating hazard ratios for major adverse cardiovascular events. The x-axis is presented on a natural log scale. Horizontal lines represent the 95% confidence intervals for each subgroup. The cumulative dose of corticosteroids was calculated using the prednisolone equivalent dose and transformed into a categorical variable based on the median value (69.75 mg). AM, antimetabolite; CHF, congestive heart failure; CNI, calcineurin inhibitor; rATG, rabbit anti-thymocyte globulin; STR, corticosteroid.

on the concomitant immunosuppressive drugs and induction therapy used.

The dissociation between sirolimus use and MACE risk was notable, particularly considering the observed prevalence of dyslipidaemia. The prevalence of pretransplant dyslipidaemia was comparable between the groups, with rates of 68.61% and 68.99%, respectively. Following transplantation, these rates significantly diverged, with

a higher prevalence of dyslipidaemia observed in the sirolimus-treated group (71.10% vs. 78.55%, respectively). This finding aligns with prior reports indicating that mTOR inhibitors are associated with an increased risk of hypercholesterolaemia.⁹

Several factors could account for the lack of increased MACE risk despite the higher incidence of dyslipidaemia in the sirolimus-treated group. One year

post-transplantation, CNIs were used less frequently in the sirolimus-treated group (97.03% vs. 73.39%). Administration of sirolimus typically results in minimized or discontinued use of CNIs, indicating that the sirolimus-treated group experienced reduced cardiovascular risks associated with CNI use compared with the control group.²⁷ KTRs undergo routine monitoring and management of blood lipids, which helps mitigate the adverse effects of sirolimus-induced dyslipidaemia.^{7,28} In the extended study of up to 48 months, sirolimus was found to have no impact on LDL levels.²⁹ Moreover, the cardioprotective effects of sirolimus may contribute to the absence of a significant impact on MACE outcomes.^{8,28}

Consistent findings were noted in the subgroup analysis. In KTRs with pre-existing CHF, sirolimus increased the risk of MACE but did not affect MACE in KTRs without CHF. Although animal studies have shown that sirolimus reduces cardiac hypertrophy and fibrosis, the effects of mTOR inhibitors in KTRs remain inconsistent. This inconsistency may be due to pre-existing cardiac remodelling caused by hypertension and activation of the renin-angiotensin system prior to transplantation.^{8,24} Our study provides evidence supporting this hypothesis, although the small number of KTRs with CHF indicates that further research is required.

This study has certain limitations. Owing to the nature of the claims data, some information was unavailable. Factors including smoking status, obesity, kidney function and causes of death could not be ascertained, which may have served as confounding variables. In South Korea, approximately 23% of KTRs were reported to have a history of smoking prior to transplantation, whereas only 8.6% were identified as current smokers post-transplantation.³⁰ Furthermore, within 1 year after transplantation, 43.1% of these KTRs ceased smoking.³¹ Notably, a univariate analysis performed on Korean KTRs indicated that smoking history does not significantly affect the incidence of CVD (HR 2.09, 95% CI .66–6.62),¹⁴ whereas only current smoking after kidney transplantation is associated with an increased risk of cardiovascular diseases.³² Major causes of death, such as cancer, were excluded from the study period, whereas infections—which are more prevalent in the early post-transplant period—were accounted for by setting a landmark point to mitigate their impact. As kidney allograft function parameters including urine volume, urine protein excretion and serum creatinine were not available,⁷ we analysed the occurrence of DCGF as a secondary endpoint. As body mass index data were unavailable, we collected data on dyslipidaemia, diabetes and blood pressure, which are factors that could be influenced by obesity. Additionally, we applied PSM to balance the sirolimus-treated and untreated groups.

Given that unmeasured confounding could not be fully ruled out, we analysed negative control outcomes including COPD, NAFLD and osteoarthritis. This analysis revealed no significant association with sirolimus use, suggesting minimal impact from unmeasured confounders. Additionally, we assessed selection bias in the landmark analysis using the clone-censor-weight method, which yielded results consistent with the main analysis, further confirming the robustness of our findings.

Our findings indicate that the use of sirolimus did not significantly increase the risk of MACEs compared with other immunosuppressive therapies. This observation is consistent with the higher prevalence of dyslipidaemia in the sirolimus-treated group. Additionally, the subgroup analysis revealed no significant differences in MACE risk across various baseline characteristics, except for an increased risk in KTRs with pretransplant CHF. These results suggest that while sirolimus can be a viable option for immunosuppression in KTRs, it should be used cautiously in those with pre-existing CHF. Careful monitoring and management of dyslipidaemia are essential to optimize the outcomes of KTRs.

AUTHOR CONTRIBUTIONS

JP participated in the study design, data analysis, and article writing. WC conducted the data analysis. JH, YK, Y-MA, J-WK, and KHC contributed to data interpretation. HYJ participated in the revision process by interpreting the reanalysed data and reviewing the manuscript to improve it. Y-KS is a principal investigator and contributed to the study design, data interpretation, and article reviewing. All authors reviewed and approved the final manuscript for publication.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from the Health Insurance Review and Assessment, but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available (<https://opendata.hira.or.kr/>).

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