

A systematic review and meta-analysis comparing everolimus and calcineurin inhibitors (CNIs) to mycophenolate and CNIs in kidney transplant patients

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Received January 9, 2023
Revised February 22, 2023
Accepted March 15, 2023

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Background: This study compared everolimus and mycophenolate mofetil, each paired with calcineurin inhibitors (CNIs) and used with or without steroids, for maintaining immunosuppression in kidney transplant (KT) patients.

Methods: Relevant studies published before August 21, 2022 were retrieved from PubMed, the Cochrane Central Register of Controlled Trials, and the gray literature. The risk of bias was assessed independently using the revised Cochrane risk of bias assessment tool (RoB 2). RevMan ver. 5.4 was used to calculate the risk ratios (RRs) with corresponding 95% confidence intervals (CIs) for biopsy-proven acute rejection, death, and infection. The mean difference (MD) was used to compare the estimated glomerular filtration rate (eGFR) between the groups.

Results: Sixteen randomized controlled trials with a total of 5,403 patients were synthesized to compare everolimus (n=2,763) with mycophenolate (n=2,542) for maintaining post-KT immunosuppression. The meta-analysis showed no significant difference in the risk for biopsy-proven acute rejection (RR=1.12; 95% CI, 0.92–1.35; $I^2=29\%$) and death (RR=0.85; 95% CI, 0.63–1.16; $I^2=0\%$). The eGFR had no significant difference between the two groups (MD=0.93; 95% CI, -2.25 to 4.1; $I^2=84\%$). The risk for any infection was significantly higher in the mycophenolate group than in the everolimus group (RR=0.83; 95% CI, 0.73–0.93; $I^2=66\%$).

Conclusions: Our meta-analysis showed that when paired with a CNI, everolimus and mycophenolate had no difference in risk for biopsy-proven acute rejection, death, or increase in eGFR. However, the mycophenolate group exhibited a significantly higher risk of infection.

Keywords: Everolimus; Mycophenolate; Rejection; Kidney transplant; Immunosuppression

INTRODUCTION

Background

Immunosuppressive agents are mainstay medications for kidney transplant (KT) patients. They often include calcineurin inhibitors (CNIs), antiproliferatives such as

mycophenolate mofetil (MMF), and steroids. Cyclosporine and tacrolimus are the two CNIs used most commonly for KT patients. They have narrow therapeutic levels and many side effects, including nephrotoxicity, neurologic disorders, diabetes, dyslipidemia, increased risk of viral infection, and cancer. To reduce these side effects, CNIs

HIGHLIGHTS

- This meta-analysis showed that everolimus and mycophenolate mofetil combined with calcineurin inhibitor have no difference in the risks for biopsy-proven acute rejection, death and increased in estimated glomerular filtration rate.
- The mycophenolate mofetil group exhibited a significant increased risks for any infection.

are usually combined with mycophenolate or with mammalian target of rapamycin (mTOR) inhibitors that work synergistically, such as everolimus and sirolimus [1]. The most commonly used immunosuppressive agents have been tacrolimus and mycophenolate, which were shown 20 years ago in a randomized controlled trial (RCT) to be effective and safe for KT patients [2]. Because immunosuppressive agents have a high maintenance cost, it is important to verify that their benefits regarding effectiveness and safety outweigh their costs.

Everolimus is a proliferation signal inhibitor with a distinct mode of action from CNIs. It blocks the transcriptional activation of early T cell-specific genes involved in cytokine production, including interleukin-2. Everolimus intervenes late in the cell cycle by inhibiting growth-factor-driven cell proliferation. The calcium-dependent action of CNIs prevents T cell progression from the G0 phase to G1, whereas the calcium-independent action of everolimus arrests the G1 phase of the cell cycle. It is highly effective in lengthening KT allograft survival [3].

Several RCTs utilized everolimus together with a reduced dose of CNIs and maintained lower therapeutic levels. This was done to reduce the adverse events and side effects of taking CNIs [4].

Significance

Because there is no standard immunosuppressive medication for KT patients, research is needed to compare the available medications, such as everolimus and mycophenolate in order to optimize efficacy and safety.

General Objectives

This study aimed to compare everolimus and MMF/sodium (hereinafter mycophenolate), in combination with CNIs and with or without steroids, for maintaining immunosuppression in KT patients.

Specific Objectives

The specific objective of this study was to compare everolimus and mycophenolate in terms of biopsy-proven acute rejection, risk of death, change in the estimated glomerular filtration rate (eGFR), and the incidence of any type of infection.

Research Question

The research question was as follows: among adult KT patients, how effective is combined maintenance immunosuppression therapy of everolimus and a CNI, compared with mycophenolate and a CNI, in preventing rejection?

METHODS

Literature Search

A concept map was created for the research question, "Among *de novo* adult KT patients, how effective is the combined immunosuppression therapy of everolimus and a CNI, compared with mycophenolate and a CNI, in preventing rejection?" (Supplementary Table 1). The keywords were used to perform a literature search from study inception to August 21, 2022 in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and the gray literature including OpenGrey (www.opengrey.eu) and Grey Literature Report (<https://www.nyam.org/library/collections-and-resources/grey-literature-report/>). The bibliographies of selected articles were likewise checked for relevant articles. No limits were applied to language or date (Supplementary Tables 2, 3, and 4).

Study Selection

Two authors independently screened titles and abstracts against the study's eligibility criteria (Supplementary Table 5). Disagreements were settled by discussion to reach a consensus. Among the articles selected, the full texts were obtained. The full articles were reexamined and the rejection scheme was employed independently once more by both authors. Disagreements were settled by further discussion for consensus. A process diagram indicating which articles were rejected and their reasons for rejection was created in the format of the PRISMA flow diagram.

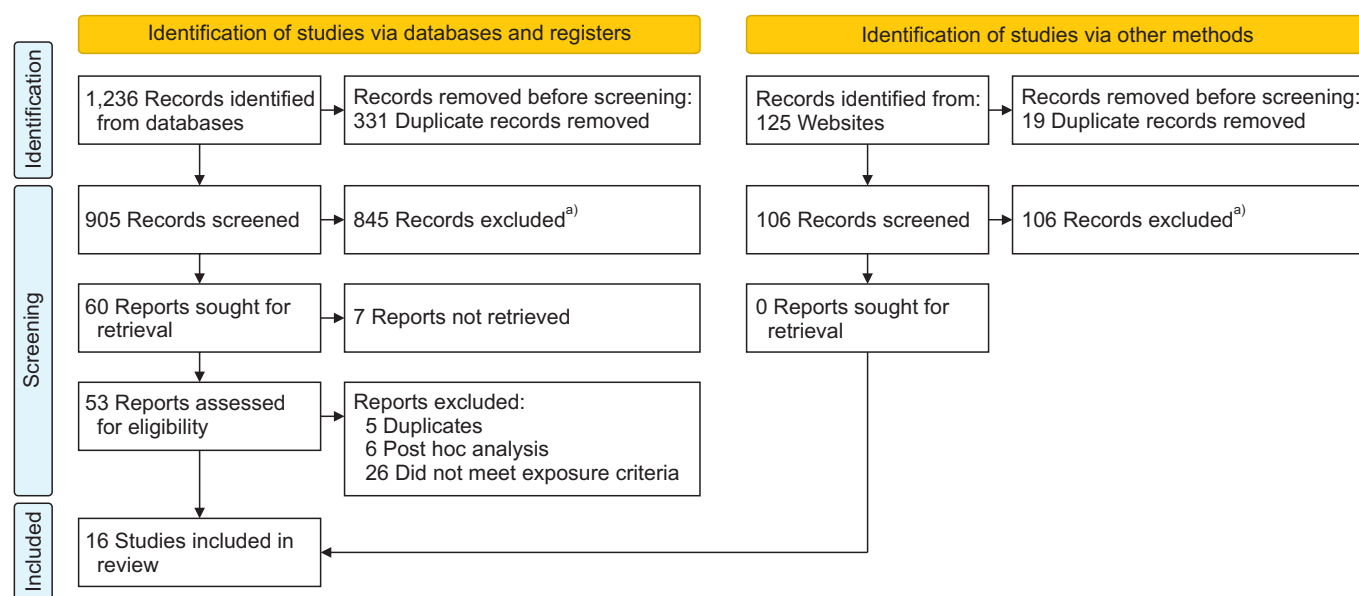


Fig. 1. PRISMA flowchart [5]. This flowchart illustrates the number of studies included in a stepwise process. ^{a)}A total of 951 records were excluded which did not meet screening process.

Data Extraction

Two authors performed data extraction. Individual patients were used as the unit of analysis. Outcomes of interest were biopsy-proven acute rejection, graft function, and mortality. Assessment of risk of bias was done independently by two authors using the revised Cochrane risk of bias assessment tool (RoB 2) [6]. Disagreements were resolved by discussion.

Statistical Analysis

Review Manager ver. 5.4 (Cochrane Collaboration) was used for meta-analysis. A P-value of <0.05 was set as the threshold for statistical significance. A random-effect model was used to estimate the effect size for each outcome measure. I^2 was used to quantify heterogeneity. Publication bias was assessed using funnel plots.

removed. A total of 1,011 articles were screened. Of these, 60 were sought for retrieval in full. Seven full texts could not be obtained. Fifty-three studies were assessed for eligibility, and 16 of them were included for synthesis (Fig. 1) [4,7-21].

Risk of Bias

Overall, the included trials had concerns for bias ranging from low to high. Two trials were available only as abstracts for poster presentations and posed a high concern for bias. One trial had high concern due to moderate concern for bias in two domains. Eight trials did not report allocation concealment. Two trials had revisions in the protocol. The study by Qazi et al. [15] revised their pre-specified non-inferiority margin during the course of the study. The study by Taber et al. [17] revised their protocol to open label from blinded due to findings of drug toxicity (Fig. 2).

Data and Analyses

Cibrik et al. [8] measured the study outcomes at 24 months, David-Neto et al. [9] measured outcomes at 178 days, and the rest of the studies measured outcomes after 1 year. There was no significant difference in the risk for biopsy-proven acute rejection between everolimus and mycophenolate, with a risk ratio of 1.12 and low heterogeneity among the studies (95% confidence interval [CI],

RESULTS

Literature Search and Included Studies

571 Articles were extracted from MEDLINE via PubMed, and 665 articles were extracted from the CENTRAL. From the gray literature, 101 articles were retrieved from Open Grey and 24 from the Grey Literature Report. In total, 1361 studies were obtained, from which 350 duplicates were

	Domain 1 (randomization process)	Domain 2 (assignment to intervention)	Domain 3 (missing outcome data)	Domain 4 (bias in measurement of the outcome)	Domain 5 (selection of reported result)	Overall bias
Bertoni et al. (2011) [17]	+	+	+	+	+	+
Ciancio et al. (2016) [4]	+	+	+	+	+	+
Cibrik et al. (2013) [8]	+	+	+	+	+	+
David-Neto et al. (2014) [9]	+	+	+	+	+	+
Hiramitsu et al. (2016) [10]	+	+	+	+	+	+
Lim et al. (2017) [11]	+	+	+	+	+	+
Lorber et al. (2005) [12]	+	+	+	+	+	+
Narumi et al. (2019) [13]	+	+	+	+	+	+
Pascual et al. (2018) [14]	+	+	+	+	+	+
Qazi et al. (2017) [15]	+	+	+	+	+	+
Sommerer et al. (2019) [16]	+	+	+	+	+	+
Taber et al. (2019) [17]	+	+	+	+	+	+
Takahashi et al. (2013) [18]	+	+	+	+	+	+
Tedesco-Silva et al. (2015) [19]	+	+	+	+	+	+
Traitanon et al. (2019) [20]	+	+	+	+	+	+
Vitko et al. (2005) [21]	+	+	+	+	+	+

Fig. 2. Quality of the included studies. Green (+), yes (high quality); yellow (?), unclear; red (-), no (low quality).

0.92–1.35; $I^2=29\%$) (Fig. 3).

The studies of David-Neto et al. [9], Sommerer et al. [16], and Taber et al. [17] were excluded from this subgroup analysis because they included previous KT patients. No significant difference was found in the risk of biopsy-proven acute rejection between everolimus and mycophenolate, with a risk ratio of 1.07 and low heterogeneity among the studies (95% CI, 0.91–1.26; $I^2=12\%$). The studies of Ciancio et al. [4] and Traitanon et al. [20] were excluded from this subgroup analysis because their studies' KT patients were steroid-free. No significant difference was found in the risk for biopsy-proven acute rejection between everolimus and mycophenolate, with a risk ratio of 1.14 and low heterogeneity among the studies (95% CI, 0.95–1.36; $P=0.18$; $I^2=25\%$).

There was no significant difference in the risk for

death between everolimus and mycophenolate, with a risk ratio of 0.85 and low heterogeneity among the studies (95% CI, 0.63–1.16; $I^2=0\%$) (Fig. 4).

The change in the eGFR showed no significant difference between the everolimus and mycophenolate groups, with a mean difference of 0.93 (95% CI, -2.25 to 4.1). However, studies indicated significant heterogeneity, with an I^2 of 84% (Fig. 5).

The risk of infection was significantly higher in the mycophenolate group than in the everolimus group, with a risk ratio of 0.83 and moderate heterogeneity among the studies (95% CI, 0.73–0.93; $P=0.0003$; $I^2=66\%$) (Fig. 6).

DISCUSSION

KT is the ideal treatment for end-stage renal disease because it allows patients' renal function to be restored to a state close to normal. However, the immune system's recognition of foreign bodies may obstruct this treatment. To ensure ongoing restoration of renal function, strong immunomodulating medications are necessary to prevent rejection of the transplanted organ. These treatments have a high risk of adverse events including infection, cardiometabolic and hematologic adverse effects, and cosmetic changes, which affect the quality of life of transplant recipients. Drug selection should be tailored to each patient, balancing consideration of its efficacy to ensure graft survival and minimize toxicity.

Conventional immunosuppression protocols include CNIs, as adjunctive agents, and steroids with or without an induction agent. Classically, the adjunctive agents were in the form of azathioprine and mycophenolate. mTOR inhibitors were introduced as an alternative to azathioprine and mycophenolate. With the advent of alternative drugs, new options became available to support the needs of patients in different situations. Everolimus is an example of an mTOR inhibitor that acts to inhibit cellular proliferation [22].

Over the last decade, a growing body of studies has evaluated the role of mTOR inhibitors in transplant immunosuppression. Previous meta-analyses have assessed the performance and side-effect profile of mTOR inhibitors. Xie et al. [23] assessed the performance of both sirolimus and everolimus compared to mycophenolate. They found that there were no significant differences in biopsy-proven acute rejection but increased risk of graft

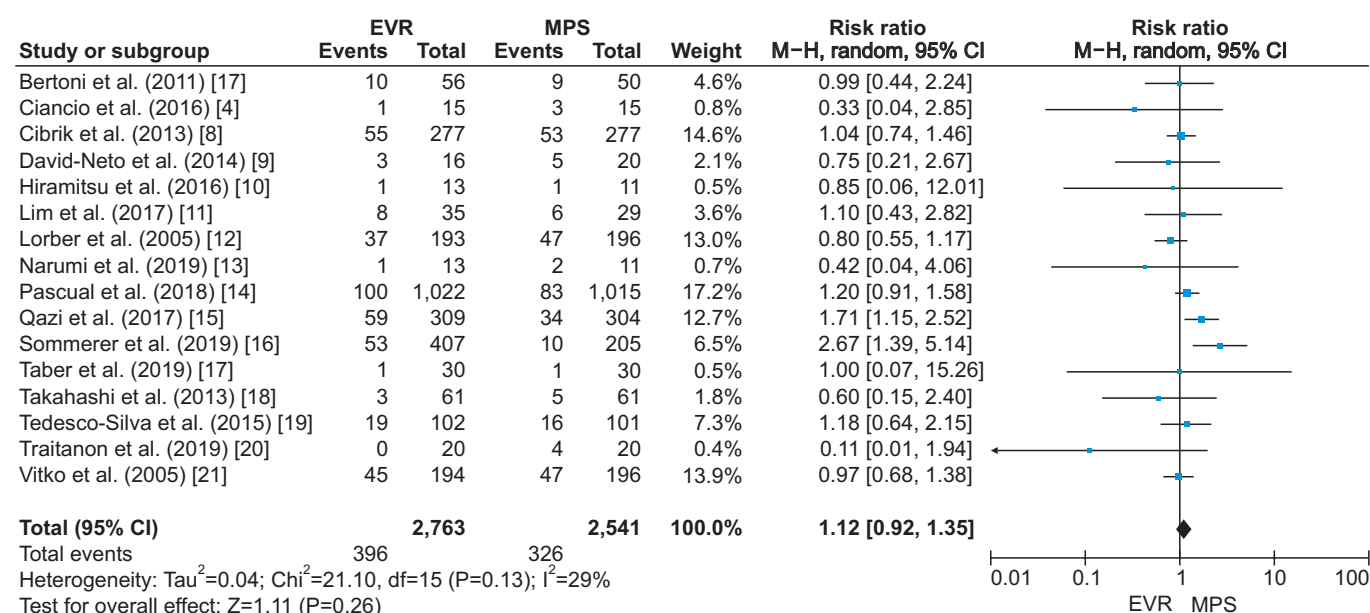


Fig. 3. Forest plot of studies among kidney transplant patients using a random-effect model showed no significant difference in the risk for biopsy-proven acute rejection between everolimus and mycophenolate, with a risk ratio of 1.12 and low heterogeneity among the studies (95% CI, 0.92–1.35; $P=0.13$ for heterogeneity; $I^2=29\%$). EVR, everolimus; MPS, mycophenolate; M-H, Mantel-Haenszel method; CI, confidence interval.

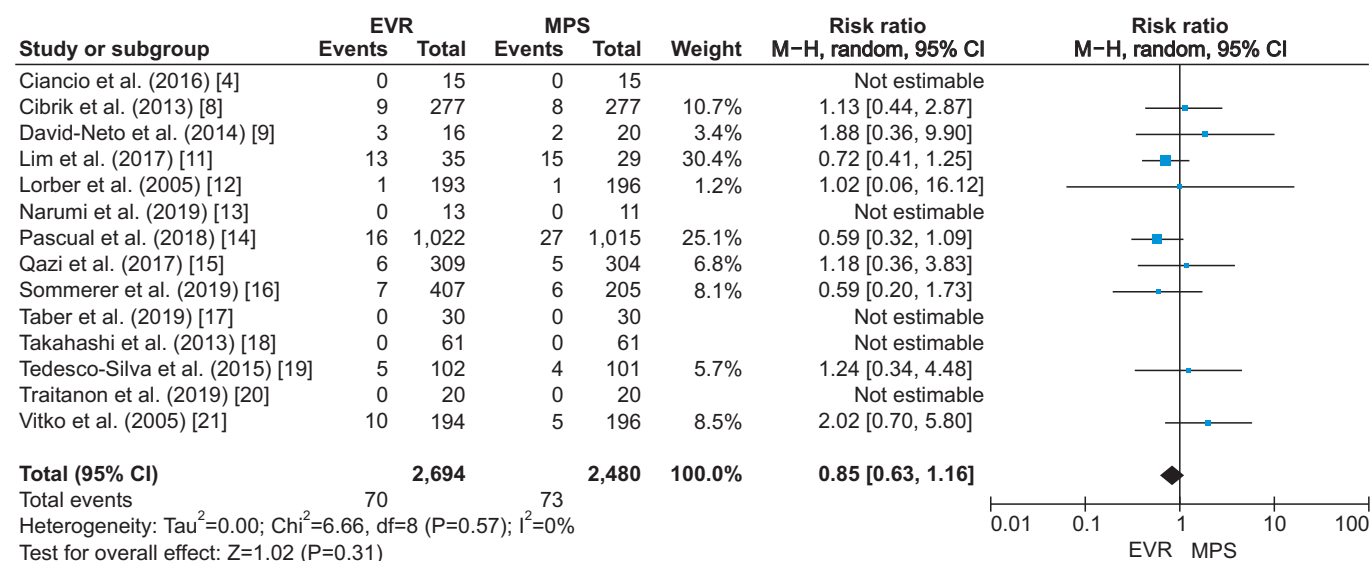


Fig. 4. Forest plot of studies among kidney transplant patients using a random-effect model showed no significant difference in the risk for death between everolimus and mycophenolate, with a risk ratio of 0.85 and low heterogeneity among the studies (95% CI, 0.63–1.16; $P=0.57$ for heterogeneity; $I^2=0\%$). EVR, everolimus; MPS, mycophenolate; M-H, Mantel-Haenszel method; CI, confidence interval.

loss and inferior graft function as measured by creatinine clearance. While mTOR inhibitors were associated with greater risk of new-onset diabetes mellitus, dyslipidemia, proteinuria, peripheral edema, thrombocytopenia and lymphocele, they had the advantage of a lower risk of cy-

tomegalovirus infection, malignancy, and leukopenia [23]. In contrast to this, a meta-analysis by Liu et al. [24] in 2016 showed that conversion from CNI to everolimus led to improved eGFR, but was associated with an increased risk of acute rejection at 1 year. In contrast, concerning

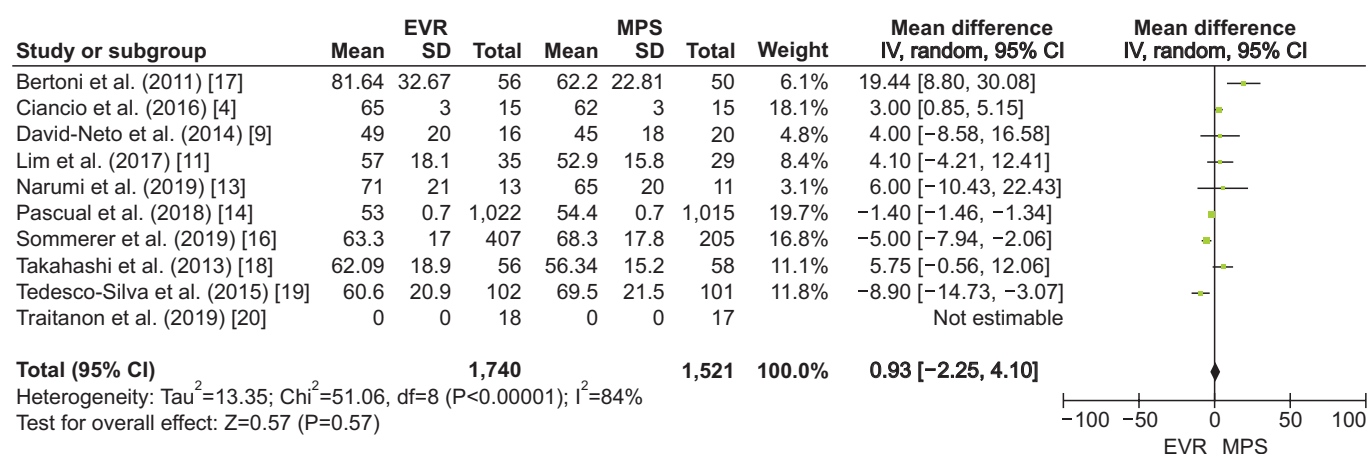


Fig. 5. Forest plot of studies among kidney transplant patients using a random-effects model showed no difference in the estimated glomerular filtration rate between the everolimus and mycophenolate groups with a mean difference of 0.93 (95% CI, -2.25 to 4.1; $P<0.00001$ for heterogeneity). However, studies showed significant heterogeneity, with an I^2 of 84%. EVR, everolimus; MPS, mycophenolate; M-H, Mantel-Haenszel method; SD, standard deviation; IV, inverse-variance method; CI, confidence interval.

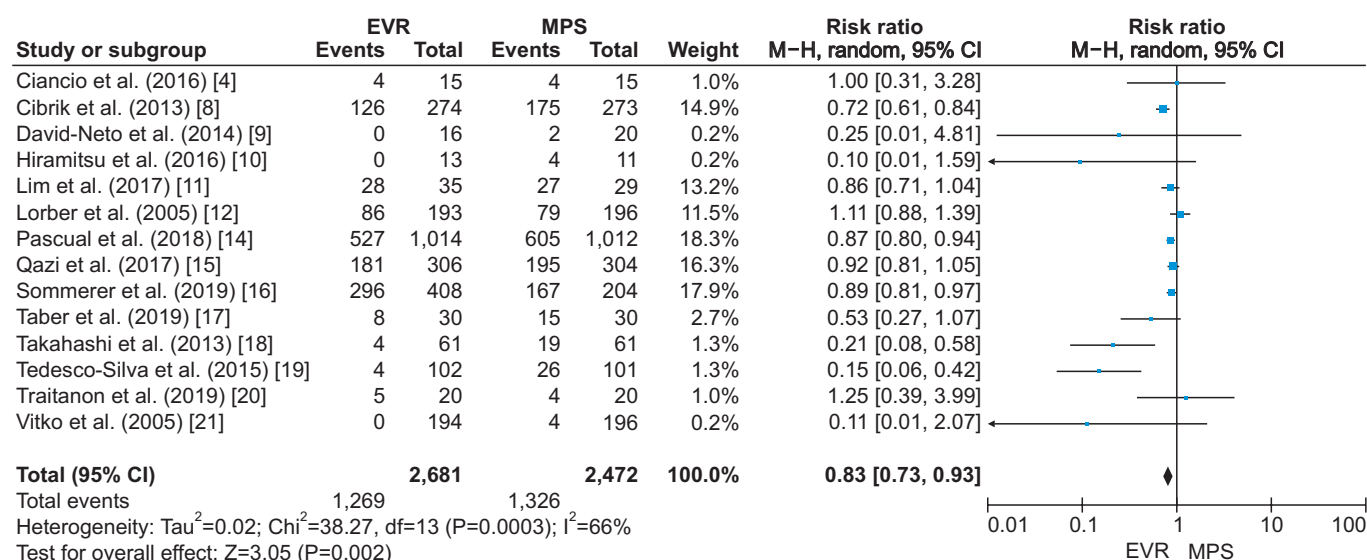


Fig. 6. Forest plot of studies among kidney transplant patients using a random-effect model showed a significantly higher risk for any infection in the mycophenolate group than in the everolimus group, with a risk ratio of 0.83 and moderate heterogeneity among the studies (95% CI, 0.73–0.93; $P=0.0003$ for heterogeneity; $I^2=66\%$). EVR, everolimus; MPS, mycophenolate; M-H, Mantel-Haenszel method; CI, confidence interval.

sirolimus, Gao et al. [25] showed no significant differences in terms of acute rejection when sirolimus was combined with tacrolimus compared to when mycophenolate was combined with tacrolimus. Likewise, no significant differences were found regarding graft survival, infectious complications, anemia, and seroma [25].

The results of our meta-analysis show that an everolimus-based immunosuppression strategy combined with

CNIs, when compared with mycophenolate, had similar efficacy regarding biopsy-proven acute rejection and mortality, as well as the risk of adverse events in terms of infection. The effect on graft function as estimated with the eGFR was also similar between both groups. Our study corroborates the meta-analysis of Gao et al. [25], indicating that mTOR inhibitors may offer an equally effective treatment option for patients suffering from toxic-

ity due to other immunosuppression regimens or patients who may benefit from the cancer-suppressing effects of mTOR inhibitors.

Our study has some limitations. Some of the studies we included had moderate to high concerns for bias. We also identified publication bias for the outcomes of biopsy-proven acute rejection and infection. Clearly, more studies are needed to determine the ideal combination of drugs for transplant immunosuppression, as well as the proper titration and dosing of each drug.

This meta-analysis showed no significant difference between everolimus and mycophenolate when combined with CNIs (cyclosporine or tacrolimus) regarding the risks of biopsy-proven acute rejection, death, and decreased eGFR. However, the mycophenolate group exhibited significantly higher risks for any infection. Everolimus and mycophenolate are equally safe and effective for recipients of KT.

ACKNOWLEDGMENTS

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Additional Information

This study was presented as an oral presentation at the Asian Transplantation Week 2022 (ATW 2022) in Seoul, Korea, November 17–19, 2022.

Supplementary Materials

Supplementary materials can be found via <https://doi.org/10.4285/kjt.23.0003>.

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