

**Abstract Type : Oral**

**Abstract Submission No. : 1190**

## **Association of metformin with cardiovascular and graft outcomes in kidney transplant recipients with post-transplantation diabetes mellitus**

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**Objectives:** Post-transplantation diabetes mellitus (PTDM) is a crucial clinical problem after kidney transplantation (KT). Metformin is the drug of choice for general population with diabetes mellitus. However, its clinical outcome and safety have not been sufficiently proven in KT recipients. We aimed to determine whether metformin affects cardiovascular and graft outcomes in patients with PTDM.

**Methods:** This retrospective cohort study included 1663 KT recipients without pre-existing diabetes mellitus. PTDM was defined as hypoglycemic treatment initiated after transplantation and maintained for over 90 days. We conducted propensity score matching between the metformin and non-metformin groups and estimated the effects of metformin on percutaneous coronary intervention (PCI), major adverse cardiovascular events (MACE), acute rejection, and graft failure.

**Results:** Out of 634 recipients with PTDM, 310 patients were diagnosed within one year after KT, and 406 recipients were treated with metformin. The incidence of PCI was 2.4% in metformin group and 7.1% in non-metformin group ( $p=0.039$ ). Recipient in the metformin group exhibited a lower risk of PCI in Cox regression analyses (HR 0.27, 95% CI 0.10-0.76;  $p=0.013$ ), especially in subgroups with male gender, older age over 49 years (median), long-term ( $\geq 1192$  days, median) metformin use, and simultaneous tacrolimus administration. Long-term metformin use was also associated with lower MACE (HR 0.09, 95% CI 0.01-0.67;  $p=0.019$ ). Graft failure was found 9.9% in the metformin group and 17.0% in the non-metformin group ( $p=0.046$ ). Both long-term metformin use and tacrolimus administration with metformin were associated with a lower risk of graft failure (HR 0.29, 95% CI 0.11-0.75;  $p=0.010$  and HR 0.39, 95% CI 0.19-0.79;  $p=0.009$ , respectively).

**Conclusions:** This study demonstrates that metformin use is associated with a decreased risk of developing coronary artery disease and better graft outcome in KT recipients with PTDM.

Figure 1. Non-occurrence rates of percutaneous coronary intervention (A), major adverse cardiovascular events (B), acute rejection (C), and graft failure (D) in the metformin and non-metformin groups in the Kaplan-Meier plot.