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Clopidogrel use as a risk factor for poor outcomes after kidney transplantation

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Abstract

BACKGROUND: Limited data are available on outcome implications of clopidogrel use before kidney transplantation.

METHODS: A novel dataset linking national transplant registry data with records from a large pharmacy claims clearinghouse (2005 to 2010) was examined to estimate risks of post-transplant death and graft failure associated with clopidogrel fills within 90 or more than 90 days before transplant.

RESULTS: Clopidogrel fills within 90 days of transplant were associated with 61% of increased relative mortality risk and 23% of increased graft failure risk. Risks were higher in those whose last clopidogrel fill was more than 90 days before transplantation (111% for death, 59% for graft loss). Adverse prognostic associations persisted among recipients of live and deceased donor allografts, older recipients, and those with diabetes or reported cardiovascular disease.

CONCLUSIONS: Clopidogrel use before kidney transplantation portends increased risks of post-transplant death and graft loss. Pharmacy claims may identify novel prognostic markers not currently captured in the transplant registry.

The authors declare no conflicts of interest.

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Cardiovascular disease is a leading cause of morbidity and mortality among patients with end-stage renal disease (ESRD) including transplant candidates and recipients.[1] Although transplantation improves long-term cardiovascular risk compared with continued dialysis, cardiovascular diseases account for 30% of deaths in patients with functioning allografts at all times after kidney transplant, with highest rates in the peritransplant period.[2–7] Among kidney transplant recipients, the highest risk of cardiovascular events occurs in the first months after transplant, but risk continues for the life of the patient.[2,4,8,9]

Because of indications among patients with coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral vascular disease (PVD), clopidogrel is a commonly prescribed medication. Currently, clopidogrel is indicated to improve outcomes related to myocardial infarction (MI), non–ST-segment elevation acute coronary syndromes and unstable angina (whether managed medically or with coronary revascularization), stroke, or established PVD.[10] According to the drug monograph, benefits include reductions in new or progressive myocardial ischemia, ischemic stroke, and other vascular deaths in patients with recent MI or stroke, or in those with established PVD.[10] In 2011, clopidogrel (tradename Plavix) was the number 2 selling prescription medication in the world, with sales in the United States alone exceeding 9.5 billion dollars.[10,11]

Although ESRD patients have a high prevalence of cardiovascular comorbidity for which clopidogrel may be indicated, clopidogrel use is associated with increased risks of bleeding and other similar complications, which are exacerbated in uremic patients.[12,13] The drug monograph states that clopidogrel should be used with caution in patients with ESRD because of decreased clearance and enhanced effects on platelet dysfunction.[10] Currently, there is limited evidence to guide when patients taking clopidogrel should be transplanted and whether pretransplant clopidogrel use impacts transplant outcomes. A recent American Heart Association Scientific Statement on "Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates" discusses danger of premature interruption of dual antiplatelet therapy (DAPT, commonly given as clopidogrel with aspirin) after coronary stent placement, but also notes that it may be reasonable to perform kidney transplantation surgery without interruption of clopidogrel therapy if the anticipated risk of perioperative bleeding is low (Class IIb; level of evidence C).[14]

In the current regulatory environment of transplantation, and in the era of public disclosure of outcomes, centers are responsible for caring for their patients while mitigating risk to steward the donor organ to the best possible outcome, and to ensure program compliance with expected graft and post-transplant survival metrics. Measures of cardiovascular comorbidity and care are not incorporated in the current national risk-adjusted survival equations used to grade transplant center performance. To advance understanding of the prognostic implications of pretransplant clopidogrel use in a nationally representative cohort, we examined a novel database that integrates the national transplant registry with pharmacy claims data. Specifically, we sought to identify patients filling clopidogrel prescriptions before transplantation and quantify associations with post-transplant death and graft failure, with consideration of differential risk according to timing of clopidogrel fills.

Methods

Data sources

The study data were constructed by linking Organ Procurement and Transplantation Network (OPTN) records for kidney transplant recipients with billing claims from a large, third party US pharmaceutical claims data (PCD) clearinghouse that captures prescription drug fill records including those reimbursed by private payers, public payers, and self-paid fills (2005 to 2010 claims).[1] The PCD comprises National Council for Prescription Drug Programs 5.1-format prescription claims aggregated from multiple sources including data clearinghouses, retail pharmacies, and prescription benefit managers for approximately 60% of US retail pharmacy transactions. Individual claim records include the date of a given pharmacy fill, National Drug Code identifying agent and dosage, quantity dispensed, and costs. The OPTN data system captures information on all transplant recipients in the United States as submitted by OPTN members, including transplant date, demographic information, and annual follow-up surveys that query information on patient and vital status. The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN contractor.

After Institutional Review Board and Health Resources and Services Administration approvals, PCD records were identified and linked with OPTN records for kidney transplant recipients. A deidentification strategy was applied wherein patient identifiers (last name, first name, date of birth, sex, and zip code of residence) were transformed before delivery to the Saint Louis University researchers with encryption technology from Management Science Associates, Inc. The patient deidentification software employs multiple encryption algorithms in succession to guarantee that the resulting "token" containing encrypted patient identifiers can never be decrypted; however, the algorithm yields the same results for a given set of data elements, such that linkages by unique anonymous tokens are possible. Because of the large sample size, the anonymity of the patients studied, and the nonintrusive nature of the research, a waiver of informed consent was granted per the Department of Health and Human Services Code of Federal Regulations (Title 45, Part 46, Paragraph 46.116). Analyses were performed using Health Information Portability and Accountability Act compliant, limited datasets from which all direct identifiers were removed. This study was approved by the Institutional Review Board of Saint Louis University.