The effect of aspirin on kidney allograft outcomes; a short review to current studies

Wisit Cheungpasitporn¹*, Charat Thongprayoon¹, Donald G. Mitema¹, Michael A. Mao¹, Ankit Sakhuja¹², Wonngarm Kittanamongkolchai¹, Maria I. Gonzalez-Suarez¹, Stephen B. Erickson¹

¹Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA
²Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, USA

Implication for health policy/practice/research/medical education:
The effects of aspirin use on allograft outcomes are unclear. In this meta-analysis including 9 studies with 19,759 kidney transplant recipients, we demonstrate significant associations between the use of aspirin and a 0.57-fold reduced risk of allograft failure, 0.11-fold reduced risk of allograft thrombosis and 0.72-fold reduced risk of major adverse cardiac events (MACEs) or mortality.


1. Background
The administration of aspirin in patients with chronic kidney disease (CKD) has been shown to provide similar potential benefit for cardiovascular risk reduction in CKD and non-CKD patients (1). Despite the fact that the use of aspirin and other antiplatelet agents in CKD patients may reduce myocardial infarction, data from randomized controlled trials (RCTs) showed that antiplatelet agents also significantly increased major bleeding in CKD patients (1-3). Thus, the use of aspirin in CKD patients may outweigh harms among patients with low annual risks of cardiovascular events (2).
In kidney transplant recipients, notwithstanding significant improvements in short-term kidney allograft survival (4), long-term graft and patients survival are still an ongoing concern (5,6). In addition, cardiovascular disease remains the most common cause of death after kidney transplantation worldwide (7,8). Previous studies of kidney transplant recipients have shown no significant benefits of antiplatelet agents, including dipyridamole and picotamide, in the reduction of allograft rejection or improvement of allograft survival (2,9-11).

The effects of aspirin administration on allograft outcomes including allograft thrombosis, delayed graft function (DGF), acute/chronic allograft rejection and major adverse cardiac events (MACEs) or mortality, however, are not clearly demarcated. A few studies have demonstrated these beneficial effects of aspirin in kidney transplant recipients (12-15). Conversely, several studies have shown no significant effects (16-20) in kidney transplant population. Thus, we conducted a meta-analysis to assess the effects of aspirin on these kidney allograft outcomes.

2. Evidence Acquisition

2.1. Search strategy

W.C. and C.T. (two investigators) independently searched published articles and conference abstracts listed in EMBASE, MEDLINE and the Cochrane database from inception through September 2016 using the following words: “aspirin” AND “transplantation” AND “kidney” or “renal” (Item S1 in online supplementary data). A manual search for additional relevant studies using references from retrieved articles was also performed. Differing decisions were resolved by mutual consensus.

2.2. Inclusion criteria and outcomes

The inclusion criteria were 1) RCTs or observational studies published as original studies or conference abstracts that assessed the effects of aspirin in kidney transplant populations, 2) studies that presented data to calculate relative risks, hazard ratios, or standardized incidence ratios with 95% confidence intervals (CI), and 3) a reference group composed of patients who were not on treatment with aspirin as control group. Our outcomes of interest in this study included allograft failure, allograft thrombosis, allograft rejection, DGF and MACEs or mortality. The quality of each study was evaluated by using the Jadad quality-assessment scale (21) for RCTs and the Newcastle-Ottawa quality assessment scale (22) for observational studies.

2.3. Data extraction

A standardized data collection form was utilized to extract the following information: study design, last name of first author, title of article, year of study, country of origin, year of publication, sample size, definition of aspirin use and control groups, and point of outcome assessment.

2.4. Statistical analysis

Review manager software (version 5.3) from the Cochrane collaboration was utilized for data analysis. Point estimates and standard errors were obtained from individual studies and were consolidated by the generic inverse variance method of DerSimonian and Laird (23). A random-effect model was employed rather than a fixed-effect model, given the high likelihood of between-study variances. Statistical heterogeneity was appraised using Cochran’s Q test. This statistic was complemented with the I² statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. An I² of 0%–25% renders insignificant heterogeneity, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity and >75% high heterogeneity (24). The possibility of publication bias was evaluated by funnel plots of the logarithm of odds ratios vs. their standard errors (25).

3. Results

The search strategy yielded 2225 potentially relevant articles: 2117 were excluded based on the title and abstract which apparently showed that they did not fulfill inclusion criteria regarding study design, article type, population, or outcome of interest (Item S2). The remaining 108 articles underwent full-length review, with 99 excluded because they were not observational studies or RCTs (n = 12) or did not report outcomes of interest (n = 87). Nine cohort studies with 19759 kidney transplant recipients that compared aspirin with no treatment were included in the meta-analysis. Table 1 includes detailed characteristics and quality assessment of all included studies.

3.1. Effects of aspirin on kidney allograft outcomes

The pooled risk ratio (RR) of allograft thrombosis in recipients (2 studies) who received aspirin was 0.11 (95% CI: 0.02-0.53, F = 66%) as shown in Figure 1. However, compared to no treatment, aspirin did not significantly reduce the risk of DGF with pooled RR (2 studies) of 1.00 (95% CI: 0.58-1.72, F = 0%) (Figure S1) or acute/chronic allograft rejection with pooled RR (3 studies) of 0.86 (RR: 0.86, 95% CI: 0.45-1.65, F = 71%) (Figure S2). Nevertheless, aspirin
### Table 1. Main characteristics of the observational studies included in this meta-analysis

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Country</th>
<th>Year</th>
<th>Total Number</th>
<th>Study Sample</th>
<th>Exposure Definition</th>
<th>Adjusted OR or RR for Outcome</th>
<th>Confounder Adjusted</th>
<th>Quality Assessment (Newcastle-Ottawa scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abendroth et al (16)</td>
<td>Germany</td>
<td>1997</td>
<td>176</td>
<td>Kidney transplant patients</td>
<td>0.5 g aspirin prior to declamping</td>
<td>1.65 (0.91-3.00) for rejection; 0.71 (0.31-1.61) for 36-month mortality; 0.48 (0.14-1.64) for 36-month mortality</td>
<td>Matched for age, gender, cold ischemia time, HLA-match, immunosuppressive regimen, and panel-reactive antibodies</td>
<td>Selection:3, Comparability: 2, Outcome: 2</td>
</tr>
<tr>
<td>Taha et al (17)</td>
<td>UK</td>
<td>2000</td>
<td>226</td>
<td>Cadaveric kidney transplant patients</td>
<td>Daily aspirin 150 mg for the first 3 postoperative months</td>
<td>0.71 (0.31-1.61) for 36-month graft failure; 0.99 (0.50-1.96) for Chronic rejection; 0.54 (0.28-1.04) for 36-month mortality</td>
<td>None</td>
<td>Selection:3, Comparability: 0, Outcome: 2</td>
</tr>
<tr>
<td>Robertson et al (12)</td>
<td>UK</td>
<td>2000</td>
<td>955</td>
<td>Cadaveric and living related kidney transplant patients receiving cyclosporine-based triple immunosuppression</td>
<td>Aspirin 75-150 mg once daily for 1 month post-transplant or long-term for high-risk patients</td>
<td>0.21 (0.09-0.51) for Renal vein thrombosis</td>
<td>None</td>
<td>Selection:2, Comparability: 0, Outcome: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abendroth et al (16)</td>
<td>UK</td>
<td>2000</td>
<td>226</td>
<td>Kidney transplant patients</td>
<td>0.5 g aspirin prior to declamping</td>
<td>1.65 (0.91-3.00) for rejection; 0.71 (0.31-1.61) for 36-month mortality; 0.48 (0.14-1.64) for 36-month mortality</td>
<td>Matched for age, gender, cold ischemia time, HLA-match, immunosuppressive regimen, and panel-reactive antibodies</td>
<td>Selection:3, Comparability: 2, Outcome: 2</td>
</tr>
<tr>
<td>Taha et al (17)</td>
<td>UK</td>
<td>2000</td>
<td>226</td>
<td>Cadaveric kidney transplant patients</td>
<td>Daily aspirin 150 mg for the first 3 postoperative months</td>
<td>0.71 (0.31-1.61) for 36-month graft failure; 0.99 (0.50-1.96) for Chronic rejection; 0.54 (0.28-1.04) for 36-month mortality</td>
<td>None</td>
<td>Selection:3, Comparability: 0, Outcome: 2</td>
</tr>
<tr>
<td>Robertson et al (12)</td>
<td>UK</td>
<td>2000</td>
<td>955</td>
<td>Cadaveric and living related kidney transplant patients receiving cyclosporine-based triple immunosuppression</td>
<td>Aspirin 75-150 mg once daily for 1 month post-transplant or long-term for high-risk patients</td>
<td>0.21 (0.09-0.51) for Renal vein thrombosis</td>
<td>None</td>
<td>Selection:2, Comparability: 0, Outcome: 2</td>
</tr>
<tr>
<td>Grotz et al (13)</td>
<td>Germany</td>
<td>2004</td>
<td>830</td>
<td>Kidney transplant patients</td>
<td>Aspirin 100 mg daily</td>
<td>0.71 (0.31-1.61) for 36-month graft failure; 0.99 (0.50-1.96) for Chronic rejection; 0.54 (0.28-1.04) for 36-month mortality</td>
<td>None</td>
<td>Selection:3, Comparability: 0, Outcome: 2</td>
</tr>
<tr>
<td>Oien et al (19)</td>
<td>Northern Europe and Canada</td>
<td>2006</td>
<td>1052</td>
<td>Kidney transplant patients</td>
<td>Aspirin use at baseline</td>
<td>0.71 (0.31-1.61) for 36-month graft failure; 0.99 (0.50-1.96) for Chronic rejection; 0.54 (0.28-1.04) for 36-month mortality</td>
<td>None</td>
<td>Selection:2, Comparability: 0, Outcome: 2</td>
</tr>
</tbody>
</table>

- **Country**
- **Study design**
- **Year**
- **Total number**
- **Study sample**
- **Exposure definition**
- **Adjusted OR or RR for outcome**
- **Confounder adjusted**
- **Quality assessment (Newcastle-Ottawa scale)**

**Notes:**
- OR = Odds Ratio
- RR = Risk Ratio
- MI = Myocardial Infarction
- HLA = Human Leukocyte Antigen
### Table 1. Continued

<table>
<thead>
<tr>
<th>Confounder adjusted</th>
<th>Statin, number of antihypertensive medications, gender, donor type, acute allograft rejection, age, number of transplantation, period of transplantation, HLA mismatch, warm ischemia time, cold ischemia time and renal diseases</th>
<th>None</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Quality assessment (Newcastle-Ottawa scale)</th>
<th>Selection:4  Comparability: 0  Outcome: 3</th>
<th>Selection:4  Comparability: 0  Outcome: 3</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>UK</th>
<th>Multi-center</th>
<th>Iran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Cohort study</td>
<td>Cohort study</td>
<td>Cohort study</td>
</tr>
<tr>
<td>Year</td>
<td>2007</td>
<td>2011</td>
<td>2012</td>
</tr>
<tr>
<td>Total number</td>
<td>797</td>
<td>15 410</td>
<td>87</td>
</tr>
<tr>
<td>Study sample</td>
<td>Cadaveric and living related kidney transplant patients</td>
<td>Kidney transplant patients</td>
<td>Pediatric kidney transplant patients</td>
</tr>
<tr>
<td>Exposure definition</td>
<td>Aspirin 75 mg daily for 28 days following transplant</td>
<td>Anti-platelet use within 4 months and 12 months post-transplant</td>
<td>Heparin 50 units/kg every 8 hours for 7 days and aspirin 5 mg/kg three times a week from day 3 of transplant for 3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjusted OR or RR for outcome</th>
<th>Renal vein thrombosis 0.04 (0.01-0.30)</th>
<th>Thrombosis 0</th>
<th>Graft failure 0.14 (0.02-1.12)</th>
<th>Acute tubular necrosis 1.44 (0.50-4.17)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Confounder adjusted</th>
<th>Age, race, BMI, cause of renal failure, time on dialysis, panel reactive antibodies, history of cardiovascular disease risk factors</th>
<th>Matched for age and sex</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Quality assessment (Newcastle-Ottawa scale)</th>
<th>Selection:2  Comparability: 0  Outcome: 2</th>
<th>Selection:4  Comparability: 2  Outcome: 3</th>
</tr>
</thead>
</table>


significantly decreased the risk of allograft failure (4 studies; RR: 0.57, 95% CI: 0.33 to 0.99, $I^2 = 55\%$) as shown in Figure 2.

### 3.2. Effects of aspirin on major adverse cardiac events or mortality

The pooled RR of MACEs or mortality in recipients (3 studies) who received aspirin was 0.86 (95% CI: 0.52-1.43, $I^2 = 63\%$) (Figure S3). When meta-analysis was limited only to the studies with adjusted analysis to minimize the effects of confounders, the pooled RR of MACEs or mortality was 0.72 (95% CI: 0.59-0.88, $I^2 = 0\%$) (Figure S4).

### 3.3. Evaluation for publication bias

Funnel plots to evaluate publication bias regarding the risks of allograft failure and MACEs or mortality in recipients using aspirin are shown in Figure S5-6. Overall, the publication bias was insignificant. However, due to the limited number of studies, the power of the test was too low to distinguish chance from real asymmetry (26).

### 4. Discussion

In this meta-analysis of 19759 kidney transplant patients, we demonstrated significant associations between the use of aspirin and a 0.57-fold reduced risk of allograft failure, 0.11-fold reduced risk of allograft thrombosis and 0.72-fold reduced risk of MACEs or mortality. However, the use of aspirin did not significantly decrease DGF or allograft rejection. In addition, the data on risk of major or minor bleeding in recipients with aspirin use were limited.

Atherosclerosis is an important and common component in the pathogenesis of chronic allograft failure (27,28). Chronic transplant vasculopathy and atherosclerosis are both recognized as special forms of inflammatory reactions within the vessel wall (27-29). Platelets have long been identified as major determinants, especially in the process of plaque rupture and vessel occlusion or stenosis (13,29). In addition, the degree of transplant vasculopathy is also correlated with the activation status of platelets (30,31). Studies have identified soluble CD40L as an important link between platelet activation and inflammation (32-34), and the blockade of the CD40 and CD40L system has been shown to suppress allograft transplant arteriopathy (31). Additionally, Grotz et al (13) demonstrated that the positive impact of aspirin treatment on long-term kidney transplantation outcome was associated with the duration of aspirin treatment (13). Therefore, our
meta-analysis confirmed associations between the use of aspirin and reduced risks of allograft thrombosis and allograft failure in kidney transplant recipients. Aspirin has been proved to be effective in primary and secondary prevention of cardiovascular disease complications (35,36). Since kidney transplant recipients are considered as moderate to high risk for cardiovascular diseases (37), not surprisingly, our studies also showed an association between reduced risk of MACEs or mortality. Despite the benefits of aspirin, studies have demonstrated that antiplatelet agents could be harmful with significantly increased risk of major bleeding in CKD patients (1-3). Unfortunately, the data on risks of major or minor bleeding associated with aspirin use in kidney transplant recipients were unclear. Although a study of 15,181 percutaneous core biopsies (including a kidney biopsy) showed that the incidence of bleeding in patients receiving aspirin within 10 days before biopsy and those not taking aspirin was not significantly different (38), the data on other types of bleeding such as gastrointestinal (GI) bleeding are limited. In the general population, a recent meta-analysis demonstrated that GI bleeding with low-dose aspirin had an incidence of 0.48-3.64 cases per 1000 person-years and an overall 1.4-fold increased risk (39). In addition, compared with aspirin alone, an increased bleeding risk was observed with use of aspirin combined with non-steroidal anti-inflammatory drugs, clopidogrel and selective serotonin reuptake inhibitors (39).

There are several limitations of our meta-analysis. First, this current study is a meta-analysis of observational studies. Thus, a causal relationship needs to be cautiously interpreted. Second, the majority of the included studies did not have available kidney allograft biopsy information, and consequently, the cause of allograft dysfunction or allograft failure was not known. However, from all available data, it is most likely that the association between aspirin use and reduced risk of allograft failure is through lowered risk of transplant vasculopathy and atherosclerosis (13,31-34). Finally, studies have shown reduced patient survival in kidney transplant recipients with elevated cardiac troponin T (cTnT) (40,41). The data on the risk and benefits of aspirin especially in these high-risk transplant populations, however, were lacking in the included studies in our meta-analysis.

5. Conclusions
In summary, this meta-analysis shows reduced risks of allograft failure, allograft thrombosis and MACEs or mortality, but not allograft rejection or DGF among renal transplant recipients treated with aspirin. Ultimately to weigh the overall risks and benefits of aspirin use in specific kidney transplant patient populations, future studies assessing the major or minor bleeding risks in aspirin treated kidney transplant recipients are required.

Conflicts of interest
The authors declare that they have no conflicting interest.

Authors’ contributions
All authors had access to the data and a role in writing the manuscript. All authors read and signed the final paper.

Funding/Support
None.

Supplementary Materials
Supplementary Data contains Item S1, Item S2, and Figures S1-S6.

References


Copyright © 2017 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.