Early Aspirin Use, Rejection, and Cardiac Allograft Vasculopathy after Heart Transplantation

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BACKGROUND
Cardiac allograft vasculopathy (CAV) remains a major cause of graft loss, heart failure, and mortality after orthotopic heart transplant (OHT).
CAV is mediated by endothelial inflammation and thrombosis.
Aspirin has anti-inflammatory and antithrombotic actions, yet has rarely been studied post-OHT.
We previously observed an association between early aspirin use post-OHT and lower rates of moderate-severe CAV (ISHLT >2).
We hypothesize that the inverse association between aspirin use and CAV will be modified by the presence of rejection or CMV infection, two potent inflammatory processes common after OHT.

METHODS
• Retrospective cohort (N=120)
• Patients receiving OHT at a single institution from 2004-2010
• Early aspirin use defined as >6mo of aspirin in first 12mo post-OHT
• Cor angiography and biopsies per institutional protocol unless clinically indicated otherwise
• Antibody mediated rejection (AMR) and acute cellular rejection (ACR) defined by biopsy

STATISTICAL ANALYSIS
Primary end point: ISHLT >2 CAV
KM Rates of the primary end point at 5 years based on aspirin use, rejection status, and CMV status
Cox PH using inverse probability of treatment weighting (IPTW)

DISCLOSURES
BAB is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women’s Hospital from: Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Braftav, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Postol, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, Zora Biosciences. BAB has also received consulting fees from: Janssen, Quark Pharmaceuticals, Abbott Vascular, and Philips.

LIMITATIONS
• Retrospective, non-randomized
• Small sample size
• Single center
• Lack of granularity concerning timing of aspirin use vs timing of rejection, CMV, and CAV
• No correction for multiple testing

CONCLUSIONS
• CAV, which is mediated by endothelial inflammation and platelet activation, remains a major cause of morbidity and mortality after OHT.
• As an anti-inflammatory and antithrombotic agent, aspirin might be expected to impact the risk of CAV, though data are lacking.
• The prevalence of aspirin use after transplant is not known; approximately half of patients receiving OHT were treated with aspirin in this single center cohort.
• Among patients who experienced rejection or CMV infection, there was a strong association between aspirin use and lower rates of moderate or severe CAV.
• These observations suggest the possibility of a biologically plausible role for aspirin and support the need for a randomized evaluation of aspirin’s efficacy and safety following heart transplantation.

Figure 1.

Figure 2.

Figure 3.

Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin (n=59)</th>
<th>No aspirin (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Men*, %</td>
<td>90</td>
<td>59</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>CAD*, %</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>VAD, %</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>Smoking*, %</td>
<td>73</td>
<td>53</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Creat., umol/L</td>
<td>124</td>
<td>124</td>
</tr>
</tbody>
</table>

CHARACTERISTICS AT THE TIME OF OHT

CHARACTERISTICS UP TO 1 YEAR POST-OHT

HTN, %
Diabetes, %
mToRI, %
CCB, %
ACEi/ARB, %
Statin, %
Vit.C/E, %

EVENTS UP TO 5 YEARS POST-OHT

ACR, %
AMR, %
CMV, %

**P<0.05
Kim et al. JHLT. 2017; 36(12):1344-1349