Cardiac transplantation remains the definitive therapy for patients with advanced heart failure, but cardiac allograft vasculopathy (CAV) continues to be a major contributor to graft failure and mortality.1 Induction therapy allows early, intense and sustained immunosuppression and may offer a unique opportunity to inhibit coronary plaque progression. Induction therapy with antithymocyte globulin (ATG) has been associated with lower incidence of angiographic CAV,2–4 but the effects of ATG induction on coronary plaque progression are unknown. See Clinical Perspective

Currently, induction therapy is used to delay initiation of nephrotoxic immunosuppressive drugs, to allow early glucocorticoid weaning, and for increasing immunosuppression in highly allo sensitized patients.5–7 However, despite its potential benefit, randomized control trials of induction therapy have had inconsistent results in part because of the heterogeneity of induction agents and their preparations.6,9 The use of induction therapy remains inconsistent as reflected in registry data in which only half of de novo cardiac transplants are induced in the current era.1 But the benefits of induction may extend beyond prevention of cardiac rejection and may, furthermore, be agent specific. Induction therapy with ATG has been associated with lower incidence of angiographic CAV, whereas induction with other agents has not.2–4 Although the significance of the association is limited by the inclusion of patients across multiple transplant eras with the potential of selection bias, the theoretical effects of consistent and sustained early immunosuppression with ATG induction therapy in attenuating coronary plaque progression have important clinical ramifications as well as significance to the research community.

In fact, there is emerging evidence for early consistent immunosuppression on attenuating downstream CAV progression. As a measure of immune activation, elevated early

## Original Article

### Induction Therapy With Antithymocyte Globulin in Patients Undergoing Cardiac Transplantation Is Associated With Decreased Coronary Plaque Progression as Assessed by Intravascular Ultrasound

Babak Azarbal, MD*; Richard Cheng, MD*; Christopher Vanichsarn, MD; Jignesh K. Patel, MD, PhD; Lawrence S. Czer, MD; David H. Chang, MD; Michelle M. Kittleson, MD, PhD; Jon A. Kobashigawa, MD

**Background**—Antithymocyte globulin (ATG) is used as induction therapy after cardiac transplant for enhancing immunosuppression and delaying the initiation of nephrotoxic drugs. It is unknown if ATG induction is associated with decreased coronary plaque progression by intravascular ultrasound (IVUS).

**Methods and Results**—Patients transplanted between March 2010 and December 2012 with baseline and 1-year IVUS were included. All patients transplanted were included in a secondary analysis. Change in plaque progression was measured in a blinded fashion on matched coronary segments and contrasted between patients induced with ATG and those who were not. One hundred and three patients were included in IVUS arms. Mean age at transplant was 55.8±12.6 years, and 33.0% were female. Patients induced with ATG were more sensitized (54.3% versus 14.3%). Plaque progression was attenuated in patients who received ATG by changes in maximal intimal area (1.0±1.2 versus 2.3±2.6 mm²; *P*=0.001), maximal percent stenosis (6.3±7.9 versus 12.8±12.3%; *P*=0.003), maximal intimal thickness (0.2±0.2 versus 0.3±0.3 mm; *P*=0.035), and plaque volume (0.5±0.7 versus 1.0±1.3 mm³/mm; *P*=0.016). Rapid plaque progression by maximal percent stenosis (≥20%) occurred less frequently in the ATG arm (4.3% versus 26.3%; *P*=0.003). Survival (*P*=0.242) and any treated rejection (*P*=0.166) were not statistically different between groups. Patients receiving ATG had a higher rate of first-year infection (*P*=0.003), perhaps related to increased intravenous antibiotic use immediately postoperatively, and a trend toward more biopsy-proven rejection (*P*=0.073).

**Conclusions**—Induction therapy with ATG is associated with reduced first-year coronary plaque progression as assessed by IVUS, despite an increased prevalence of sensitized patients with a trend toward more rejection. (Circ Heart Fail. 2016;9:e002252. DOI: 10.1161/CIRCHEARTFAILURE.115.002252.)

**Key Words:** allografts ■ biopsy ■ immunosuppression ■ incidence ■ prevalence

---

### See Clinical Perspective

Cardiac transplantation remains the definitive therapy for patients with advanced heart failure, but cardiac allograft vasculopathy (CAV) continues to be a major contributor to graft failure and mortality.1 Induction therapy allows early, intense and sustained immunosuppression and may offer a unique opportunity to inhibit coronary plaque progression. Induction therapy with antithymocyte globulin (ATG) has been associated with lower incidence of angiographic CAV,2–4 but the effects of ATG induction on coronary plaque progression are unknown.

© 2016 American Heart Association, Inc.
posttransplant T-cell immune function scores have been associated with both coronary plaque progression by intravascular ultrasound (IVUS) and angiographic CAV.10,11 Recently, mammalian target of rapamycin (mTOR) inhibitors have been shown to decrease CAV as measured by a decreased incidence of rapid plaque progression from baseline to 1-year IVUS when used as immunosuppression for de novo cardiac transplantation in place of mycophenolate mofetil.12 Drug side effects led to an increased rate of premature discontinuation of the study drug, but the importance of early immunosuppression is highlighted13 and offers an opportunity to more carefully scrutinize other immunosuppressive therapies in the early posttransplantation period.

We sought to examine whether ATG induction therapy is associated with decreased coronary plaque progression by IVUS in the first year after transplant. Safety end points of ATG induction with regards to mortality, rejection, and infection are additionally investigated in a secondary analysis of the entire transplanted cohort.

**Methods**

### Intravascular Ultrasound Protocol

Between March 2010 and December 2012, consecutive patients with performed baseline and 1-year IVUS were included in the primary analysis. IVUS was performed with a Revolution 45 Hz catheter (Volcano, San Diego, CA) or with an iLab 40 Hz catheter (Boston Scientific, Marlborough, MA). Plaque characteristics of the left main, proximal and mid-left anterior descending artery on baseline and 1-year IVUS were measured in a blinded fashion on up to 40 mm segments digitally prepared into 0.5 mm cross-sections matched by the origination of the left anterior descending artery and side branches and quantified with advanced quantification software (QIvus; Medis Medical Imaging Systems, Raleigh, NC). Maximal intimal thickness, maximal intimal area, maximal percent stenosis, and plaque volume were measured.

All patients who were eligible underwent IVUS per institutional protocol. Patients were excluded from routine IVUS screening because of absence of health-care plan coverage for the procedure, follow-up at outside institutions where IVUS was not part of posttransplant care, heart–kidney dual transplants, kidney insufficiency, active infection, active bleeding, inadequate vascular access, or hypersensitivity or contraindications to contrast media and anticoagulation (with heparin or bivalirudin).

Patients were divided into 2 arms: those who received induction (IVUS ATG+), which at our institution has been exclusively ATG during the study period, and those who did not receive induction (IVUS control). Indications for induction therapy at our institution included allowing for delayed initiation of calcineurin inhibitors in the setting of kidney insufficiency and for sensitized patients.

### End Points

The primary end points were first-year plaque progression and incidence of rapid plaque progression. Rapid plaque progression has been previously defined as first-year change from baseline ≥0.5 mm in maximal intimal thickness, ≥3.5 mm² in maximal intimal area, or ≥20% in maximal percent area of stenosis and is associated with increased subsequent mortality, nonfatal major adverse cardiac events, and development of CAV.14 Secondary end points included biopsy-proven acute rejection ≥grade 2R or AMR2 (BPAR2+), any treated rejection, first-year infection, and development of first-year posttransplant de novo donor-specific antibodies (DSA). Baseline characteristics of recipient age and sex, ischemic time, high-risk cytomegalovirus (CMV) mismatch, pretransplant peak panel reactive antibodies (PRA), pretransplant sensitization, ischemic or nonischemic pathogenesis, pretransplant mechanical circulatory support, donor age, IVUS segment length, time between paired IVUS, and immunosuppression regimen were compared between the 2 arms. Sensitization was defined as a pretransplant peak PRA ≥25%, and first-year infection was defined as prolonged intravenous antibiotics at time of transplant (≥10 days) or outside of this window treatment with antibiotics in the first year after transplant (≥5 days).

A multivariate logistic regression analysis of rapid plaque progression was performed including prespecified variables of induction therapy, pretransplant sensitization, high-risk CMV mismatch, and mTOR inhibitor use at 6 months.

### Entire Transplanted Cohort Analysis

A secondary analysis of all patients transplanted in the same time period was performed. All patients who received induction therapy (ATG+) were compared with those who did not receive induction (no ATG). Safety end points of freedom from death, BPAR2+, and any treated rejection are reported. Incidence of first-year infection, as defined above, is also reported. Baseline characteristics of recipient age and sex, ischemic time, high-risk CMV mismatch, pretransplant peak PRA, pretransplant sensitization, ischemic or nonischemic pathogenesis, pretransplant mechanical circulatory support, and donor age are reported.

Statistics were performed using SPSS (IBM, Armonk, NY). The Fisher exact test was used for categorical variables, the 2-tailed Student’s t test was used for continuous variables, and Cox proportional hazard analysis for survival curves. The study was approved by our institutional review board.

### Results

#### Intravascular Ultrasound Arms

One hundred and three patients transplanted between the March 2010 and December 2012 had complete baseline and 1-year IVUS. Mean age at transplant was 55.8±12.6 years, and 33.0% of recipients were female. Patients routinely received an immunosuppressive regimen of tacrolimus, mycophenolate mofetil, and prednisone at time of transplant. Forty-six of 103 (44.7%) patients received ATG induction therapy at time of transplant and received an average of 3.9±1.2 doses. The remaining 57 of 103 (55.3%) were not induced. Baseline and 1-year IVUS were performed at 44.5±12.1 and 379.1±27.0 days after transplant, respectively, and mean IVUS segment length was 37.2±4.2 mm. An additional 149 patients were transplanted in the same period but did not have paired baseline and 1-year IVUS and were not included in the analysis because of the exclusion criteria outlined in the Methods section as summarized in Figure 1.

#### Baseline Characteristics of Intravascular Ultrasound Arms

Recipient age, sex, ischemic pathogenesis, pretransplant mechanical circulatory support, donor age, high-risk CMV mismatch, total ischemic time, IVUS segment length, time between paired IVUS, tacrolimus use at 6 months, and mTOR inhibitor use at 6 months were not significantly different between the 2 arms. Pretransplant peak PRA was significantly higher in the patients who were induced (IVUS ATG+) 40.0±38.9% than the control arm 9.2±21.7% (P<0.001), as was highly sensitized status (peak PRA ≥25%) 25 of 46 (54.3%) versus 8 of 56 (14.3%), P<0.001. These results are summarized in Table 1. Immunosuppression regimen during the first year after transplant is summarized in Figure 2.

#### Coronary Plaque Progression by Intravascular Ultrasound

Coronary plaque progression was attenuated in patients who received ATG when compared with the control arm by...
changes in maximal intimal area (1.0±1.2 versus 2.3±2.6 mm²; \( P = 0.001 \)), maximal percent stenosis (6.3±7.9% versus 12.8±12.3%; \( P = 0.003 \)), maximal intimal thickness (0.2±0.2 versus 0.3±0.3 mm; \( P = 0.035 \)), and plaque volume per 1 mm coronary segment (0.5±0.7 versus 1.0±1.3 mm³/mm; \( P = 0.016 \)). These results are illustrated as boxplots in Figure 3 and summarized in Table 1. Change in percent atheroma volume was attenuated in patients who received ATG when compared with the control arm (4.4±5.0% versus 7.3±7.8%; \( P = 0.022 \)). Additionally, rapid plaque progression by maximal percent stenosis (≥20%) occurred in 2 of 46 (4.3%) patients in the IVUS ATG+ arm and 15 of 57 (26.3%) patients in the control arm (\( P = 0.003 \)). Rapid plaque progression by maximal intimal thickness (≥0.5 mm) occurred in 4 of 46 (8.7%) patients in the IVUS ATG+ arm and 15 of 57 (26.3%) patients in the control arm (\( P = 0.003 \)). Rapid plaque progression by maximal intimal thickness (≥0.5 mm) occurred in 4 of 46 (8.7%) patients in the IVUS ATG+ arm and 15 of 57 (26.3%) patients in the control arm (\( P = 0.003 \)). Rapid plaque progression by maximal percent stenosis (≥20%) occurred in 2 of 46 (4.3%) patients in the IVUS ATG+ arm and 15 of 57 (26.3%) patients in the control arm (\( P = 0.003 \)). Rapid plaque progression by maximal percent stenosis (≥20%) occurred in 2 of 46 (4.3%) patients in the IVUS ATG+ arm and 15 of 57 (26.3%) patients in the control arm (\( P = 0.003 \)). Rapid plaque progression by maximal percent stenosis (≥20%) occurred in 2 of 46 (4.3%) patients in the IVUS ATG+ arm and 15 of 57 (26.3%) patients in the control arm (\( P = 0.003 \)). Rapid plaque progression by maximal percent stenosis (≥20%) occurred in 2 of 46 (4.3%) patients in the IVUS ATG+ arm and 15 of 57 (26.3%) patients in the control arm (\( P = 0.003 \)).

**Multivariate Logistic Regression Analysis of Rapid Plaque Progression**

Pr-specified variables of ATG induction, pretransplant sensitization, high-risk CMV mismatch, and mTOR inhibitor use at 6 months were included in the regression analysis. Only 23 of 46 (50.0%) patients in the IVUS ATG+ arm and 18 of 57 (31.6%) patients in the control arm (\( P = 0.070 \)). First-year posttransplant DSA occurred in 15 of 45 (33.3%) patients in the IVUS ATG+ arm and 4 of 56 (7.1%) patients in the control arm (\( P = 0.002 \)), and de novo DSA occurred in 9 of 45 (20.0%) patients in the IVUS ATG+ arm and 3 of 56 (5.4%) in the control arm (\( P = 0.031 \)), reflecting the increased pretransplant sensitization of the IVUS ATG+ arm. These results are summarized in Table 1. Donor-associated atherosclerosis as defined as maximal intimal thickness ≥0.5 mm on baseline IVUS was not significantly different between those who received ATG and those who did not (19/46 [41.3%] versus 23/58 [39.7%]; \( P = 1.000 \)). Progression of donor-associated atherosclerosis defined as a change of maximal intimal thickness ≥0.3 mm between the baseline and 1-year IVUS occurred in 7 of 19 (36.8%) and 7 of 23 (30.4%) of cases, which was not significant \( P = 0.748 \).
ATG induction was statistically significant with an odds ratio of 0.200 (95% CI, 0.041–0.982); \( P = 0.047 \). These results are summarized in Table 2.

### Entire Transplanted Cohort Analysis

Two hundred and fifty-two patients were transplanted between March 2010 and December 2012. Mean age at transplant was 55.7±12.4 years, and 33.3% of recipients were female; 105 of 252 (41.7%) patients received ATG induction therapy at time of transplant. The remaining 147 of 252 (58.3%) were not induced.

Recipient age, sex, ischemic pathogenesis, pretransplant mechanical circulatory support, donor age, high-risk CMV mismatch, and total ischemic time were not significantly different between the 2 arms. Pretransplant peak PRA was significantly higher in the patients who were induced (ATG+; 39.2±37.7%) than the control arm (7.7±20.7%; \( P<0.001 \)), as was sensitized status 57 of 105 (54.3%) versus 17 of 147 (11.6%), \( P<0.001 \). These results are summarized in Table 3.

Mean clinical follow-up was 28.5±17.5 months. Survival was 226 of 252 (89.7%). Freedom from BPAR2+ and any treated rejection were 219 of 252 (86.9%) and 199 of 252 (79.0%), respectively. First-year infection occurred in 111 of 252 (44.0%) patients. There were no differences between the 2 arms with regards to survival (\( P=0.242 \)) and any treated rejection.

### Table 1. Baseline Characteristics and Primary and Secondary End Points of Intravascular Ultrasound Arms

<table>
<thead>
<tr>
<th>IVUS baseline characteristics</th>
<th>IVUS ATG+</th>
<th>IVUS Control</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (y)</td>
<td>55.1±13.0</td>
<td>56.4±12.4</td>
<td>0.609</td>
</tr>
<tr>
<td>Recipient female sex (%)</td>
<td>19/46 (41.3)</td>
<td>15/57 (26.3)</td>
<td>0.141</td>
</tr>
<tr>
<td>Pretransplant peak PRA (%)</td>
<td>40.0±38.9</td>
<td>9.2±21.7</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Sensitized status* (%)</td>
<td>25/46 (54.3)</td>
<td>8/56 (14.3)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Ischemic pathogenesis (%)</td>
<td>16/45 (35.6)</td>
<td>17/56 (30.4)</td>
<td>0.671</td>
</tr>
<tr>
<td>Pretransplant mechanical circulatory support (%)</td>
<td>13/46 (28.3)</td>
<td>13/56 (23.2)</td>
<td>0.650</td>
</tr>
<tr>
<td>Donor age (y)</td>
<td>34.4±14.1</td>
<td>32.3±12.5</td>
<td>0.426</td>
</tr>
<tr>
<td>High-risk CMV mismatch* (%)</td>
<td>9/46 (19.6)</td>
<td>9/56 (16.1)</td>
<td>0.795</td>
</tr>
<tr>
<td>Total ischemic time (min)</td>
<td>178.8±60.7</td>
<td>168.2±60.5</td>
<td>0.396</td>
</tr>
</tbody>
</table>

*Included in multivariate logistic regression analysis.
†\( P<0.05 \).
‡\( P \) values by univariate analysis.

ATG indicates antithymocyte globulin; CMV, cytomegalovirus; IVUS, intravascular ultrasound; mTOR, mammalian target of rapamycin; and PRA, panel reactive antibodies.

Figure 2. Posttransplantation immunosuppression regimen. At transplant: tacrolimus, 100%; mycophenolate, 100%. Three months: tacrolimus, 96.1%; cyclosporine, 3.9%; mycophenolate, 96.1%; everolimus, 2.9%; sirolimus, 1.0%. Six months: tacrolimus, 96.1%; cyclosporine, 3.9%; mycophenolate, 89.3%; everolimus, 6.8%; sirolimus, 3.9%; tacrolimus, 95.1%; cyclosporine, 4.9%; mycophenolate, 83.5%; everolimus, 9.7%; sirolimus, 6.8%; tacrolimus, 95.1%; cyclosporine, 4.9%; mycophenolate, 76.7%; everolimus, 12.6%; sirolimus, 10.7%.
rejection ($P=0.166$) by Cox proportional hazard analysis. There was a trend toward increased biopsy-proven rejection BPAR2+ ($P=0.073$) in the ATG arm. First-year infection was significantly higher in the ATG+ arm (58/106 [55.2%]) than in the control arm (53/147 [36.1%]; $P=0.003$), driven primarily by increased prolonged intravenous antibiotic use immediately postoperatively ($\geq$10 days). These results are illustrated in Figure 4 and summarized in Table 3. With regards to malignancy and CMV-related deaths, in the ATG arm, malignancy-related death occurred in 1 patient because of metastatic urothelial carcinoma 761 days after transplantation. In the control arm, CMV-related death occurred in 1 patient 527 days after transplantation.

**Discussion**

CAV continues to be a major contributor to graft failure and mortality, and era-to-era improvement in survival after cardiac transplantation has stagnated over the past decade. Induction therapy is not consistently used across transplant centers, and there is significant regional and interinstitutional variability in its use. In the absence of prospective multicenter randomized trials, demonstrable benefits of induction therapy should be weighed against their risks in each individual patient.

This study demonstrates that CAV progression as assessed by maximal intimal thickness, maximal intimal area, maximal percent stenosis, and plaque volume was reduced in patients who received induction therapy with ATG. These findings were confirmed by multivariate analysis including adjusting for CMV status, sensitization status, and mTOR inhibitor use. Across all 4 metrics, the changes in plaque characteristics were statistically significantly decreased in the IVUS ATG+ arm. These reductions are observed in spite of the fact that the ATG group has a higher percentage of sensitized patients and patients with DSA.

With respect to maximal intimal thickness increase $\geq$0.5 mm, which represents one of the most studied markers of subsequent mortality, nonfatal major adverse cardiac events, and angiographic CAV, there was a trend toward reduction of rapid plaque progression by maximal intimal thickness in the IVUS ATG+ arm (8.7% versus 22.8%; $P=0.066$). Rapid plaque progression by maximal percent stenosis ($\geq$20%) has been similarly validated with respect to subsequent mortality, nonfatal major adverse cardiac events, and angiographic CAV. In our study, there was a $>80\%$ reduction in that metric, which was statistically significant.

This is a large IVUS study in a modern cohort of patients on current era immunosuppression transplanted within a 3-year period. A significant portion of patients were highly sensitized with peak PRA $\geq$25% (32.4% in IVUS arms, 29.4% in the entire transplanted cohort). Not surprisingly, patients who were sensitized were 4 times as likely to receive ATG induction therapy in our cohort. There was an increased incidence of development of de novo DSA after transplant in the patients induced with ATG and is likely a reflection of their pretransplant sensitization status. Although the development of DSA may accelerate CAV, we nonetheless observed a consistent 50% decrease in coronary plaque progression in patients induced with ATG across all IVUS indices.

**Table 2. Multivariate Logistic Regression Analysis of Rapid Plaque Progression**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$ Maximal percent stenosis $\geq$20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitized status</td>
<td>0.199 (0.023–1.696)</td>
<td>0.140</td>
</tr>
<tr>
<td>Induction with ATG</td>
<td>0.200 (0.041–0.982)</td>
<td>0.047*</td>
</tr>
<tr>
<td>mTOR inhibitors use at 6 months</td>
<td>0.666 (0.127–3.507)</td>
<td>0.632</td>
</tr>
<tr>
<td>High-risk CMV mismatch</td>
<td>0.668 (0.127–3.513)</td>
<td>0.633</td>
</tr>
</tbody>
</table>

ATG indicates antithymocyte globulin; CI, confidence interval; CMV, cytomegalovirus; and mTOR, mammalian target of rapamycin. *$P<0.05$. 

**Figure 3.** Coronary plaque progression by intravascular ultrasound. Boxplots of change between baseline IVUS and 1-year IVUS in maximal intimal thickness (A), maximal intimal area (B), maximal percent stenosis (C), and plaque volume per 1 mm coronary segment (D) are compared between patients who received ATG induction and control in the IVUS arms. ATG indicates antithymocyte globulin; and IVUS, intravascular ultrasound.
In multivariate analysis, use of mTOR inhibitors at 6 months was not found to be a predictor of rapid plaque progression. This may be because of the heterogeneous indications for their use in this retrospective cohort. However, the odds ratio estimate suggested a protective relationship in line with their expected effect in reducing the incidence of rapid plaque progression.12

In the secondary analysis of the entire transplanted cohort, there was a trend toward decreased freedom from BPAR2+ rejection, most likely reflecting the 4-fold increased prevalence of pretransplant sensitization in the group of patients who received ATG. This trend toward decreased freedom from BPAR2+ rejection is expected from prior observations that pretransplant sensitization in the group of patients who received ATG is associated with decreased incidence of BPAR2+ rejection was not seen when outcomes are restricted to the first-year posttransplant (as illustrated in the secondary outcomes of the IVUS arms) and suggest the potential association to be more likely related to pretransplant sensitization status than to ATG induction.

First-year infection was increased in the those who received ATG, is driven primarily by prolonged intravenous antibiotics use immediately postoperatively, may reflect the prophylactic use of prolonged antibiotics given known ATG induction status, and may, furthermore, be overused as treatment of nonspecific postoperative fevers, which may be a benign side effect of ATG administration. However, mortality was not significantly different between the patients who received ATG and those who did not and was similarly low. Nominally, there was an increased survival in the ATG arm that was not statistically significant further supporting the safe use of ATG induction.

The observation in this study that ATG induction therapy is associated with a decrease in CAV by coronary plaque progression on IVUS has pathophysiological grounding. The pathogenesis of CAV is thought to be both immunologic from the activation and proliferation of T-cells, macrophages, platelet-derived growth factor, donor-specific CD4+ cells, and other immune components and also nonimmunologic from infectious and ischemia-perfusion injury, among other factors. ATG-reperfusion injury leads to release of innate immune ligands and is associated with allograft coronary endothelial dysfunction. ATG has the potential to act on both immunologic and nonimmunologic pathways. In addition to the consistent and sustained early immunosuppression induction therapy can provide, experimental models have demonstrated its benefit in rescuing ischemia-perfusion injury in endothelial cells. ATG added to endothelial cells stimulated with tumor necrosis factor-α reduced the expression of adhesion molecules. Similarly, ATG when used in reperfusion of limbs after 60 minutes of induced ischemia in cynomolgus monkeys caused a reduction of expression of adhesion and inflammation molecules both in the endothelium and in the reperfused tissue.

The results of this study are in line with prior clinical observations. ATG induction has been associated with lower incidence of angiographic CAV. The largest study of 662 patients was a retrospective case–control study where induction with ATG was associated with decreased incidence of CAV with a risk ratio of 0.63. In the next largest study of 211 patients in which 163 patients received ATG induction therapy, there was a trend toward lower incidence of CAV. The results of our study on a large modern cohort of patients on current era immunosuppression with advanced IVUS imaging and plaque quantification bridge the gap between prior clinical findings and our understanding of the mechanisms of action of ATG therapy and the pathogenesis of CAV.

### Table 3. Baseline Characteristics and Secondary Outcomes of the Entire Transplanted Cohort

<table>
<thead>
<tr>
<th></th>
<th>ATG+</th>
<th>No ATG</th>
<th>P</th>
<th>PValue vs. IVUS Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire transplanted cohort baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient age (y)</td>
<td>55.3±13.1</td>
<td>55.9±12.2</td>
<td>0.736</td>
<td>0.869</td>
</tr>
<tr>
<td>Recipient female sex (%)</td>
<td>42/105 (40.0)</td>
<td>42/147 (28.6)</td>
<td>0.078</td>
<td>1.000</td>
</tr>
<tr>
<td>Pretransplant peak PRA</td>
<td>39.2±37.7</td>
<td>7.7±20.7</td>
<td>&lt;0.001*</td>
<td>0.507</td>
</tr>
<tr>
<td>Sensitized status (%)</td>
<td>57/105 (54.3)</td>
<td>17/147 (11.6)</td>
<td>&lt;0.001*</td>
<td>0.525</td>
</tr>
<tr>
<td>Ischemic pathogenesis (%)</td>
<td>40/105 (38.1)</td>
<td>60/147 (40.8)</td>
<td>0.697</td>
<td>0.185</td>
</tr>
<tr>
<td>Pretransplant mechanical circulatory support (%)</td>
<td>28/105 (26.7)</td>
<td>32/147 (21.8)</td>
<td>0.373</td>
<td>0.892</td>
</tr>
<tr>
<td>Donor age (y)</td>
<td>35.2±13.3</td>
<td>34.3±13.8</td>
<td>0.605</td>
<td>0.200</td>
</tr>
<tr>
<td>High-risk CMV mismatch (%)</td>
<td>23/105 (21.9)</td>
<td>26/147 (17.7)</td>
<td>0.423</td>
<td>0.765</td>
</tr>
<tr>
<td>Total ischemic time (min)</td>
<td>175.9±73.5</td>
<td>165.5±71.1</td>
<td>0.264</td>
<td>0.361</td>
</tr>
<tr>
<td><strong>Entire transplanted cohort end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (%)</td>
<td>8/105 (7.6)</td>
<td>18/147 (12.2)</td>
<td>0.242†</td>
<td></td>
</tr>
<tr>
<td>BPAR2+ (%)</td>
<td>19/105 (18.1)</td>
<td>14/147 (9.5)</td>
<td>0.073†</td>
<td></td>
</tr>
<tr>
<td>Any treated rejection (%)</td>
<td>27/105 (25.7)</td>
<td>26/147 (17.7)</td>
<td>0.166†</td>
<td></td>
</tr>
<tr>
<td>First-year infection (%)</td>
<td>58/105 (55.2)</td>
<td>53/147 (36.1)</td>
<td>0.003*</td>
<td></td>
</tr>
</tbody>
</table>

ATG indicates antithymocyte globulin; BPAR2+, biopsy-proven acute rejection ≥grade 2R or AMR2; CMV, cytomegalovirus; IVUS, intravascular ultrasound; and PRA, panel reactive antibodies.

*P < 0.05.
†Cox proportional hazard.
Figure 4. Entire transplanted cohort secondary analysis. Survival curves with Cox proportional hazard P values (A), freedom from BPAR2+ (B), and any treated rejection (C) are compared between patients who received ATG induction to control in the as-treated arms. Numbers at-risk at each time point are labeled. ATG indicates antithymocyte globulin; BPAR2+, biopsy-proven acute rejection ≥ grade 2R or AMR2.

Limitations
As a nonrandomized study, the relationship between decreased coronary plaque progression and ATG induction therapy is observational. A prospective randomized study would be needed to demonstrate a causative nature. Moreover, this is a single center study limiting the generalizability of the findings. As all patients did not undergo routine IVUS examinations post-transplant, a possible selection bias could have been introduced. The multivariate logistic regression analysis is limited by the number of patients with rapid coronary plaque progression.

Conclusions
Induction therapy with ATG is associated with reduced coronary plaque progression as assessed by IVUS, despite an increased prevalence of sensitized patients in the ATG arm. Further investigation is warranted to define the effect of ATG induction on CAV development and progression and to guide clinicians as to which patients may benefit from ATG induction posttransplantation.

Disclosures
Dr Patel has received research grants from Alexion Pharmaceuticals. Dr Kobashigawa has received honoraria and research grants from XDx Inc., Novartis Pharmaceuticals Inc., and TransMedics Inc. The other authors report no conflicts.

References
CLINICAL PERSPECTIVE

Cardiac allograft vasculopathy (CAV) continues to be a major contributor to graft failure and mortality after cardiac transplantation. Induction therapy with antithymocyte globulin (ATG) allows early, intense, and sustained immunosuppression and may offer a unique opportunity to inhibit coronary plaque progression. We sought to examine whether ATG induction therapy is associated with decreased coronary plaque progression by intravascular ultrasound (IVUS) in the first year after transplant. Secondary end points of ATG induction with regards to mortality, rejection, and infection are additionally investigated in a secondary analysis of the entire transplanted cohort. One hundred and three patients transplanted during a 34-month period with matched baseline and 1-year IVUS were included in the primary analysis. Patients who received ATG induction therapy were more sensitized, but plaque progression was in fact attenuated by maximal intimal thickness, area, and percent stenosis, in addition to plaque volume and percent atheroma volume. This finding held up on multivariable analysis. In the secondary analysis of the entire transplanted cohort, there was more intravenous antibiotic use and a trend toward more biopsy-proven rejection in the more highly sensitized ATG arm. However, there were no differences in survival and as-treated rejection. We conclude that induction therapy with ATG is associated with reduced first-year coronary plaque progression as assessed by IVUS despite an increased prevalence of sensitized patients. The use of ATG induction therapy remains inconsistent in current practice, and our findings may support its increased use.
Induction Therapy With Antithymocyte Globulin in Patients Undergoing Cardiac Transplantation Is Associated With Decreased Coronary Plaque Progression as Assessed by Intravascular Ultrasound

Babak Azarbal, Richard Cheng, Christopher Vanichsarn, Jignesh K. Patel, Lawrence S. Czer, David H. Chang, Michelle M. Kittleson and Jon A. Kobashigawa

Circ Heart Fail. 2016;9:e002252
doi: 10.1161/CIRCHEARTFAILURE.115.002252

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/9/1/e002252

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/