The most common cause of death after heart transplantation is cardiovascular events and graft failure. Today, donor hearts are not selected on the basis of HLA matching, and HLA typing is mainly applied to determination of donor-specific antibodies in sensitized heart transplant recipients. ABO blood group compatibility, size of recipient and donor, age, sex, and medical urgency are the main criteria for matching potential recipients with the appropriate donor.

In the field of kidney transplantation, there is strong support for the beneficial effect of minimizing donor-recipient HLA incompatibility on improvement of the long-term prognosis of kidney transplant patients. Generally, an impact on cardiac transplant survival for HLA matching has been controversial. Opelz and Wujciak showed that 3-year rate of heart transplantation was associated with HLA-A compatibility in HLA-B,DR incompatible grafts. This was confirmed in multivariable Cox regression analysis where HLA-A compatibility (vs HLA-A incompatibility) was associated with higher mortality in transplants incompatible for HLA-DR or HLA-B and DR (hazard ratio [HR], 1.59; 95% confidence interval [95% CI], 1.11–2.28; P = 0.007, and P = 0.002, respectively) but not in HLA-B- and or HLA-DR-compatible grafts. This was confirmed in multivariable Cox regression analysis where HLA-A compatibility (vs HLA-A incompatibility) was associated with higher mortality in transplants incompatible for HLA-DR or HLA-B and DR (hazard ratio [HR], 1.59; 95% confidence interval [95% CI], 1.11–2.28; P = 0.012 and HR, 1.69; 95% CI, 1.17–2.43; P = 0.005, respectively). In multivariable analysis, the largest compromise in survival for HLA-A compatibility (vs HLA incompatibility) was for chronic rejection in HLA-B and DR incompatible grafts (HR, 1.91; 95% CI, 1.22–3.01; P = 0.005). Conclusions. Decreased long-term survival in heart transplantation was associated with HLA-A compatibility in HLA-B,DR incompatible grafts.

Received 17 June 2015. Revision received 13 August 2015. Accepted 13 August 2015.

1 Department of Clinical Sciences Lund, Cardiothoracic Surgery, Lund University and Skåne University Hospital, Lund, Sweden.
2 Department of Clinical Sciences Malmö, Surgery, Transplantation Unit, Lund University and Skåne University Hospital, Malmö, Sweden.
3 Department of Laboratory Medicine, Clinical Chemistry and Pharmacology, Lund University, Lund, Sweden.
4 Department of Astronomy and Theoretical Physics, Computational Biology and Biophysical Sciences, Lund University, Lund, Sweden.
5 Department of Clinical Sciences Lund, Surgery, Lund University and Skåne University Hospital, Lund, Sweden.
6 Department of Laboratory Medicine, Clinical Chemistry and Pharmacology, Lund University, Lund, Sweden.

This work was supported by grants from Swedish National Infrastructure for Computing, Swedish Heart-Lung Foundation, Swedish Society of Medicine, Government grant for clinical research, Region Skåne Research Funds, Donation Funds of Lund University Hospital and the Crafoord Foundation.
donor and recipient for HLA-A–related antigens induces a downregulatory reaction on the immune response to incompatible HLA-B and HLA-DR antigens.\(^5\) This prompts the question whether similar observation can be made in heart transplantation, that is, an interaction between HLA-A matching and the other HLA loci, which impact long-term survival. The aim of this study was to investigate possible associations between HLA-A matching in relation to HLA-B, -DR matching and long-term survival after heart transplantation.

**MATERIALS AND METHODS**

**Source Of Data**

The International Society for Heart and Lung Transplantation (ISHLT) International Registry for Heart and Lung Transplantation (www.ishlt.org) includes data since 1980s and contains almost 400 variables, including pretransplantation, transplantation, discharge, and follow-up variables. Posttransplant information is reported at the end of the annual follow-up period and at the time of death. The date of death after heart transplantation is provided by the transplant center. A complete list of data collects, participating institutions, and ISHLT registration data elements are available at http://www.ishlt.org/registries/.

**Patients And Study Design**

Data from heart donors and the corresponding recipients transplanted between January 1, 1988, and June 31, 2011, were collected from the ISHLT registry (n = 93 507). Pediatric cases (recipients younger than 18 years, n = 13 136); recipients with panel-reactive antibodies (PRA) of 10% or greater (class I or class II) (n = 4 483); history of previous cardiac surgery including mechanical circulatory support, or previous transplantation (n = 10 129); recipients who died inoperatively (n = 726); and those with missing value on recipient or donor HLA-A, duration of follow-up, or cause of death not reported (n = 39 430) were excluded. The final study population comprised 25 583 patients with at least 1 day of follow-up duration. The latest annual follow-up was on October 9, 2011. The primary endpoint was all-cause mortality. Secondary endpoints were mortality attributable to graft failure (primary failure, rejection: hyperacute, acute or chronic, technical, graft infection, recurrent disease, nonspecific), cardiovascular causes (myocardial infarction, cardiac arrest, arterial embolism, ventricular failure, coronary artery disease, atherosclerosis, rhythm disorder, carditis, aortic aneurysm, cardiogenic shock, other), infection (bacterial sepsis, bacterial pneumonia, bacterial—other, viral cytomegalovirus, hepatitis, viral sepsicemia, viral—other, fungal, protozoal, mixed), or malignancy (metastatic, primary, posttransplant lymphoproliferative disorder, lymphoma, skin, other) as defined by the ISHLT Registry. The Ethics Committee for Clinical Research at Lund University, Sweden approved the study protocol.

**Statistical Analysis**

Statistical analyses were performed using the Stata MP statistical package version 13.1 (2013) (StataCorp LP, College Station, TX). Unpaired Mann-Whitney U tests or t tests were used to compare continuous variables, and \(\chi^2\) or Fisher exact tests were used to compare categorical variables among groups. Log-rank test was used to compare the Kaplan-Meier survival curves. Independent predictors of cumulative mortality were identified using Cox proportional hazard (CPH) regression. Any variable from the univariable test (simple CPH) with a \(P\) value less than 0.25 was selected as a candidate for stepwise backward selection Cox regression analysis, resulting in a main effect model. We further split episodes into 2 episodes at implied time points. Each resulting covariate record contained the follow-up on 1 subject through 1 time band.\(^6\) Hazard ratios (HRs) are presented with 95% confidence intervals (95% CIs). All tests were 2-sided, and \(P\) values less than 0.05 were deemed significant.

To minimize potential bias arising from missing data, multiple imputation was performed using the chained equations imputation technique as described by White et al.\(^7\) The imputation method was predictive mean matching for continuous variables, logistic regression for binary variables, and ordered logistic for ordinal variables. The number of iterations for each chain was 10, and the number of imputed data sets was 10.

**RESULTS**

In total, the 25 583 patients accrued 157 938 patient-years of observation. Median follow-up time was 6.0 (range, 0-23.6) years. The mean recipient and donor age was 51 ± 11 and 33 ± 12 years, respectively, and 20% of the recipients and 31% of the donors were women. The most common diagnoses were nonischemic cardiomyopathy (48%) and ischemic cardiomyopathy (45%). The overall patient survival rates were 56% after 10 years and 25% after 20 years. A total of 10 233 patients (40%) died during follow-up. The main causes of death were major adverse cardiovascular event (n = 2 337), graft failure (n = 1 762), malignancy (n = 1 710), and infection (n = 1 598).

The study population was divided into 2 groups; patients with HLA-A–compatible (no HLA-A mismatches) and HLA-A–incompatible (1-2 HLA-A mismatches) grafts. As shown in Table 1, there were significant differences between the groups in diagnosis, use of amiodarone, use of inotropic support, and medical condition at transplant. The median recipient age was slightly higher in the HLA–incompatible group (54 vs 53 years; \(P = 0.048\)). The proportion of patients with donor-recipient sex match was higher in the HLA-A–compatible group (74.7% vs 70.9%; \(P = 0.003\)). Other demographic data, blood group, blood group match, previous blood transfusion, comorbidity, hemodynamic, and laboratory status were similar in the 2 groups.

Tacrolimus (TAC), mycophenolate mofetil (MMF), and steroids as maintenance therapy at discharge were significantly more common among patients with HLA-A–incompatible grafts (28.4% vs 23.5%, \(P = 0.005\); 64.0% vs 50.6%, \(P < 0.001\); and 83.6% vs 62.8%, \(P < 0.001\), respectively). The CYA and azathioprine were more common in the HLA-A–compatible group (78.0% vs 73.6%, \(P = 0.006\) and 57.1% vs 52.0%, \(P = 0.004\), respectively). Induction basiliximab was more common in the HLA-A–incompatible group (8.2% vs 4.6%; \(P = 0.001\)) whereas induction steroids were more common in the HLA-A–compatible group (84.7% vs 79.2%; \(P < 0.001\)). As seen in Table 2, in the immunotherapy decrease during the follow-up and at 15 years after transplantation, there were no differences between the groups. At 1 year after transplantation, a greater proportion of patients in the HLA-A–incompatible group received...
### Table 1
Characteristics of patients with HLA-A–Compatible and HLA-A–Incompatible grafts

| Variables                      | N   | HLA-A–compatible (n = 1304) | HLA-A–incompatible (n = 24279) | P     |
|--------------------------------|-----|-----------------------------|-------------------------------|-------|
| **Recipient**                  |     |                             |                               |       |
| Age, y                         | 25572 | 53 (44-59)                  | 54 (46-60)                    | 0.048 |
| Female sex, %                  | 25582 | 250 (19.2)                  | 4961 (20.4)                   | 0.270 |
| Weight, kg                     | 21379 | 77.0 ± 15.4                 | 77.9 ± 15.8                   | 0.083 |
| Height, cm                     | 21193 | 173.9 ± 9.1                 | 173.9 ± 9.5                   | 0.924 |
| **Diagnosis**                  |     |                             |                               |       |
| Coronary artery disease        | 25529 | 569 (43.9)                  | 10896 (45.0)                  | 0.033 |
| Cardiomyopathy                 |     | 614 (47.4)                  | 11682 (48.2)                  |       |
| Miscellaneous                  |     | 47 (3.6)                    | 605 (2.5)                     |       |
| Congenital                     |     | 32 (2.5)                    | 419 (1.7)                     |       |
| Heart valve disease            |     | 34 (2.6)                    | 631 (2.6)                     |       |
| **Blood group**                |     |                             |                               |       |
| A                              | 25516 | 614 (47.2)                  | 10860 (44.9)                  | 0.088 |
| B                              |     | 143 (11.0)                  | 3222 (13.3)                   |       |
| O                              |     | 470 (36.0)                  | 8777 (36.3)                   |       |
| Amiodarone                     | 12469 | 120 (30.8)                  | 3076 (25.5)                   | 0.018 |
| Inotropic support prior to transpl | 19819 | 236 (35.0)                  | 8151 (42.6)                   |       |
| Obstructive pulmonary disease  | 12589 | 13 (3.4)                    | 383 (3.1)                     | 0.799 |
| Diabetes (insulin-treated)     | 12803 | 66 (17.9)                   | 2387 (19.2)                   | 0.545 |
| Hypertension                   | 12683 | 150 (38.7)                  | 4700 (38.2)                   | 0.863 |
| Preoperative cytomegalovirus   | 7380  | 181 (74.2)                  | 5162 (72.3)                   | 0.527 |
| Dialysis pretransplant         | 12427 | 6 (1.6)                     | 318 (2.6)                     | 0.216 |
| **Medical condition at transplant** | 20041 |                             |                               |       |
| Home                           |     | 372 (52.2)                  | 9170 (47.4)                   | 0.030 |
| Hospital                       |     | 87 (12.2)                   | 2360 (12.2)                   |       |
| Intensive care unit            |     | 254 (35.6)                  | 7798 (40.4)                   |       |
| Ventilator                     | 19326 | 16 (2.6)                    | 403 (2.2)                     | 0.498 |
| ECMO                           | 19330 | 1 (0.2)                     | 45 (0.2)                      | 0.683 |
| Creatinine most recent, μmol/L | 13836 | 106 (88-134)                | 106 (88-133)                  | 0.649 |
| PVR (wood units)               | 11035 | 2.1 (1.5-3.0)               | 2.1 (1.4-3.2)                 | 0.676 |
| Previous blood transfusion     | 8214  | 100 (37.3)                  | 3224 (40.8)                   | 0.285 |
| Albumin, g/L                   | 6262  | 38.0 ± 6.5                  | 37.1 ± 7.5                    | 0.147 |
| Stroke                         | 12346 | 1 (0.3)                     | 147 (1.2)                     | 0.191 |
| Working for income             | 3860  | 8 (8.5)                     | 236 (6.3)                     | 0.386 |
| **Donor**                      |     |                             |                               |       |
| Age, y                         | 25573 | 32 (22-43)                  | 31 (22-43)                    | 0.476 |
| Female sex                     | 25565 | 400 (30.7)                  | 7602 (31.3)                   | 0.644 |
| Weight, kg                     | 23599 | 76.3 ± 16.7                 | 77.4 ± 16.8                   | 0.024 |
| Height, cm                     | 21112 | 175.5 ± 9.0                 | 174.9 ± 9.3                   | 0.032 |
| Blood group                    | 25519 |                             |                               | 0.122 |
| A                              |     | 537 (41.3)                  | 9488 (39.2)                   |       |
| B                              |     | 37 (2.8)                    | 651 (2.7)                     |       |
| O                              |     | 613 (47.1)                  | 11494 (47.5)                  |       |
| Diabetes                       | 13942 | 4 (0.9)                     | 271 (2.0)                     | 0.103 |
| Cytomegalovirus (positive)     | 20979 | 447 (55.2)                  | 11791 (58.5)                  | 0.064 |
| Hepatitis C virus (positive)   | 13696 | 3 (0.8)                     | 141 (1.1)                     | 0.801 |
| Hypertension                   | 14038 | 46 (10.2)                   | 1698 (12.9)                   | 0.141 |
| Ischemic time, min             | 21104 | 174 (126-215)               | 170 (127-212)                 | 0.372 |
| **Transplant era**             |     |                             |                               |       |
| 1988-2000                      | 25583 | 824 (63.2)                  | 15255 (62.8)                  | 0.794 |
| 2001-2011                      | 25583 | 480 (36.8)                  | 9024 (37.2)                   | 0.794 |
| Blood group match              | 25481 | 1119 (86.1)                 | 20874 (86.3)                  | 0.856 |
| Sex match                      | 25564 | 972 (74.7)                  | 17196 (70.9)                  | 0.003 |

Qualitative data are expressed as n (%), and quantitative data as mean ±SD or median (interquartile range) as appropriate.

HLA-A–compatible, grafts with no HLA-A mismatches; HLA-A–incompatible, graft with 1-2 HLA-A mismatches; N, number of non-missing values. PVR, pulmonary vascular resistance; ECMO, extracorporeal membrane oxygenation; transplant.
Steroids for rejection (20.6% vs 15.3%, \( P < 0.001 \)). However, at 3, 10 and 15 years after transplantation, there was no difference between the groups in the proportion of patients receiving steroids for rejection (\( P = 0.114, P = 1.000, \) and \( P = 1.000, \) respectively).

We first examined the effect of HLA-A compatibility versus HLA-A incompatibility for the entire cohort on all-cause mortality (Figure 1). We found no significant difference in survival between the groups over the entire follow-up period (\( P = 0.187, \) Log-rank test). However, as shown in Figure 1, there was a trend toward lower survival with HLA compatibility (vs HLA incompatibility; \( P = 0.064, \) Log rank test) during the later time interval (>15 years after transplantation).

To determine whether the other HLA loci interacted with HLA-A, we performed a subgroup analysis including only HLA-B-, HLA-DR– or HLA-B–, and DR–incompatible grafts. In the later time interval (>15 years), HLA-A compatibility was associated with lower survival in transplants incompatible for HLA-B (\( P = 0.027, \) Log-rank test), and the decrease in survival became more pronounced in HLA-DR–incompatible grafts (\( P = 0.007, \) Log-rank test) and even more so in HLA-B– and DR–incompatible grafts (\( P = 0.002, \) Log-rank test) (Figures 2A, C, and E). This observation was not found in compatible HLA-B, DR–incompatible grafts (Figures 2B, D, and F).

We next performed a multivariable Cox regression analysis resulting in a final main model that incorporated 18 significant independent covariates. When HLA-A compatibility and interactions between HLA-A and HLA-B, HLA-DR, or HLA-B,DR were added to the model, we found no significant difference in mortality between the groups in the early time period after transplantation. Nor was there any significant difference in the late era for the entire cohort (\( P = 0.102 \)). However, among those who survived to 15 years after transplantation, an increased mortality was perceived for HLA-A compatibility versus HLA-A incompatibility in HLA-DR–incompatible grafts (HR, 1.59; 95% CI, 1.11-2.28; \( P = 0.012, \) CPH test) and in HLA-B,DR–incompatible grafts (HR, 1.69; 95% CI, 1.17-2.43; \( P = 0.005, \) CPH test) (Table 3A). Stratification of recipients by number of HLA-A mismatches further reinforced these results, demonstrating an association between fewer mismatches and higher mortality starting 15 years after transplantation. Figure 3 shows this trend in HLA-B,DR–incompatible grafts. These results were reflected in the adjusted HRs for HLA-A compatibility grafts (0 HLA-A mismatch) versus 2 HLA-A mismatches (HR, 1.79; 95% CI, 1.22-2.61; \( P = 0.003 \)) and 1 HLA-A mismatch (HR, 1.68; 95% CI, 1.14-2.47; \( P = 0.008 \)), respectively.

We performed the same univariate and multivariable analyses for the secondary endpoints, that is, cause of death. There was a trend for lower survival in the later posttransplant eras for HLA compatibility for cardiovascular-, infection-, and malignancy-related deaths but not for graft failure-related deaths. As cardiovascular disease could be a manifestation of chronic rejection and infection and malignancy related

|   | 1 y                                      | 5 y                                      |
|---|------------------------------------------|------------------------------------------|
|   | HLA-A comp | HLA-A incomp | \( P \) | HLA-A comp | HLA-A incomp | \( P \) |
| CYA | 244 (38.6) | 4743 (28.8) | <0.001 | 218 (39.9) | 4874 (38.9) | 0.652 |
| TAC | 165 (30.0) | 4477 (32.0) | 0.312 | 125 (25.6) | 2410 (28.8) | 0.130 |
| MMF | 265 (56.7) | 7010 (57.3) | 0.791 | 229 (53.0) | 5545 (51.4) | 0.516 |
| AZA | 78 (12.3)  | 1168 (7.1)  | <0.001 | 69 (12.6)  | 1676 (13.4) | 0.653 |
| RAP | 24 (4.8)   | 648 (5.3)   | 0.803 | 30 (7.0)   | 906 (8.4)   | 0.292 |
| CS  | 336 (53.1) | 7116 (43.3) | <0.001 | 197 (36.0) | 4868 (38.8) | 0.184 |

Values in parenthesis are percentages.
AZA, azathioprine; RAP, rapamycin; CS, corticosteroids.
to immunosuppressive agents given for chronic rejection, we studied the combined deaths caused by chronic rejection, cardiovascular disease, infection, and malignancy. HLA-compatible grafts had lower survival in the later post-transplant time eras ($P = 0.044$, Log-rank test). Table 3B shows the results of the multivariable analysis for this outcome. Noteworthy, HR increased from 1.69 to 1.91 (95% CI, 1.22-3.01; $P = 0.005$) in HLA-B,DR-incompatible grafts. However, for the entire cohort, the HR was not significant ($P = 0.063$). Thus, in multivariable analysis, the largest compromise in survival for HLA-A compatibility (vs HLA-incompatibility) was for chronic rejection (including cardiovascular-, infection- and malignancy-related deaths) in HLA-B- and -DR-incompatible grafts, which is also shown in Figure 4.

We also analyzed HLA-B match versus mismatch and HLA-DR match versus mismatch in different HLA combinations (Tables 4A and 4B). Although a trend toward lower survival seen in the survival curves for HLA-B compatibility versus HLA-B incompatibility in later posttransplant eras, this could not be confirmed in univariate or multivariable analyses.

Finally we examined the effects of HLA-A matching on graft loss, defined as death or repeat transplantation ($n = 575$). The results remained essentially unchanged.

**DISCUSSION**

This represents the first report to specifically investigate the association between HLA-A donor-recipient matching...
TABLE 3A. Univariable and multivariable Cox Proportional Hazards regression analysis in the later time interval (>15 y posttransplant) affecting All-Cause mortality for HLA-A compatibility versus incompatibility in different HLA combinations

|               | Univariable | Multivariable |
|---------------|-------------|---------------|
|               | N           | Hazard ratio  | P      | Hazard ratio | P      |
| HLA-A         |             |               |       |             |       |
| Incomp        | 24,276      | 1.00          |       | 1.00         |       |
| Comp          | 1,304       | 1.36 (0.98-1.90) | 0.066 | 1.32 (0.95-1.84) | 0.102 |
| HLA-A HLA-B   |             |               |       |             |       |
| Incomp        | 22,767      | 1.00          |       | 1.00         |       |
| Comp          | 1,130       | 1.46 (1.04-2.05) | 0.028 | 1.41 (1.00-1.98) | 0.052 |
| HLA-A HLA-DR  |             |               |       |             |       |
| Incomp        | 21,031      | 1.00          |       | 1.00         |       |
| Comp          | 1,076       | 1.64 (1.14-2.36) | 0.007 | 1.59 (1.11-2.28) | 0.012 |
| HLA-A HLA-B and DR |   |               |       |             |       |
| Incomp        | 19,791      | 1.00          |       | 1.00         |       |
| Comp          | 974         | 1.75 (1.22-2.51) | 0.002 | 1.69 (1.17-2.43) | 0.005 |

Values in parenthesis are 95% confidence intervals. Incomp, incompatible; Comp, compatible; n, number of patients. Adjusted for transplant era, donor age (year), recipient age (year), albumin level (g/L), recipient diabetes, recipient age (year), albumin level (g/L), recipient diabetes, recipient hepatitis C virus status, recipient weight (kg), recipient infection within 2 weeks, recipient previous transfusion, recipient on ventilator, recipient obstructive pulmonary disease, donor sex, recipient hypertension, maintenance therapy, mycophenolate mofetil, maintenance therapy; corticosteroids, maintenance therapy; azathioprine, induction therapy; OXFT5, Orthoclone OKT3.

FIGURE 3. Kaplan-Meier survival curves by number of HLA-A mismatches in the 15 to 20 years posttransplant time interval in HLA-B,DR–incompatible grafts for all-cause mortality. The red solid line shows the observed cumulative survival and red dotted lines show the 95% confidence interval (estimated with Kaplan-Meier survival function) in the HLA-A cohort with zero mismatch. The blue solid line shows survival, and the blue dotted lines show the 95% confidence interval (estimated with Kaplan-Meier survival function) for transplanted patients in the HLA-A cohort with 1 mismatch. The green solid line shows survival, and the green dotted lines show the 95% confidence interval (estimated with Kaplan-Meier survival function) for transplanted patients in the HLA-A cohort with 2 mismatches. mm; mismatches.

TABLE 3B. Univariable and multivariable Cox Proportional Hazards regression analysis in the later time interval (>15 y after transplantation) affecting mortality caused by chronic rejection, cardiovascular disease, infection or malignancy for HLA-A compatibility versus incompatibility in different HLA combinations

|               | Univariable | Multivariable |
|---------------|-------------|---------------|
|               | N           | Hazard Ratio  | P      | Hazard Ratio | P      |
| HLA-A         |             |               |       |             |       |
| Incomp        | 24,279      | 1.00          |       | 1.00         |       |
| Comp          | 1,304       | 1.52 (1.01-2.28) | 0.046 | 1.48 (0.98-2.23) | 0.063 |
| HLA-A HLA-B   |             |               |       |             |       |
| Incomp        | 22,767      | 1.00          |       | 1.00         |       |
| Comp          | 1,130       | 1.68 (1.11-2.55) | 0.015 | 1.62 (1.07-2.47) | 0.024 |
| HLA-A HLA-DR  |             |               |       |             |       |
| Incomp        | 21,031      | 1.00          |       | 1.00         |       |
| Comp          | 1,076       | 1.82 (1.16-2.84) | 0.009 | 1.76 (1.13-2.77) | 0.013 |
| HLA-A HLA-B and DR |   |               |       |             |       |
| Incomp        | 19,791      | 1.00          |       | 1.00         |       |
| Comp          | 974         | 1.98 (1.26-3.10) | 0.003 | 1.91 (1.22-3.01) | 0.005 |

Values in parenthesis are 95% confidence intervals. Adjusted for transplant era, donor age (year), recipient age (year), albumin level (g/L), recipient diabetes, recipient hepatitis C virus status, recipient previous transfusion, recipient on ventilator, donor sex, recipient stroke, donor cytomegalovirus status, maintenance therapy; corticosteroids, maintenance therapy; cyclosporine, maintenance therapy; mycophenolate mofetil, induction therapy; antithymocyte globulin.

in relation to other HLA loci using the ISHLT database in adult heart transplant patients. We found an association between increased mortality in the late posttransplant period and higher degree of HLA-A matching in patients with HLA-B- and/or -DR-incompatible grafts. Early reports found that well-matched heart transplants had a significantly better graft survival rate than poorly matched ones. Although the majority of later studies confirmed this correlation, some studies have indicated that HLA matching does not improve outcomes in heart transplantation. Moreover, analysis of interactions between the different HLA-loci is lacking in the previous studies. The fact that HLA-A mismatching was associated with lower mortality related to chronic rejection indicated a possible immunologic cause for the improved survival. HLA-DR or HLA-B mismatching was not associated
TABLE 4A.
Univariable and multivariable Cox Proportional Hazards regression analysis in the later time interval (>15 y after transplantation) affecting All-Cause mortality for HLA-B compatibility versus incompatibility in different HLA combinations

| HLA-B | Univariable | Multivariable |
|-------|-------------|---------------|
|       | N           | Univariable   | Multivariable |
|       | Hazard ratio | P             | Hazard ratio | P         |
| Incomp | 23,897      | 1.00          | 1.00         |
| Comp   | 436         | 1.01 (0.50-2.04) | 0.971 (0.48-1.96) | 0.933 |
| HLA-B HLA-A | Incomp | 22,767      | 1.00          | 1.00         |
| Comp   | 357         | 1.10 (0.49-2.45) | 0.824 (0.45-2.28) | 0.981 |
| HLA-B HLA-DR | Incomp | 20,765      | 1.00          | 1.00         |
| Comp   | 301         | 0.90 (0.33-2.40) | 0.828 (0.32-2.30) | 0.753 |
| HLA-B HLA-A and -DR | Incomp | 19,791      | 1.00          | 1.00         |
| Comp   | 276         | 1.18 (0.44-3.17) | 0.739 (0.40-2.95) | 0.864 |

Values in parenthesis are 95% confidence intervals. Adjusted for transplant era, donor age (y), recipient age (y), recipient weight (kg), donor hepatitis C virus status, recipient weight (kg), recipient infection within 2 weeks, recipient previous transplantation, recipient on ventilator, recipient obstructive pulmonary disease, donor sex, recipient hypertension, maintenance therapy, mycophenolate mofetil, maintenance therapy, corticosteroids, maintenance therapy, azathioprine, induction therapy, OKT3.

with improved survival in the whole cohort or in incompatible grafts of the other 2 loci.

We believe that tolerance is a crucial part of the immune response in transplantation and in other responses to, for example, cancer, infection, or autoimmunity. In our opinion, the immune response comprises interactions between upregulative and downregulative processes. As an illustration of a general principle, the activation of upregulative response may induce and activate a downregulative immune response as shown by interaction of CD28 and CTLA-4 antigens with CD80, CD86 ligands. In contrast to the 1980s or 1990s at the present time, numerous of tolerance inducing genes/structures have been identified, for example, nonclassical HLA class I genes (HLA-G, -F, -E), where the tolerance induction of HLA-G genes were extensively studied in pregnancy and transplantation. Furthermore, some of the epitopes of HLA-A antigens have been found in association with decreased risk of delayed allograft function in renal transplantation. It could be speculated whether our results may be explained by the existence of a gene involved in the induction of tolerance across a class I disparity. Actually, the possibility is explained by the existence of a gene involved in the induction of transplantation. Furthermore, some of the epitopes of HLA-A antigens have been found in association with decreased risk of delayed allograft function in renal transplantation. However, in our study, the number of patients at risk 15 years after transplantation was small, which should prompt caution in interpreting the results.

The time from an initiation of transplant rejection to graft failure is years for chronic rejection and days to months for acute rejection. Chronic rejection or cardiac allograft vasculopathy (CAV) is characterized by a progressive fibroproliferative disease, resulting in intimal thickening and occlusion of the grafted coronary vessels. Although some studies have shown a correlation between HLA matching and CAV, several studies have failed to show any association between HLA matching and development of CAV. However, compared with our report, these studies had shorter follow-up time and looked at the incidence of CAV in contrast to mortality due to CAV. Studies have found an increased level of antibodies to cardiac self-antigens, myosin and vimentin, as well as an increased frequency of IL-17 secreting CD4+ T cells against myosin and vimentin, in patients with CAV, indicating that they may be involved the pathogenesis of CAV. Also, donor-specific antibodies to mismatched HLA are significantly associated with the development of antibodies to self-antigens. However, no such data were available for analysis in this study.

Our results may have been influenced by differences in immunotherapy given to the patients in the HLA-A-compatible and -incompatible groups. The TAC and MMF were more common among the HLA-A-incompatible patients at discharge. This could be because the HLA-A-compatible patients experienced more rejection episodes shortly after transplantation, and consequently CYA and azathioprine were exchanged with the more modern drugs, TAC and MMF. Furthermore, a higher proportion of the patients in the HLA-A-compatible group were treated with steroids for rejection at 1 year. This may have lead to higher incidence of chronic rejection in the long run. We aimed to correct for the differences in immunotherapy by performing a multivariable analysis.

TABLE 4B.
Univariable and multivariable Cox Proportional Hazards regression analysis in the later time interval (>15 y after transplantation) affecting All-Cause mortality for HLA-DR compatibility versus incompatibility in different HLA combinations

| HLA-DR | Univariable | Multivariable |
|--------|-------------|---------------|
|        | N           | Hazard ratio  | P             |
|        |             | Hazard ratio  | P             |
| Incomp | 22,107      | 1.00          | 1.00         |
| Comp   | 1028        | 0.91 (0.57-1.44) | 0.684 (0.58-1.45) | 0.702 |
| HLA-DR HLA-A | Incomp | 21,031      | 1.00          | 1.00         |
| Comp   | 908         | 1.02 (0.64-1.64) | 0.931 (0.64-1.65) | 0.923 |
| HLA-DR HLA-B | Incomp | 20,765      | 1.00          | 1.00         |
| Comp   | 875         | 0.87 (0.52-1.45) | 0.586 (0.53-1.48) | 0.638 |
| HLA-DR HLA-A and -B | Incomp | 19,791      | 1.00          | 1.00         |
| Comp   | 805         | 0.96 (0.57-1.61) | 0.888 (0.58-1.65) | 0.944 |

Values in parenthesis are 95% confidence intervals. Adjusted for transplant era, donor age (y), recipient age (y), recipient weight (kg), donor hepatitis C virus status, recipient weight (kg), recipient infection within 2 weeks, recipient previous transplantation, recipient on ventilator, recipient obstructive pulmonary disease, donor sex, recipient hypertension, maintenance therapy, mycophenolate mofetil, maintenance therapy, corticosteroids, maintenance therapy, azathioprine, induction therapy, OKT3.
The results of this study carry limitations associated with the retrospective analysis of a registry database. We do not know to what degree the donors in the individual transplant centers were allocated based on HLA matching. Therefore, the distribution of HLA matching may not represent random chance but influenced by unknown factors, not accounted for. Missing values in this study were accounted for by multiple imputation technique, which is probably the best method available today. Data on donor-specific antibodies were not available in the ISHLT database. To avoid the confounding effect of preexisting donor-specific antibodies, recipients with a history of cardiac surgery, including ventricular assist device or previous transplantation, were excluded. We also excluded patients with PRA of 10% or greater, the cutoff value above which PRA is associated with worse survival after transplantation. Our analysis was limited to the HLA-A, -B, and -DR loci. Unfortunately, the ISHLT registry does not collect data on HLA-DQ and -C typing. In the future, the addition of HLA-C and DQ may improve risk stratification based on HLA matching.

In conclusion, this study represents the largest analysis of HLA-matching in heart transplantation with a follow-up that is longer than any other study on HLA and heart transplantation. Study limitations necessitate caution in the interpretation of the results, but the fact that HLA-A mismatching was associated with lower mortality related to chronic rejection indicated a possible immunologic cause for the improved survival. Elucidating a possible protective mechanism of HLA-A mismatching on patient and graft survival should be the subject of further investigation. This knowledge could help guide diagnostic and therapeutic interventions in patients with HLA-A-compatible and HLA-B,DR–incompatible grafts.

REFERENCES

1. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report—2013; focus theme: age. J Heart Lung Transplant. 2013;32:951–964.

2. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant. 2006;25:1024–1042.

3. Susal C, Opež C. Current role of human leukocyte antigen matching in kidney transplantation. Curr Opin Organ Transplant. 2013;18:438–444.

4. De Mattos AM, Head MA, Everett J, et al. HLA-DR mismatching correlates with early cardiac allograft rejection, incidence, and graft survival when high-confidence-level serological DR typing is used. Transplantation. 1994;57:626–630.

5. Raffoux C, Mayor V, Cabrol C, et al. The influence of HLA matching in cardiac allograft recipients in a single center. Transplant Proc. 1987;19:3559–3560.

6. Foerster A, Abdelnoor M, Geiran O, et al. Risk factors for total and cause-specific mortality in human cardiac transplantation. Prolonged extracorporeal bypass time: a high risk factor for rejection and infection. Eur J Cardiothorac Surg. 1991;5:641–647.

7. Opež C. Effect of HLA matching in heart transplantation. Transplant Proc. 1989;21:794–796.

8. Opež G, Wujciak T. The influence of HLA compatibility on graft survival after heart transplantation. The Collaborative Transplant Study. N Engl J Med. 1994;330:816–819.

9. Thompson JS, Thacker LR, Takemoto S. The influence of conventional and cross-reactive group HLA matching on cardiac transplant outcome: an analysis from the United Network of Organ Sharing Scientific Registry. Transplantation. 2000;69:2176–2186.

10. Ansari D, Bucin D, Nilsson J. Human leukocyte antigen matching in heart transplantation: systematic review and meta-analysis. Transpl Int. 2014;27:793–804.

11. Tenderich G, Zittermann A, Prohaska W, et al. No evidence for an improvement of long-term survival by HLA matching in heart transplant recipients. Transplant Proc. 2007;39:1575–1579.

12. Poli F, Scalregmona M, Mascaretti L, et al. Genomic HLA-DR compatibility in solid organ transplantation: a retrospective analysis of 1209 cases. Transplant Proc. 1995;27:647–650.

13. Hornick P, Smith J, Permerling A, et al. Influence of acute rejection episodes, HLA matching, and donor/recipient phenotype on the development of “early” transplant-associated coronary artery disease. Circulation. 1997;96:148–153.

14. Bucin D, Elberg H, Lindholm A, et al. HLA-A incompatibility associated with enhanced long-term renal graft survival in HLA-B, DR mismatch transplants. Immunol Cell Biol. 1994;72:455–460.

15. Bucin D. Blood transfusion in renal transplantation—the induction of tolerance by incompatibility for class I antigens. Med Hypotheses. 1989;27:19–27.

16. Weesie J. Survival analysis with time-varying covariates. Stat T ech Bull. 1998;7:25–43.

17. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med. 2011;30:377–390.

18. Mascaretti L, Poli F, Scalregmona M, et al. HLA-DR matching defined by DNA typing in heart transplantation. Transplant Proc. 1997;29:1464–1466.

19. Walker LS, Treg and CTLA-4: two intertwining pathways to immune tolerance. J Autoimmun. 2013;45:49–57.

20. Krummey SM, Ford ML. Braking bad: novel mechanisms of CTLA-4 inhibition. J Autoimmun. 2013;49:144–153.

21. Brugiere O, Thabut G, Krawiec-Radanne I, et al. Role of HLA-G as a predictive marker of low risk of chronic rejection in lung transplant recipients: a clinical prospective study. Am J Transplant. 2015;15:461–471.

22. Rebmann V, da Silva Nardi F, Wagner B, et al. HLA-G as a tolerogenic molecule in transplantation and pregnancy. J Immunol Res. 2013;2013:297073.

23. Kamoun M, Holmes JH, Israni AK, et al. HLA-A amino acid polymorphism and delayed kidney allograft function. Proc Natl Acad Sci U S A. 2008;105:18883–18888.

24. Lee PW, Hanekep JS, Viliant V, et al. Evidence for a gene controlling the induction of transplantation tolerance. Am J Transplant. 2014;14:952–959.

25. Bucin D. Specific immune tolerance related to disparity in MHC class I region. Med Hypotheses. 1995;44:132–136.

26. Hayry P, Isoniemi H, Yilmaz S, et al. Chronic allograft rejection. Immuno Rev. 1993;134:33–81.

27. Arbusini E, Dal Bello B, Morbini P, et al. Factors increasing the risk of allograft vascular disease in heart transplant recipients. G Ital Cardiol. 1997;27:985–999.

28. Stempiel HU, Mudra H, Strem C, et al. Influence of HLA compatibility on the occurrence of cardiac allograft vasculopathy after heart transplantation. Transplant Proc. 1995;27:1977–1978.

29. Aziz TM, Sheldon S, al-Gamel A, et al. Implication of HLA mismatch in the clinical outcome of orthotopic heart transplantation. Transplant Proc. 1998;30:1917–1919.

30. Kaczmarek I, Deutsch MA, Rohrer ME, et al. HLA-DR matching improves survival after heart transplantation: is it time to change allocation policies? J Heart Lung Transplant. 2008;27:1057–1062.

31. Nath DS, Ilses Bashia H, Trivedi V, et al. Characterization of immune responses to cardiac self-antigens myosin and vimentin in human cardiac allograft recipients with antibody-mediated rejection and cardiac allograft vasculopathy. J Heart Lung Transplant. 2010;29:1277–1285.