

## ORIGINAL ARTICLE

**Waiting for a thoracic transplant in Eurotransplant\***Jacqueline M. A. Smits,<sup>1</sup> Johan Vanhaecke,<sup>2,6</sup> Axel Haverich,<sup>3,6</sup> Erwin de Vries,<sup>1</sup> Leo Roels,<sup>4</sup> Guido Persijn<sup>1</sup> and Gunther Laufer<sup>5,6</sup>

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6 On Behalf of the Eurotransplant Thoracic Transplant Programs

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**Introduction**

The distributional effects of an organ allocation system must routinely be evaluated. These effects depend on the allocation algorithm itself (e.g. first-come-first-served versus the-sickest-first), the composition and the size of the waiting list, and the availability of donor organs; where the threshold for an effect is higher in a situation of a high donation rate. As for the algorithm, when less emphasis is put on waiting time but more on disease severity, a prerequisite for its success is to have a correct and careful assessment of the patients on the list. In a system where upgrading to a higher urgency (HU) class is the *conditio sine qua non* for obtaining an organ offer,

**Summary**

The prospects of patients on the thoracic waiting list are governed by the chance of receiving an organ in time and by the outcome of the transplantation. The former probability is determined by a triad of disease severity, resource size and allocation rules. The aim of this study was to provide an objective description of the distributional effects of the thoracic allocation system in Eurotransplant. It appears that the interpretation of waiting-list outflow indicators is not straightforward and that it is difficult to assess the fairness of an organ allocation system in the framework of changing donor–organ availability. The timing of listing for heart transplantation can substantially be improved; whether this is also true for lung transplantation cannot be determined from the available data. Allocation schemes cannot solve the problem of organ shortage; a shift of attention toward collaboration with procurement professionals is needed.

audits of patient profiles before HU listing are an integral part of this procedure.

Benefit-driven allocation schemes, where post-transplant outcome is also taken into account, are very attractive alternatives because we want to ensure that organs are not wasted on patients who will not benefit from them [1]. However, the design of such schemes is very complex, even more difficult to validate and to control as the outcome of transplantation is not uniform across centers [2].

In conducting this study, we also hope to make the transplant community aware that by solely focusing on new allocation schemes as a panacea for all waiting-list problems, it is not doing all it can to enhance the prospects of the patients.

## Methods

### Allocation rules

Thoracic organ allocation in Eurotransplant is driven by two major factors: urgency and waiting time. Urgency status has two classes [high urgency (HU) and elective] and all organs are assigned to individual patients within the donor country, first to the HU patients and then to the elective patients according to ABO blood group, age- and size-matching rules.

In 2000, changes in the law led to the following adaptations to the allocation scheme: a shift from a center-oriented toward a patient-oriented allocation, an increased influence of urgency at the expense of waiting time; and a slimming down of the international organ exchange for HU patients [3]. Furthermore, some countries broadened their definition of a HU status and applied restricted ABO blood group matching rules for HU transplants. A detailed description of the allocation rules and the changes made to them over the years is beyond the scope of this paper.

### Waiting time

A patient's waiting time starts at the time of the registration on the waiting list. Patients can become temporarily nontransplantable, e.g. when suffering from infection. Their waiting-list status then changes to 'nonactive'. Only 'active' patients are considered if an organ becomes available. The calculation of waiting-list size and the duration of waiting time are based on the active waiting time.

### Patients

All adult patients registered for a thoracic allograft between January 1, 1998 and December 31, 2001 in the Eurotransplant countries (population in millions) [Austria (8.2), Belgium (10.4), Germany (82.4), Luxembourg (0.5), The Netherlands (16.3) and Slovenia (2.0)] were included in this study. Transplant candidates under the age of 16 years at the time of listing were defined as children and were excluded. All patients were followed as long as they were on the waiting list. For HU patients, the duration of their HU status was taken as waiting time, for elective patients the elective waiting time was calculated. Outcome on the waiting list was recorded up to December 31, 2002. Outcome after transplantation was not considered in this analysis as these data are described elsewhere [2,4,5].

The following variables were recorded: year and country of registration, recipient's age at time of registration, sex, ABO blood group, size, primary disease, urgency status, and cytomegalovirus (CMV) status. Additional data

for lung transplant candidates included: toxoplasma status, total lung capacity (TLC) and the need for a single- or double-lung allograft. For heart transplant candidates, the disease severity at the time of listing as assessed by both the Heart Failure Survival Score (HFSS) and the German Transplant Society Score (GTSS) was additionally recorded [6,7].

### Waiting-list outflow indicators

The reasons for removing patients from the waiting list are: transplantation, death and de-listing without the transplantation [8]. To assess the extent to which each of these contributed to the total outflow rate, the chances of surviving until an organ became available and the chance of dying on the waiting list without being transplanted were calculated using the competing risk methodology. The probability of de-listing was also calculated but the results are not presented.

The factor country was considered a proxy variable for donation rate. Based on observed donor rates in the study period, a new factor with two categories: high-donor-rate country (Austria, Belgium, Slovenia) and low-donor-rate country (Germany and The Netherlands) was created. The interaction between primary disease and donor-rate-country was also analyzed.

The test of equality between the different levels of the factor stratified by urgency status was performed with a likelihood ratio test, two-sided *P*-values were given.

To test the association between prognostic factors and the probability of the event after listing, a Cox' proportional hazards model was built using a forward selection procedure for each event stratified by urgency status. The number of events in the cohorts of HU heart, HU lung and elective heart-lung transplant candidates was insufficient for multivariate analysis. Therefore, only univariate results are reported. Only demographic statistics are shown for the HU heart-lung transplant candidates. For elective heart- and elective lung-transplant candidates at each factor level, the number of patients, the event rate at 1 year after listing and univariate and multivariate *P*-values are provided. Status after 1 month was evaluated for HU transplant candidates. It should be noted that the lack of a significant effect does not mean that no effect was present, all results should be interpreted as such.

## Results

Figures 1 and 2 show the number of donor organs used for transplantation. The probabilities of dying without a transplant or of receiving a transplant in the first month (HU patients) or first year (elective patients) of listing are shown in Tables 1–6.

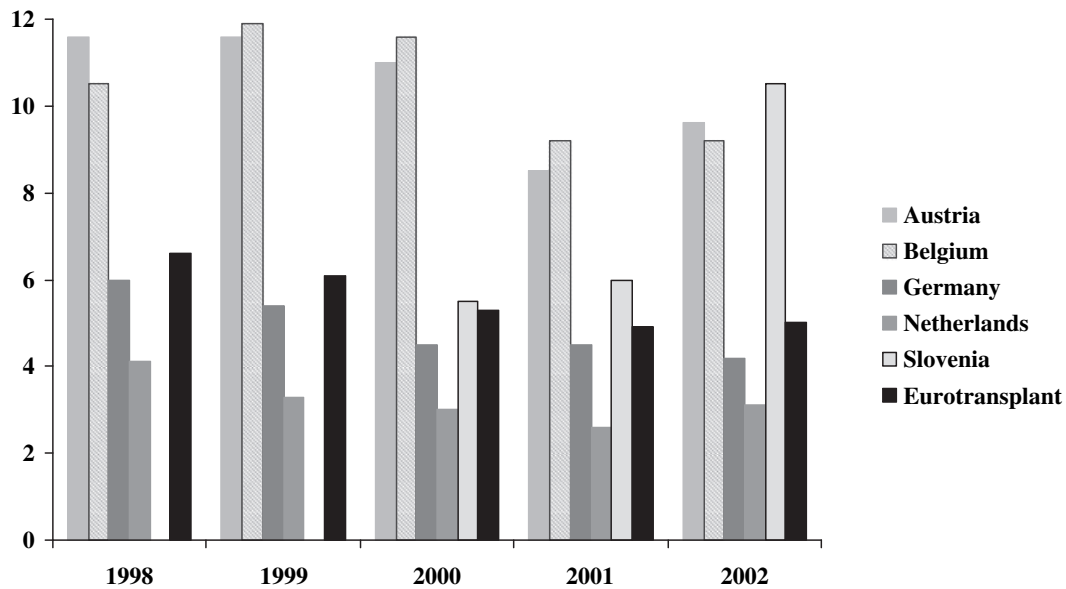


Figure 1 Number of heart donors used for transplantation per million population.

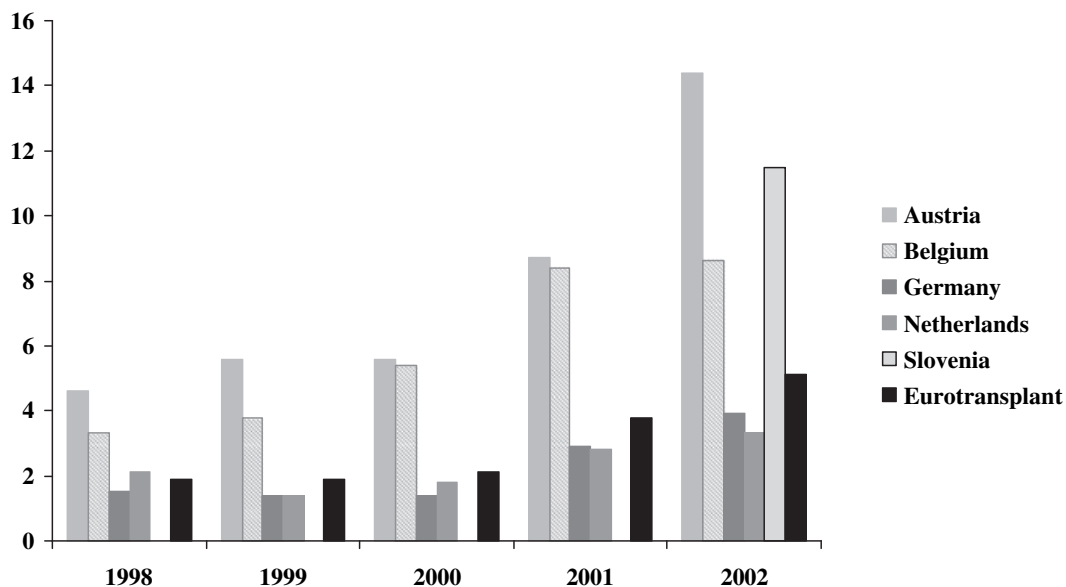


Figure 2 Number of lung donors used for transplantation per million population.

### HU heart patients

The year of listing was of borderline significance for the 1-month waiting-list mortality during the study period ( $P = 0.06$ ), where in the more recent years more HU patients had to compete for an organ offer, and in 2001 more of these HU patients died on the waiting list (Table 1). Without any correction for the influence of confounders, waiting-list mortality on the HU list was

significantly different between countries ( $P = 0.01$ ). Also, the proportion of all transplant candidates listed as HU varied considerably: 1% in Austria, 5% in Belgium, 9.4% in Germany, 14% in The Netherlands and 10% in Slovenia (Tables 1–2). Countries with strict criteria for HU patients, i.e. sicker patients listed as HU (Austria and Belgium), had higher mortality rates than other countries.

Underlying disease significantly affected patients' chances of receiving a transplant ( $P < 0.0001$ ) with the highest

**Table 1.** Waiting-list outcome of adult HU heart transplant candidates.

| Factor            | <i>n</i> | Death on the waiting list |                            | Transplantation |                            |
|-------------------|----------|---------------------------|----------------------------|-----------------|----------------------------|
|                   |          | 1 month (%)               | <i>P</i> -value univariate | 1 month (%)     | <i>P</i> -value univariate |
| Year of listing   |          |                           |                            |                 |                            |
| 1998              | 12       | 16.7                      | 0.06                       | 50.0            | 0.9                        |
| 1999              | 19       | 0                         |                            | 68.4            |                            |
| 2000              | 65       | 0                         |                            | 67.7            |                            |
| 2001              | 153      | 5.9                       |                            | 68.6            |                            |
| Sex               |          |                           |                            |                 |                            |
| Male              | 207      | 3.9                       | 0.6                        | 68.6            | 0.4                        |
| Female            | 42       | 7.1                       |                            | 61.9            |                            |
| Age (years)       |          |                           |                            |                 |                            |
| 16–40             | 59       | 0                         | 0.1                        | 69.5            | 0.5                        |
| 41–55             | 102      | 5.9                       |                            | 62.7            |                            |
| 56–65             | 80       | 5                         |                            | 71.3            |                            |
| 66+               | 8        | 12.5                      |                            | 75.0            |                            |
| ABO blood group   |          |                           |                            |                 |                            |
| A                 | 116      | 2.6                       | 0.6                        | 71.6            | 0.4                        |
| AB                | 9        | 0                         |                            | 77.8            |                            |
| B                 | 17       | 11.8                      |                            | 52.9            |                            |
| O                 | 107      | 5.6                       |                            | 64.5            |                            |
| Size (cm)         |          |                           |                            |                 |                            |
| <155              | 6        | 16.7                      | 0.3                        | 66.7            | 0.3                        |
| 156–165           | 25       | 8                         |                            | 72.0            |                            |
| 166–175           | 80       | 5                         |                            | 71.3            |                            |
| 176–185           | 105      | 2.9                       |                            | 64.8            |                            |
| 186+              | 33       | 3                         |                            | 63.6            |                            |
| End-stage disease |          |                           |                            |                 |                            |
| CAD               | 46       | 10.9                      | 0.1                        | 87.0            | <0.0001                    |
| DCM               | 121      | 2.5                       |                            | 71.1            |                            |
| Other             | 82       | 3.7                       |                            | 51.2            |                            |
| CMV               |          |                           |                            |                 |                            |
| Pos               | 67       | 9.0                       | 0.4                        | 53.7            | 0.05                       |
| Neg               | 53       | 1.9                       |                            | 69.8            |                            |
| NT                | 129      | 3.1                       |                            | 73.6            |                            |
| HFSS at listing   |          |                           |                            |                 |                            |
| High risk         | 15       | 0                         | 0.3                        | 100             | 0.01                       |
| Medium risk       | 55       | 9.1                       |                            | 74.5            |                            |
| Low risk          | 179      | 3.4                       |                            | 62.6            |                            |
| GTSS at listing   |          |                           |                            |                 |                            |
| High risk         | 12       | 0                         | 0.3                        | 83.3            | 0.6                        |
| Medium risk       | 20       | 0                         |                            | 80.0            |                            |
| Low risk          | 217      | 5.1                       |                            | 64.4            |                            |
| Country           |          |                           |                            |                 |                            |
| Austria           | 3        | 33.3                      | 0.01                       | 67.7            | <0.0001                    |
| Belgium           | 21       | 19.1                      |                            | 71.4            |                            |
| Germany           | 198      | 2.0                       |                            | 74.2            |                            |
| Netherlands       | 25       | 4                         |                            | 12              |                            |
| Slovenia          | 2        | 50                        |                            | 50              |                            |

chance for CAD (coronary artery disease) patients (Table 1). CMV status also influenced patients' access to transplantation ( $P = 0.05$ ). All high-risk HFSS patients on the HU list were transplanted within the first month ( $P = 0.01$ ). Of the 249 patients on this HU list, only 15 (6%) and 12 (5%) had a high-risk HFSS or GTSS,

respectively, at first listing for transplantation. The number of patients on the HU list that had at first listing a medium HFSS or GTSS was 55 (22%) and 20 (8%). Patients' chances of receiving a heart transplant within 1 month on the HU waiting list differed significantly between the Eurotransplant countries ( $P < 0.0001$ ).

| Factor            | n    | Death on the waiting list |            |              | Transplantation |            |              |
|-------------------|------|---------------------------|------------|--------------|-----------------|------------|--------------|
|                   |      | 1 year (%)                | P-value    |              | 1 year (%)      | P-value    |              |
|                   |      |                           | Univariate | Multivariate |                 | Univariate | Multivariate |
| Year of listing   |      |                           |            |              |                 |            |              |
| 1998              | 912  | 17.2                      | 0.8        | 0.9          | 57.0            | <0.0001    | <0.0001      |
| 1999              | 766  | 15.1                      |            |              | 62.9            |            |              |
| 2000              | 633  | 15.3                      |            |              | 65.2            |            |              |
| 2001              | 514  | 16.3                      |            |              | 56.4            |            |              |
| Sex               |      |                           |            |              |                 |            |              |
| Male              | 2268 | 16.5                      | 0.09       | 0.8          | 57.8            | <0.0001    | 0.04         |
| Female            | 557  | 14.2                      |            |              | 70.6            |            |              |
| Age (years)       |      |                           |            |              |                 |            |              |
| 16–40             | 397  | 15.6                      | 0.9        | 0.9          | 63.9            | <0.0001    | <0.0001      |
| 41–55             | 1105 | 16.1                      |            |              | 57.6            |            |              |
| 56–65             | 1181 | 16.3                      |            |              | 61.0            |            |              |
| 66+               | 142  | 14.8                      |            |              | 66.2            |            |              |
| ABO blood group   |      |                           |            |              |                 |            |              |
| A                 | 1289 | 16.2                      | 0.9        | 0.8          | 59.1            | <0.0001    | <0.0001      |
| AB                | 169  | 10.7                      |            |              | 83.4            |            |              |
| B                 | 348  | 17.0                      |            |              | 62.4            |            |              |
| O                 | 1019 | 16.5                      |            |              | 57.4            |            |              |
| Size (cm)         |      |                           |            |              |                 |            |              |
| <155              | 62   | 9.7                       | 0.8        | 0.9          | 77.4            | <0.0001    | <0.0001      |
| 156–165           | 410  | 14.9                      |            |              | 72.0            |            |              |
| 166–175           | 1172 | 15.7                      |            |              | 61.3            |            |              |
| 176–185           | 698  | 16.7                      |            |              | 56.8            |            |              |
| 186+              | 213  | 19.2                      |            |              | 43.7            |            |              |
| End-stage disease |      |                           |            |              |                 |            |              |
| CAD               | 853  | 17.8                      | 0.005      | 0.002        | 56.4            | 0.7        | 0.9          |
| DCM               | 1437 | 13.9                      |            |              | 62.1            |            |              |
| Other             | 535  | 18.9                      |            |              | 62.1            |            |              |
| CMV               |      |                           |            |              |                 |            |              |
| Pos               | 842  | 13.7                      | 0.04       | 0.03         | 63.1            | 0.05       | 0.4          |
| Neg               | 583  | 15.8                      |            |              | 64.0            |            |              |
| NT                | 1400 | 17.6                      |            |              | 57.2            |            |              |
| HFSS at listing   |      |                           |            |              |                 |            |              |
| High risk         | 201  | 24.3                      | 0.002      | 0.8          | 52.7            | 0.7        | 0.2          |
| Medium risk       | 943  | 17.0                      |            |              | 57.8            |            |              |
| Low risk          | 1681 | 14.6                      |            |              | 62.7            |            |              |
| GTSS at listing   |      |                           |            |              |                 |            |              |
| High risk         | 123  | 37.4                      | <0.0001    | <0.0001      | 48.0            | 0.01       | 0.04         |
| Medium risk       | 236  | 23.7                      |            |              | 48.3            |            |              |
| Low risk          | 2466 | 14.3                      |            |              | 62.1            |            |              |
| Country           |      |                           |            |              |                 |            |              |
| Austria           | 371  | 10.2                      | 0.001      | 0.02         | 69.3            | <0.0001    | <0.0001      |
| Belgium           | 370  | 8.9                       |            |              | 85.1            |            |              |
| Germany           | 1915 | 19.1                      |            |              | 53.2            |            |              |
| Netherlands       | 151  | 9.9                       |            |              | 70.2            |            |              |
| Slovenia          | 18   | 16.7                      |            |              | 50              |            |              |

**Table 2.** Waiting-list outcome of adult elective heart transplant candidates.

### Elective heart patients

No significant change in 1-year waiting-list mortality was observed over the study period ( $P = 0.9$ ) (Table 2). Patients with dilated cardiomyopathy (DCM) were signifi-

cantly less likely to die within the first year of listing compared with the patients suffering from CAD or other diseases ( $P = 0.002$ ). Unexpectedly, CMV-positive patients had a 2% lower 1-year waiting-list mortality rate compared with CMV-negative patients ( $P = 0.03$ ). Disease severity

**Table 3.** Waiting-list outcome of adult HU lung transplant candidates.

| Factor            | n   | Death on the waiting list |                    | Transplantation |                    |
|-------------------|-----|---------------------------|--------------------|-----------------|--------------------|
|                   |     | 1 month (%)               | P-value univariate | 1 month (%)     | P-value univariate |
| Year of listing   |     |                           |                    |                 |                    |
| 1998              | 8   | 0                         | 0.9                | 25.0            | 0.7                |
| 1999              | 22  | 4.6                       |                    | 45.5            |                    |
| 2000              | 63  | 3.2                       |                    | 42.9            |                    |
| 2001              | 109 | 5.5                       |                    | 50.4            |                    |
| Sex               |     |                           |                    |                 |                    |
| Male              | 79  | 3.8                       | 0.8                | 51.9            | 0.2                |
| Female            | 123 | 4.9                       |                    | 43.1            |                    |
| Age (years)       |     |                           |                    |                 |                    |
| 16–40             | 104 | 5.8                       | 0.3                | 48.1            | 0.7                |
| 41–55             | 77  | 3.9                       |                    | 41.6            |                    |
| 56–65             | 21  | 0                         |                    | 57.1            |                    |
| 66+               | 0   | –                         |                    | –               |                    |
| ABO blood group   |     |                           |                    |                 |                    |
| A                 | 60  | 1.7                       | 0.2                | 70.0            | <0.0001            |
| AB                | 5   | 0                         |                    | 40.0            |                    |
| B                 | 20  | 15.0                      |                    | 45.0            |                    |
| O                 | 117 | 4.3                       |                    | 35.0            |                    |
| TLC (L)           |     |                           |                    |                 |                    |
| <4.5              | 27  | 7.4                       | 0.2                | 44.4            | 0.9                |
| 4.51–6.0          | 100 | 6.0                       |                    | 46.0            |                    |
| 6.01+             | 75  | 1.3                       |                    | 48.0            |                    |
| End-stage disease |     |                           |                    |                 |                    |
| Cystic fibrosis   | 41  | 7.3                       | 0.3                | 39.0            | 0.8                |
| COPD              | 38  | 0                         |                    | 47.4            |                    |
| Eisenm            | 5   | 0                         |                    | 20.0            |                    |
| Other             | 53  | 5.7                       |                    | 52.8            |                    |
| PF                | 50  | 6.0                       |                    | 44.0            |                    |
| PH                | 15  | 0                         |                    | 60.0            |                    |
| Organ(s) needed   |     |                           |                    |                 |                    |
| 1 lung            | 38  | 2.6                       | 0.6                | 52.6            | 0.3                |
| 2 lungs           | 164 | 4.9                       |                    | 45.1            |                    |
| CMV               |     |                           |                    |                 |                    |
| Pos               | 44  | 6.8                       | 0.7                | 40.9            | 0.3                |
| Neg               | 37  | 5.4                       |                    | 37.8            |                    |
| NT                | 121 | 3.3                       |                    | 51.2            |                    |
| Toxoplasma        |     |                           |                    |                 |                    |
| Pos               | 17  | 5.9                       | 0.9                | 35.3            | 0.2                |
| Neg               | 24  | 4.2                       |                    | 33.3            |                    |
| NT                | 161 | 4.3                       |                    | 49.7            |                    |
| Country           |     |                           |                    |                 |                    |
| Austria           | 13  | 0                         | 0.6                | 69.2            | 0.047              |
| Belgium           | 13  | 0                         |                    | 61.5            |                    |
| Germany           | 161 | 5.0                       |                    | 45.3            |                    |
| Netherlands       | 15  | 6.7                       |                    | 26.7            |                    |

was a significant predictor of waiting-list mortality for this group of elective patients. GTSS high-risk patients had a 37.4% chance of dying within 1 year compared with 14.3% for GTSS low-risk patients ( $P < 0.0001$ ). As expected, the proportion of patients with high or medium risk HFSS or GTSS was similar to that on the HU list, as this score was calculated at first listing, and was not updated when wait-

ing-list status was upgraded. Finally, the countries with the highest heart-donor rates yielded the lowest waiting-list mortality rates: 10.2% for Austria, 8.9% for Belgium, 19.1% for Germany, 9.9% for The Netherlands and 16.7% for Slovenia ( $P = 0.02$ ).

The difference in outcome on the waiting list for patients with different end-stage diseases in countries with either a

| Factor            | n    | Death on the waiting list |            |              | Transplantation |            |              |
|-------------------|------|---------------------------|------------|--------------|-----------------|------------|--------------|
|                   |      | 1 year (%)                | P-value    |              | 1 year (%)      | P-value    |              |
|                   |      |                           | Univariate | Multivariate |                 | Univariate | Multivariate |
| Year of listing   |      |                           |            |              |                 |            |              |
| 1998              | 314  | 18.5                      | 0.07       | 0.6          | 50.6            | 0.04       | 0.001        |
| 1999              | 400  | 19.3                      |            |              | 51.3            |            |              |
| 2000              | 321  | 20.6                      |            |              | 51.7            |            |              |
| 2001              | 298  | 18.8                      |            |              | 43.9            |            |              |
| Sex               |      |                           |            |              |                 |            |              |
| Male              | 679  | 20.5                      | 0.03       | 0.03         | 56.8            | <0.0001    | 0.07         |
| Female            | 654  | 18.0                      |            |              | 42.0            |            |              |
| Age (years)       |      |                           |            |              |                 |            |              |
| 16–40             | 462  | 21.2                      | 0.04       | 0.2          | 46.8            | 0.09       | 0.6          |
| 41–55             | 539  | 17.1                      |            |              | 49.2            |            |              |
| 56–65             | 319  | 20.7                      |            |              | 53.6            |            |              |
| 66+               | 13   | 7.7                       |            |              | 69.2            |            |              |
| ABO blood group   |      |                           |            |              |                 |            |              |
| A                 | 603  | 16.9                      | 0.4        | 0.3          | 55.1            | <0.0001    | <0.0001      |
| AB                | 79   | 12.7                      |            |              | 64.6            |            |              |
| B                 | 143  | 19.6                      |            |              | 57.3            |            |              |
| O                 | 508  | 23.0                      |            |              | 38.6            |            |              |
| TLC (L)           |      |                           |            |              |                 |            |              |
| <4.5              | 103  | 24.3                      | 0.02       | 0.3          | 35.9            | <0.0001    | <0.0001      |
| 4.51–6.0          | 587  | 16.9                      |            |              | 42.9            |            |              |
| 6.01+             | 643  | 20.7                      |            |              | 57.9            |            |              |
| End-stage disease |      |                           |            |              |                 |            |              |
| Cystic fibrosis   | 176  | 21.6                      | <0.0001    | <0.0001      | 45.4            | 0.02       | <0.0001      |
| COPD              | 454  | 7.0                       |            |              | 57.3            |            |              |
| Eisenm            | 19   | 21.1                      |            |              | 36.8            |            |              |
| Other             | 283  | 22.3                      |            |              | 41.7            |            |              |
| PF                | 313  | 31.0                      |            |              | 49.8            |            |              |
| PH                | 88   | 26.1                      |            |              | 45.4            |            |              |
| Organ(s) needed   |      |                           |            |              |                 |            |              |
| 1 lung            | 552  | 21.2                      | 0.01       | 0.3          | 53.4            | <0.0001    | 0.4          |
| 2 lungs           | 781  | 17.9                      |            |              | 46.9            |            |              |
| CMV               |      |                           |            |              |                 |            |              |
| Pos               | 365  | 20.3                      | 0.8        | 0.7          | 50.4            | 0.7        | 0.9          |
| Neg               | 235  | 20.4                      |            |              | 43.8            |            |              |
| NT                | 733  | 18.4                      |            |              | 51.0            |            |              |
| Toxoplasma        |      |                           |            |              |                 |            |              |
| Pos               | 139  | 23.0                      | 0.5        | 0.7          | 35.9            | 0.001      | 0.4          |
| Neg               | 169  | 23.1                      |            |              | 35.5            |            |              |
| NT                | 1025 | 18.1                      |            |              | 53.8            |            |              |
| country           |      |                           |            |              |                 |            |              |
| Austria           | 258  | 7.4                       | 0.005      | 0.1          | 83.3            | 0.01       | <0.0001      |
| Belgium           | 181  | 12.7                      |            |              | 59.7            |            |              |
| Germany           | 780  | 24.6                      |            |              | 40.6            |            |              |
| Netherlands       | 114  | 20.2                      |            |              | 18.4            |            |              |

**Table 4.** Waiting-list outcome of adult elective lung transplant candidates.

high (Austria, Belgium, Slovenia) or a low (Germany, The Netherlands) donor rate is illustrated in Fig. 3. Both in low- and in high-donor-rate countries patients with DCM had a higher survival rate. Donor rate, however, was a better predictor of death on the list than end-stage disease of these elective patients (Likelihood ratio tests not given).

Although 1-year transplantation rates rose by almost 10% in 2000 compared with 1998, they fell again in 2001, and no obvious trend was detected ( $P < 0.0001$ ) (Table 2). In this cohort of elective heart-transplant recipients, some had a smaller chance of receiving a transplant within 1 year than others; for example, tall males with blood group O

**Table 5.** Demographic statistics of adult HU heart–lung transplant candidates.

| Factor            | <i>n</i> |
|-------------------|----------|
| Year of listing   |          |
| 1998              | 1        |
| 1999              | 3        |
| 2000              | 2        |
| 2001              | 7        |
| Sex               |          |
| Male              | 5        |
| Female            | 8        |
| Age (years)       |          |
| 16–40             | 9        |
| 41–55             | 4        |
| 56–65             | 0        |
| 66+               | 0        |
| ABO blood group   |          |
| A                 | 6        |
| AB                | 0        |
| B                 | 1        |
| O                 | 6        |
| TLC (L)           |          |
| <4.5              | 2        |
| 4.51–6.0          | 6        |
| 6.01+             | 5        |
| CMV               |          |
| Pos               | 1        |
| Neg               | 1        |
| NT                | 11       |
| Toxoplasma        |          |
| Pos               | 0        |
| Neg               | 2        |
| NT                | 11       |
| End-stage disease |          |
| Eisenmenger       | 5        |
| Other             | 4        |
| PH                | 4        |
| Country           |          |
| Austria           | 0        |
| Belgium           | 0        |
| Germany           | 13       |
| Netherlands       | 0        |

and a GTSS high-risk profile from countries with low heart-donor rates had significantly less chance of receiving a heart allograft within 1 year of being registered on the waiting list than other groups of patients.

### HU lung patients

Table 3 shows the outcome for HU lung transplant candidates. No single effect was significantly associated with 1-month mortality rate, which is probably the result of the low number of events in the cohort. Therefore, all observed rates must be interpreted with care.

Patients with blood group A had a significantly higher chance of receiving a lung allograft within 1 month than

patients with other blood groups ( $P < 0.0001$ ). As a result, a smaller percentage of patients with this blood group died within the first month after listing, although there was no statistically significant difference in mortality rates. The same holds true for the factor ‘country of listing’ where access to transplantation was significantly different between the four countries ( $P = 0.047$ ), but differences in waiting-list mortality failed to reach statistical significance. As with the hearts, the proportion of all lung transplant candidates listed as HU varied across countries: 5% in Austria, 7% in Belgium, 17% in Germany and 12% in The Netherlands.

### Elective lung patients

Sex but not TLC was a significant predictor of 1-year waiting-list mortality, and women had a better survival rate than men ( $P = 0.03$ ) (Table 4). End-stage disease was also a significant predictor of waiting-list mortality, and mortality was lowest in patients with chronic obstructive pulmonary disease (COPD) and highest in patients with pulmonary fibrosis (PF) ( $P < 0.0001$ ). When stratified for the factor donor-rate-country, the impact of primary disease on waiting-list mortality was not unequivocal. Patients with COPD had in low- and high-donor-rate countries, a significantly better survival rate than other patients; but patients with a rapidly progressive disease like PF and pulmonary hypertension (PH) were at a very high risk of dying prior to transplantation only in the low-donor-rate countries (Fig. 4).

Access to transplantation decreased over the years ( $P = 0.001$ ). Patients with a TLC under 4.5 l, with blood group O, and suffering from diseases other than COPD had significantly less chance of receiving a lung allograft. In high-donor-rate countries, transplant rates for elective patients were significantly higher than in low-donor-rate countries ( $P < 0.0001$ ).

### HU heart–lung patients

Within 1 month of HU listing, none of the 13 patients had died and one patient was transplanted. As these numbers are too small in order to provide sensible outcome rates, only demographic statistics are given in Table 5.

### Elective heart–lung patients

Elective patients with blood group B were more likely to die prior to transplantation than those with another blood group ( $P < 0.0001$ ) (Table 6). Patients with end-stage PH had a significantly higher waiting-list mortality than those with Eisenmenger syndrome or other end-stage diseases ( $P = 0.02$ ). Patients with PH on the elective



| Factor             | n  | Death on the waiting list |                    | Transplantation |                    |
|--------------------|----|---------------------------|--------------------|-----------------|--------------------|
|                    |    | 1 year (%)                | P-value univariate | 1 year (%)      | P-value univariate |
| Year of listing    |    |                           |                    |                 |                    |
| 1998               | 45 | 26.7                      | 0.3                | 26.7            | 0.4                |
| 1999               | 22 | 31.8                      |                    | 22.7            |                    |
| 2000               | 13 | 30.8                      |                    | 53.9            |                    |
| 2001               | 17 | 41.2                      |                    | 35.3            |                    |
| Sex                |    |                           |                    |                 |                    |
| Male               | 44 | 34.1                      | 0.3                | 29.5            | 0.9                |
| Female             | 53 | 28.3                      |                    | 32.1            |                    |
| Age (years)        |    |                           |                    |                 |                    |
| 16–40              | 55 | 32.7                      | 0.4                | 29.1            | 0.9                |
| 41–55              | 37 | 24.3                      |                    | 37.8            |                    |
| 56–65              | 5  | 60                        |                    | 20              |                    |
| 66+                | 0  | –                         |                    | –               |                    |
| ABO blood group    |    |                           |                    |                 |                    |
| A                  | 52 | 25                        | <0.0001            | 38.5            | 0.7                |
| AB                 | 0  | –                         |                    | –               |                    |
| B                  | 12 | 66.7                      |                    | 16.7            |                    |
| O                  | 33 | 24.2                      |                    | 24.2            |                    |
| TLC (L)            |    |                           |                    |                 |                    |
| <4.5               | 5  | 20.0                      | 0.2                | 40.0            | 0.7                |
| 4.51–6.0           | 52 | 26.9                      |                    | 32.7            |                    |
| 6.01+              | 40 | 37.5                      |                    | 27.5            |                    |
| End-stage disease  |    |                           |                    |                 |                    |
| Eisenmenger        | 34 | 17.6                      | 0.02               | 41.2            | 0.6                |
| Other              | 36 | 33.3                      |                    | 27.8            |                    |
| PH                 | 27 | 44.4                      |                    | 22.2            |                    |
| Toxoplasma         |    |                           |                    |                 |                    |
| Pos                | 13 | 30.8                      | 0.8                | 15.4            | 0.7                |
| Neg                | 18 | 33.3                      |                    | 16.7            |                    |
| NT                 | 66 | 30.3                      |                    | 37.9            |                    |
| CMV                |    |                           |                    |                 |                    |
| Pos                | 27 | 29.6                      | 0.2                | 33.3            | 0.9                |
| Neg                | 16 | 18.8                      |                    | 18.8            |                    |
| NT                 | 54 | 35.2                      |                    | 33.3            |                    |
| Country of listing |    |                           |                    |                 |                    |
| Austria            | 9  | 11.1                      | 0.3                | 55.6            | 0.1                |
| Belgium            | 16 | 12.5                      |                    | 50.0            |                    |
| Germany            | 67 | 37.3                      |                    | 23.9            |                    |
| Netherlands        | 5  | 40                        |                    | 20              |                    |

**Table 6.** Waiting-list outcome of adult elective heart–lung transplant candidates.

lung list were twice as likely to be offered an organ than PH patients on the elective heart–lung list: (45.4% vs. 22.2%), and about half as likely to die on the waiting list (26.1% vs. 44.4%). However, the observed differences in patients' chances of undergoing heart–lung transplantation should be interpreted with caution as no single test reached the statistical significance.

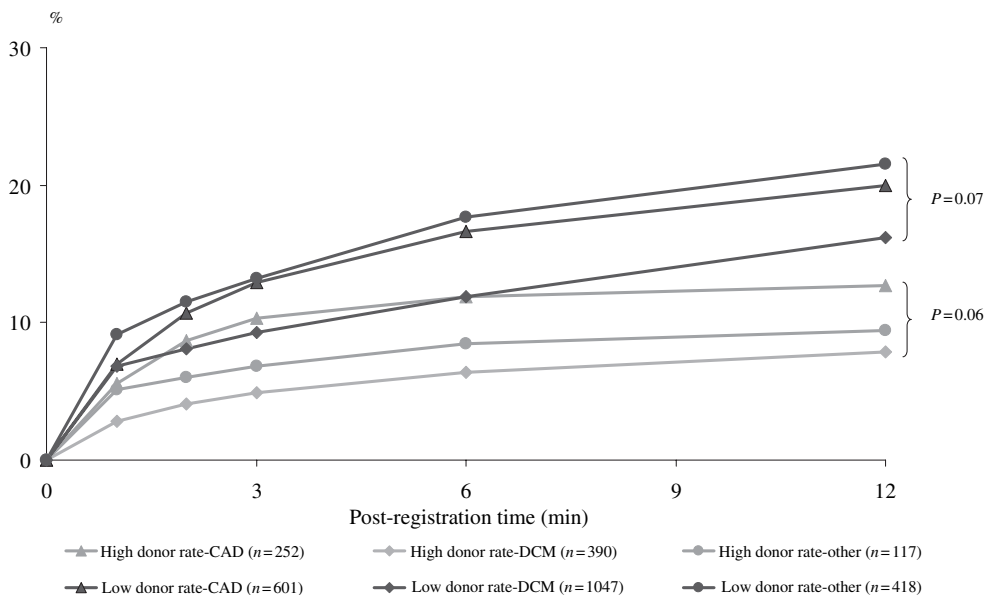
## Discussion

### Heart waiting-list outflow

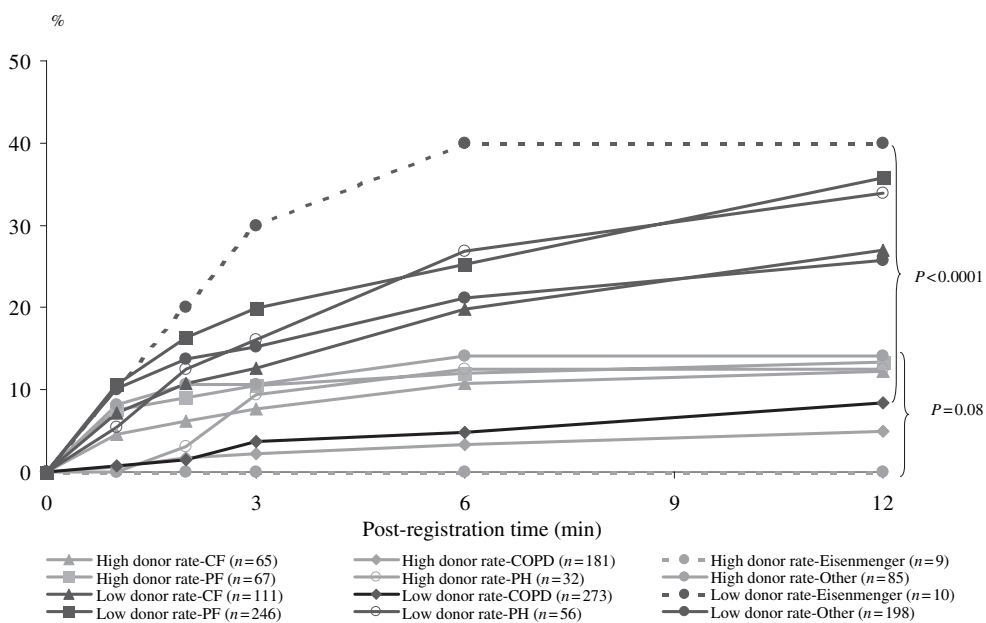
One of the shortcomings of the new procedure of expanding the criteria for HU patients is that with a lar-

ger number of HU patients competing for an organ offer, not everyone could be served in time. As the implementation of the new allocation system, more HU patients have died on the waiting list, while the mortality rates for elective patients did not change. This illustrates that allocation schemes cannot remedy organ shortage. The findings of this study have initiated a revision of the Eurotransplant heart allocation procedure.

Distributional inequalities were present for the different ABO blood group types, and blood group AB patients had the most favorable prospects. Although only height was a matching criterion, the probability of receiving a heart allograft significantly varied according to sex, age,



**Figure 3** The probability of death on the waiting list stratified by end-stage disease and donor rate for elective heart transplant patients.



**Figure 4** The probability of death on the waiting list stratified by end-stage disease and donor rate for elective lung transplant patients.

and height. Similar observations were made by the Organ Procurement and Transplantation Network (OPTN) Registry [9].

Despite the fact that prior to HU listing all heart candidates were audited by a team of independent experts, the HFSS further differentiated with respect to probability of receiving a transplant within 1 month. The GTSS also provided a differential outcome, although it failed to reach statistical significance.

Waiting-list mortality for elective adult heart transplant candidates varied significantly according to end-stage heart disease. As a result of the natural history of their disease, patients with DCM have a lower mortality rate both in high- and low-donor-rate countries. Similar findings were reported by Aaronson *et al.* for a stable outpatient cohort [7].

Probably, the most striking observation is that at the time of listing for heart transplantation, 60.5% of the

total patient cohort had a low-risk HFSS. According to the current standards [10], which have recently been challenged for probably being not stringent enough [11], these patients represent inadequate indication for heart transplantation. There still is a major task ahead of us in terms of proper heart failure care and waiting-list management.

The interpretation of the factor 'country' is far from simple. In this study, we have used 'country' as a proxy variable for 'donor rate'. Apart from that, there may be country and center-specific pretransplant treatment interventions. A major drawback of this study is that we lack the necessary data on medical management of end-stage heart failure. In a similar way, but beyond the scope of this study, differences in post-transplant outcome are not taken into account. Integrating them into policy making is not self-evident.

The higher mortality rates among HU patients in high-donor-rate countries can be explained by the fact that these countries applied stricter criteria for HU listing, as evidenced by their lower proportion of patients on HU status, and vice versa for low-donor-rate countries. For the elective patients, the mortality rates were as expected: low for high-donor-rate countries and vice versa. More formative research on clinical profiles is needed to understand the clinical context of practice, but it is reasonable to assume that this practice of HU listing depends on the likelihood of receiving suitable donor organ offers.

### Lung waiting-list outflow

Although the number of events was smaller, a similar trend as for the heart transplant candidates was observed: under the new system more lung transplant candidates were put on the HU list and a larger number of them did not receive an organ in time. The chances of receiving a transplantation for HU patients increased, which was the aim of the urgency-driven allocation system, but the increased competition led to a simultaneous decrease of the transplant chances of elective patients. Based on these observations, the Eurotransplant Thoracic Advisory Committee has taken the first step toward revision of the lung allocation scheme.

A major factor influencing the waiting-list outcome was the ABO blood group. No lung allocation simulation models are at hand that help in choosing the best ABO matching rule for HU patients [12]. But, given our results, a modified restricted ABO compatibility might increase the availability of lungs for ABO-B and ABO-O patients.

The recipient's sex, and not TLC, was seen to be a significant predictor of mortality for elective patients. TLC did, however, influence the likelihood of transplantation

for the elective transplant candidates. The so-called sex effect is thought to be a size effect, but our data show that there is something else going on. After the data were corrected for size, elective female patients were less likely to undergo transplantation than male patients but they also had a higher survival rate. The explanation lies in the clinical profiles. US experience shows the importance of this risk assessment for survival on the waiting list [13].

The Eurotransplant lung allocation scheme does not include the underlying disease. The discussion of prioritizing patients according to their primary disease already dates back several years [14]. The main reason for not doing so is the absence of an efficient audit procedure at the central office. At present, all HU candidates are prospectively assessed by the transplant physicians according to the country-specific protocols tailored to the underlying disease. Disease-specific mortality rates among elective patients varied according to the availability of donor organs; excess mortality was observed PF and PH patients in low-donor-rate countries. By contrast, in high-donor-rate countries, mortality rates were lower for COPD and Eisenmenger syndrome patients compared with the other patients.

The establishment in the US of a lung allocation scheme where the sole mechanism is transplant benefit is a unique and remarkable initiative [2]. The ability to implement and manage this scheme in our complex organization where several national high level priorities are competing is currently being investigated.

### Heart–lung waiting-list outflow

Notwithstanding the fact that within Eurotransplant heart–lung transplant candidates are given preference over single heart or lung transplant candidates, elective heart–lung patients still had as much chance of getting a transplant as of dying on the list without one.

The end-stage disease of heart–lung transplant candidates was significantly associated with the waiting-list survival, and patients with PH had the worst prognosis. This finding is in accordance with our previous results and those of other groups [13,15]. In view of the generally known lower availability of donor heart–lung blocks and given the relatively better outcome for PH patients on the lung waiting list, the request for a heart–lung transplant might not be the best treatment option for these patients.

### Thoracic allocation

Thoracic organ allocation in Eurotransplant has always been driven by waiting time and urgency. Within the group of elective patients, no further prioritization is applied: an ABO and size fitted organ is allocated to

patient with the longest-waiting time. Our data demonstrated differences in waiting-list mortality for these elective patients, and support the argument of incorporating other patient characteristics, such as disease severity and end-stage disease, into thoracic allocation schemes. However, our data also show that the impact of, for instance, end-stage disease as an allocation factor can change in a high-donor-rate setting.

### Increasing donation rates – the Donor Action experience

Waiting lists are purely a function of an imbalance between supply and demand. Whereas the demand side of the equation needs to be scrutinized, it remains true that there would be no waiting list and no waiting-list mortality if the availability of donor organs exceeds the demand. In reality, supply is finite and designers of allocation schemes – treating physicians – try their utmost to obtain and sustain a just distribution system for a scarce resource. But as a result of differences in legislative environment, organizational structure and a host of other reasons, the Eurotransplant countries differ hugely in their donation rates [16]. This fact makes the assessment of allocation rules in Eurotransplant, a complex enterprise; at the same time, it allows us to learn from each other's approach.

Although the politicization of the debate about allocation schemes usually results in bulletins unfavorable for transplantation, the thoracic transplant community continues to place hope in this same politicization process when it comes to the increasing donation rates [17]. In an exhaustive study, members of the International Society of Heart and Lung Transplantation (ISHLT) were questioned about donation [18]. Thirty-nine percent of the 739 members who responded supported the view that the enactment of presumed-consent legislation was the single best way to increase the donation. One conclusion not reached by the authors of this study but one that is all too obvious is the fact that transplant professionals are insufficiently informed when it comes to thinking strategically on the donation rates. Procurement professionals know that interventions designed to increase public awareness, financial incentives and legislative changes are unpredictable and should not be the sole avenue pursued.

Another widely held misconception is the fact that the solution to the problem of organ shortage is to use marginal or extended-criteria donors (ECD). In a study by Rayburn *et al.*, potential additional donor–organ availability was assessed by comparing the two scenarios: increased acceptance of ECD heart by 50% and increased donor consent rate by 50% [19]. The latter approach was shown to be 80% more effective in providing additional donor hearts, without jeopardizing the quality of the

organ. The Donor Action (DA) program, which takes a systematic approach toward achieving the quality assurance in the whole donation process, has proven the feasibility of this approach. Implementation of improvement measures in 10 countries has demonstrated an immediate overall increase of donation rates of 59% after 1 year [20].

Allocation schemes are in place to govern very complicated decisions on matching donors to recipients. With the disparities observed in our study, it can be questioned if the right decisions were made. But as long as not all elements necessary to launch and sustain a highly successful donation program are in place, adapting the allocation scheme is no more than scratching the surface of the possibilities for helping our thoracic transplant patients.

### References

1. Merion RM, Hulbert-Shearon TE, Bustami RT, *et al.* Proposed lung allocation system based on medical urgency and transplant benefit. *Am J Transplant* 2004; **4**: 414.
2. Smits JMA, De Meester J, Deng MC, *et al.* Mortality rates after heart transplantation. How to compare center-specific outcome data? *Transplantation* 2003; **75**: 90.
3. www.eurotransplant.nl
4. Smits JMA, Mertens BJA, van Houwelingen HC, Haverich A, Persijn GG, Laufer G. Predictors of lung transplant survival in Eurotransplant. *Am J Transplant* 2003; **3**: 1400.
5. Smits JMA, Vanhaecke J, Haverich A, *et al.* Three-year survival rates for all consecutive heart-only and lung-only transplants performed in Eurotransplant, 1997–1999. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants*. Los Angeles, CA: UCLA Tissue Laboratory, 2003: 89–100.
6. Aaronson KD, Schwartz JS, Chen TMC, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997; **95**: 2660.
7. Smits JMA, Deng MC, Hummel H, *et al.* A prognostic model for predicting waiting list mortality for a total national cohort of adult heart transplant candidates. On behalf of the COCPIT study group. *Transplantation* 2003; **76**: 1185.
8. Bailey RC, Jia-Yeong Lin M, Krakauer H. Time-to-event modeling of competing risks with intervening states in transplantation. *Am J Transplant* 2003; **3**: 192.
9. Harper AM, Taranto SE, Edwards EB. The OPTN waiting list, 1988–2001. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants*. Los Angeles, CA: UCLA Tissue Typing Laboratory, 2002: 79–92.
10. Deng MC. Cardiac transplantation. *Heart* 2002; **87**: 177.
11. Butler J, Khadim G, Paul KM, *et al.* Selection of patients for heart transplantation in the current era of heart failure therapy. *JACC* 2004; **43**: 787.

12. De Meester J, Bogers M, De Winter H, *et al.* Which ABO-matching rule in liver transplantation should be the decisive factor in the choice between a highly urgent and elective patient? *Transplant International* 2002; **15**: 431.
13. Egan TM, Bennett LE, Garrity ER, *et al.* Predictors of death on the UNOS lung transplant waiting list: results of a multivariate analysis. *J Heart Lung Transplant* 2001; **20**: 242.
14. De Meester J, Smits JMA, Persijn GG, Haverich A. Lung transplant waiting list: differential outcome of type of end-stage lung disease, one year after registration. *J Heart Lung Transplant* 1999; **18**: 563.
15. Sharples I, Belcher C, Dennis C, Higenbottam T, Walwork J. Who waits longest for heart and lung transplantation. *J Heart Lung Transplant* 1994; **13**: 282.
16. Roels L, De Meester J. The relative impact of presumed-consent legislation on thoracic organ donation in the Eurotransplant area. *J Transpl Coord* 1996; **6**: 174.
17. Young JB. The Brouhaha surrounding cardiac transplantation: the need to place outcomes in perspective. *Curr Opin Cardiol* 1997; **12**: 131.
18. Oz MC, Kherani AR, Rowe A, *et al.* How to improve organ donation: results of the ISHLT/FACT poll. *J Heart Lung Transplant* 2003; **22**: 389.
19. Rayburn BK, Burton TM, Wannenburg T, Pennington DG, Oaks TE. Are efforts at expanding the donor pool misdirected? *J Heart Lung Transplant* 1998; **17**: 998.
20. Roels L, Cohen B, Gachet C, Miranda BS. Joining efforts in tackling the organ shortage: the Donor Action experience. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants 2002*. Los Angeles, CA: UCLA Tissue Typing Laboratory, 2002: 111–120.