

Special article

Spanish Heart Transplantation Registry. 24th Official Report of the Spanish Society of Cardiology Working Group on Heart Failure and Heart Transplantation (1984-2012)

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ABSTRACT

Introduction and objectives: The present article reports the characteristics and results of heart transplantation in Spain since this therapeutic modality was first used in May 1984.

Methods: We summarize the main features of recipients, donors, and surgical procedures, as well as the results of all heart transplantations performed in Spain until December 31, 2012.

Results: A total of 247 heart transplantations were performed in 2012. The whole series consisted of 6775 procedures. Recent years have seen a progressive worsening in the clinical characteristics of recipients (34% aged over 60 years, 22% with severe kidney failure, 17% with insulin-dependent diabetes, 29% with previous heart surgery, 16% under mechanical ventilation) and donors (38% aged over 45 years, 26% with recipient: donor weight mismatch >20%), and in surgical conditions (29% of procedures at >4 h ischemia and 36% as emergency transplantations). The probability of survival at 1, 5, 10, and 15 years of follow-up was 78%, 67%, 53%, and 38%, respectively. These results have remained stable since 1995.

Conclusions: In recent years, the number of heart transplantations/year in Spain has remained stable at around 250. Despite the worsening of recipient and donor clinical characteristics and of time-to-surgery, the results in terms of mortality have remained stable and compare favorably with those of other countries.

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Registro Español de Trasplante Cardíaco. XXIV Informe Oficial de la Sección de Insuficiencia Cardíaca y Trasplante Cardíaco de la Sociedad Española de Cardiología (1984-2012)

RESUMEN

Introducción y objetivos: Este artículo presenta las características y los resultados del trasplante cardíaco en España desde que empezó su actividad en mayo de 1984.

Métodos: Se realiza un análisis descriptivo de las características de receptores, donantes, procedimiento quirúrgico y resultados de los trasplantes cardíacos realizados en España hasta el 31 de diciembre de 2012.

Resultados: Durante 2012 se han realizado 247 procedimientos, con lo que en la serie histórica constan 6.775 trasplantes. En los últimos años, se observa un empeoramiento del perfil clínico tanto de los receptores (el 34% mayores de 60 años, el 22% con insuficiencia renal grave, el 17% con diabetes mellitus insulino dependiente, el 29% con cirugía cardíaca previa y el 16% con ventilación mecánica), como de

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los donantes (el 38% mayores de 45 años y el 26% con discordancia de peso > 20%) y del procedimiento (el 29% con tiempo de isquemia > 4 h y el 36% en procedimientos urgentes). La supervivencia a 1, 5, 10 y 15 años ha sido del 78, el 67, el 53 y el 38% respectivamente. Estas cifras permanecen estables desde 1995.

Conclusiones: La actividad del trasplante cardiaco en España permanece estable en los últimos años, con alrededor de 250 procedimientos al año. A pesar del claro empeoramiento en las características de donantes, receptores y tiempos quirúrgicos, se mantienen unos resultados en mortalidad comparables a los de nuestro entorno.

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Abbreviations

RETIC: Spanish Heart Transplantation Registry

INTRODUCTION

Since 1991, the Spanish Heart Transplantation Registry (*Registro Español de Trasplante Cardíaco* [RETIC]) has published a description of the clinical and surgical characteristics and general results of heart transplantation procedures performed in Spain (*Appendix*).^{1–23} The present article describes these data and includes patients undergoing transplantation prior to December 31, 2012. The major strengths of the RETIC lie in its inclusion of practically all heart transplantation procedures in hospitals throughout Spain since May 1984, independently of their characteristics and outcomes. Moreover, data are collected prospectively and are recorded in a single database, following criteria unanimously agreed on by all heart transplantation teams.

METHODS

Patients and Centers

Of the 19 centers providing the RETIC with data, 18 are currently active (*Table 1*). The numbers of procedures per year are shown in

Table 1
Centers Participating in the Spanish Heart Transplantation Registry (1984–2012) (in Chronological Order of First Transplantation Procedures)

1.	Hospital de la Santa Creu i Sant Pau, Barcelona
2.	Clínica Universitaria de Navarra, Pamplona
3.	Clínica Puerta de Hierro, Majadahonda
4.	Hospital Marqués de Valdecilla, Santander
5.	Hospital Reina Sofía, Córdoba
6.	Hospital Universitario y Politécnico La Fe, Valencia
7.	Hospital Gregorio Marañón, Madrid
8.	Fundación Jiménez Díaz, Madrid*
9.	Hospital Virgen del Rocío, Sevilla
10.	Hospital 12 de Octubre, Madrid
11.	Hospital Universitario de A Coruña, A Coruña
12.	Hospital de Bellvitge, L'Hospitalet de Llobregat
13.	Hospital La Paz, Madrid
14.	Hospital Central de Asturias, Oviedo
15.	Hospital Clínic, Barcelona
16.	Hospital Virgen de la Arrixaca, El Palmar
17.	Hospital Miguel Servet, Zaragoza
18.	Hospital Clínico, Valladolid
19.	Hospital Vall d'Hebron, Barcelona

* This center performed transplantations in the period 1989–1994.

Figure 1. Importantly, in the whole time series, the RETIC has no data on 14 patients and consequently the present study included a total of 6761 patients. Procedure types for 2012 and the whole time series are given in *Table 2*.

Procedures

The database consists of 175 pre-established clinical variables, unanimously agreed on by all teams collecting data on recipients, donors, surgical techniques, immunosuppression, and follow-up. In 2012, the major innovation was the introduction of a web-based tool that enables groups to enter and update data directly online. The database support is a Microsoft Excel file. This replaced the earlier data-collection method that involved each center sending data to the registry director by e-mail in Microsoft Access format. Database maintenance, quality control, and statistical analyses are outsourced to an external external CRO (contract research organization): currently ODDS, SL.

Ethics committee approval, auditing, and registration with the Spanish Ministry of Health, Social Services and Equality meet the requirements of the Spanish Data Protection Law 15/1999.

Statistical Analysis

Variables are presented as mean (standard deviation) and percentage. Results were classified by transplantation year, dividing the whole sample into six 5-year groups (although the most recent period, 2009–2012, only included 4 years). Survival curves were calculated using the Kaplan-Meier test and were compared using the log rank test. Unless otherwise indicated, our analysis refers to the whole time series, including retransplantations and simultaneous transplantations. A *P* value of <.05 was considered significant.

RESULTS

Recipient Characteristics

In 2012, the age of recipients was 52 (15) years and 82% were men; the most common baseline diagnoses were ischemic heart disease (30.9%) and idiopathic dilated cardiomyopathy (24.8%).

Table 2
Spanish Heart Transplantation Registry (1984–2012). Procedure Types

Procedure	2012	1984–2012
<i>De novo</i> heart transplantation	239	6441
Retransplantation	4	195
Simultaneous transplantations	4	139
Heart-lung	1	78
Heart-kidney	3	53
Heart-liver	–	8
Total	247	6775

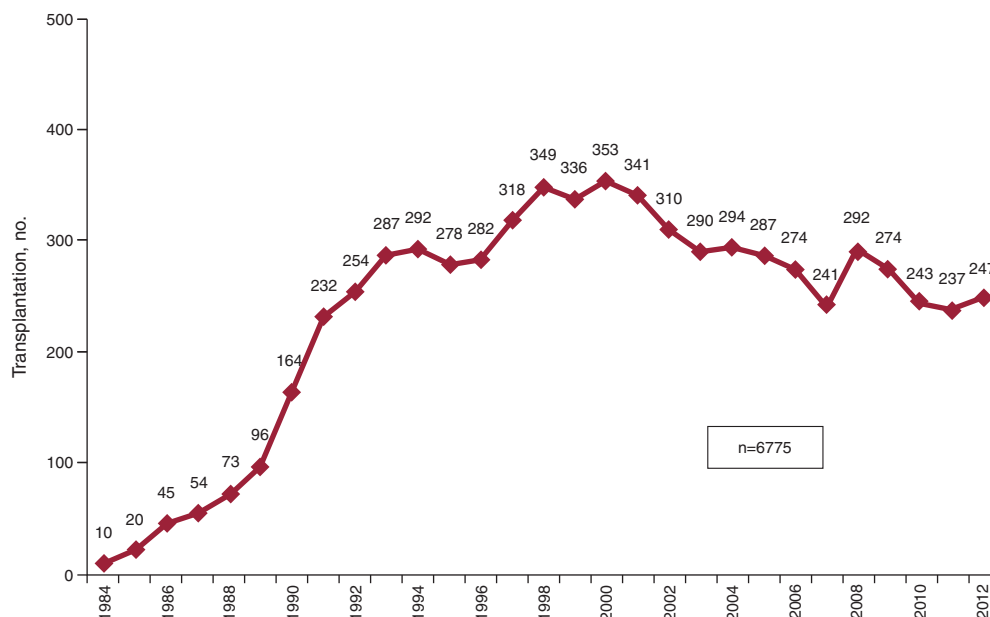


Figure 1. Number of heart transplantations per year.

Recipient characteristics categorized in 4-year periods are shown in Table 3. Notably, in the most recent period, more than one-third of recipients were aged over 60 years and more than 25% were women. Similarly, we found an increase in risk conditions such as renal dysfunction, diabetes mellitus, infection in the 15 days prior to transplantation, and the need for mechanical ventilation prior to transplantation. The percentage of emergency transplantations has gradually increased to the current 36%. In contrast, retransplantation has remained stable at around 3%.

Since 2004, the use of mechanical circulatory support other than the traditional intra-aortic counterpulsation balloon has grown constantly. In 2012, extracorporeal membrane oxygenation was used in 5.5% of procedures, continuous ventricular assist devices in 4.2%, and pulsatile devices in 5.1%. In the last year, the use of these devices (14.8%) surpassed that of the counterpulsation balloon as the only method of assistance (12.7%). The distribution of ventricular assist device procedures by periods is shown in Figure 2.

Table 3 Recipient Characteristics in the Spanish Heart Transplantation Registry (1984-2012)

	1984-1988	1989-1993	1994-1998	1999-2003	2004-2008	2009-2012	P (tendency)
Patients, no.	207	1023	1517	1630	1385	999	
Age, years	41.5 (12.6)	48.3 (13.3)	50.9 (14.8)	50.9 (14.4)	50.1 (15.9)	50.6 (16.8)	<.001
<16 years, %	4.3	3.3	4.5	3.8	5.3	7.0	<.001
>60 years, %	2.4	15.2	29.4	27.9	29.1	34.2	
Men, %	85.0	85.9	80.9	81.2	77.8	74.8	<.001
BMI	23.1 (3.6)	24.7 (10.0)	25.5 (21.7)	25.8 (12.7)	25.3 (7.2)	25.1 (7.2)	.10
Baseline etiology, %							<.001
Dilated	48.3	37.8	36.5	36.3	35.2	36.1	
Ischemic	32.9	41.5	44.5	42.8	35.5	36.2	
Valvular	9.2	10.7	8.5	6.7	8.2	6.5	
Other	9.6	10.0	10.5	14.2	21.1	21.2	
PVR, WU	2.4 (1.6)	2.4 (1.5)	2.2 (1.4)	2.2 (1.4)	2.4 (1.8)	2.2 (1.5)	.001
Creatinine>2 mg/dl, %	—	13.8	12.2	16.8	20.8	21.5	<.001
Bilirubin>2 mg/dl, %	19.7	19.8	18.9	16.1	19.7	16.5	.07
Insulin-dependent diabetes mellitus, %	8.3	8.4	9.6	15.3	16.3	17.4	<.001
Moderate-severe COPD, %	6.0	10.0	12.3	10.3	10.3	7.9	.01
Previous infection, %	2.5	4.2	7.8	10.7	13.3	13.4	<.001
Previous heart surgery, %	21.8	26.0	28.5	24.6	27.4	28.9	.06
Heart retransplantation, %	3.0	2.8	1.9	2.4	3.5	2.0	.12
Pretransplantation mechanical ventilation, %	4.4	9.0	9.7	10.8	15.8	15.9	<.001
Emergency transplantation, %	9.5	19.8	24.1	23.1	30.5	36.4	<.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; PVR, pulmonary vascular resistances. Unless otherwise indicated, data are expressed as mean (standard deviation).

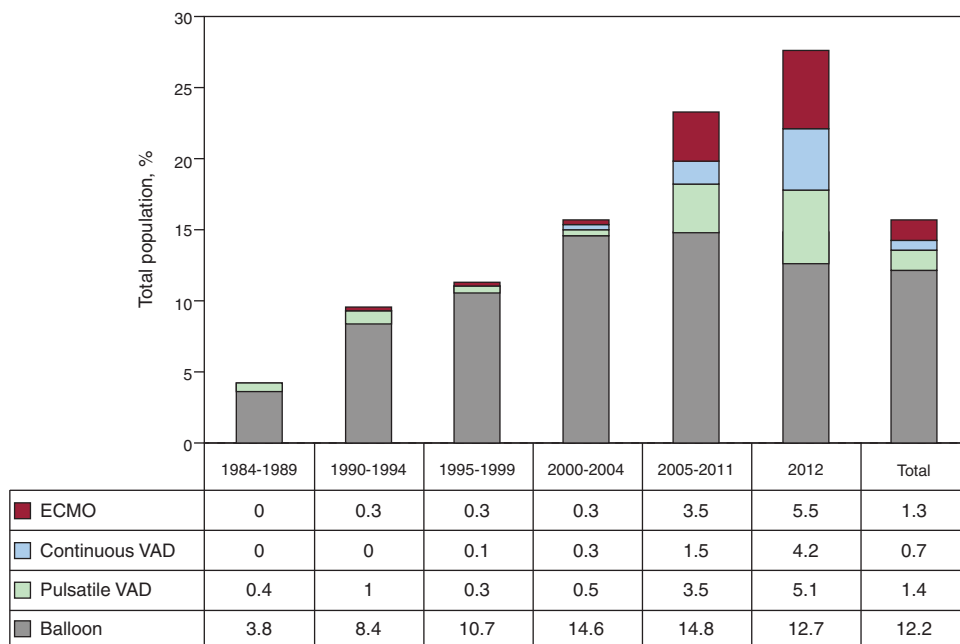


Figure 2. Distribution of pretransplantation ventricular assist device types by periods. ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

Donor Characteristics and Ischemia Time

In 2012, the mean donor age was 39.7 (13.4) years (41.3% over 45 years); 71.0% were men. In 19.5% of procedures, donor weight exceeded recipient weight by 20%; the opposite occurred in 8.7%. In 19.5% of procedures, a male recipient received a graft from a female donor.

Donor characteristics are shown in Table 4; the causes of donor death are listed in Figure 3. In the periods described, the incidence of stroke as the main cause of death increased, as opposed to traumatic brain injury.

Ischemia time gradually increased in the whole time series: in 2009-2012, ischemia time was nearly 1.30 h greater than in the initial period of 1984-1988. In the most recent period, ischemia time was >4 h in almost one-third of procedures (Table 4).

Immunosuppression

In 2012, 87.3% of recipients received some kind of induced immunosuppression treatment, usually basiliximab (85.2%). Figure 4 shows that induction gradually increased to its current almost widespread use. In the most recent period, more than 80% of patients received induction with interleukin-2 antagonists (basiliximab or daclizumab, mainly the former).

In 2012, initial immunosuppression was mainly with tacrolimus (75.9%) as a calcineurin inhibitor, mycophenolate mofetil (94.9%) as an antiproliferative agent, and steroids (96.4%). Figure 5 shows the drugs used in initial and end-of-follow-up immunosuppression for the whole time series. During the mean 6.7 years of follow-up, 58% of patients continued to receive corticoids. The use of tacrolimus has clearly tended to equal that of cyclosporine;

Table 4
Donor Characteristics and Ischemia Time in the Spanish Heart Transplantation Registry (1984-2012)

	1984-1988	1989-1993	1994-1998	1999-2003	2004-2008	2009-2012	P (tendency)
Patients, no.	207	1023	1517	1630	1385	999	
Age, years	24.7 (8.1)	26.9 (10.5)	30.2 (12.3)	32.5 (13.0)	34.6 (13.8)	38.7 (14.1)	<.001
Age>45 years, %	1.1	7.6	13.2	20.1	26.1	38.3	<.001
Men, %	85.9	77.0	70.4	71.1	68.4	66.2	<.001
Female donor, male recipient, %	11.7	18.8	22.3	19.7	20.6	20.1	<.001
Weight, kg	67.7 (12.0)	69.6 (13.6)	68.4 (16.0)	71.3 (15.7)	72.3 (18.0)	73.1 (18)	<.001
Recipient/donor weight	0.97 (0.19)	0.98 (0.17)	0.99 (0.22)	0.98 (0.21)	0.97 (0.21)	0.94 (0.19)	.036
Recipient/donor weight>1.20	10.5	11.1	16	12.3	12.2	6.6	.02
Recipient/donor weight<0.8	16.8	13.3	14	15.9	18.6	19.6	.02
Ischemia time, min	132 (54)	167 (61)	182 (60)	187 (63)	202 (64)	211 (62)	<.001
<120 min, %	48.5	22.6	18.6	17.3	12.9	9.6	<.001
120-180 min, %	30.5	37.4	29.6	27.1	24.1	19.7	
180-240 min, %	18.0	30.2	37.6	35.9	36.8	41.4	
>240 min, %	3.0	9.8	14.2	19.7	26.2	29.2	

Unless otherwise indicated, data are expressed as mean (standard deviation).

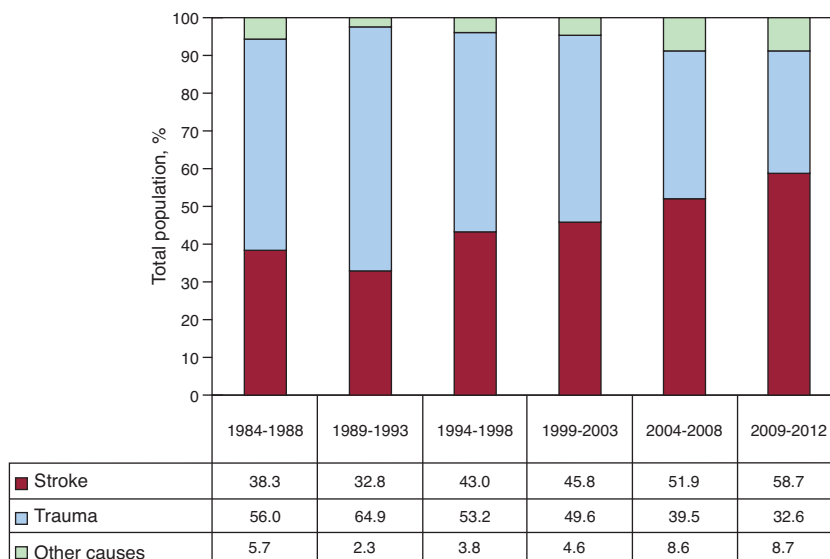


Figure 3. Causes of death in heart donors by periods analyzed.

azathioprine was barely used and, surprisingly, almost 1 of 4 patients was being treated with mTOR inhibitors (everolimus or sirolimus) at the last follow-up.

Survival

Figure 6 shows the trend in surgical mortality (first 30 days post-surgery) by year and by 5-year periods. In 2012, mortality was 12%, slightly less than that of the historical cohort, which ranged, with slight variations, between 15% and 16%.

Actuarial survival in the whole time series at 1 month and at 1, 5, 10, 15, and 20 years is shown in Figure 7. This represented approximately 2% to 3% mean annual mortality, with a median survival of 11.2 years. Differences by age and procedure type were significant. Survival was significantly worse in patients undergoing retransplantation and heart-lung transplantation vs first transplantation, both in adults and in recipients aged under 16 years old (Fig. 8). Similarly, significant differences appeared when emergency transplantations were compared with elective transplantations (Fig. 9) and according to the period when the procedure was performed (Fig. 10). Figure 10 shows that the results improved markedly after 1994, to the detriment of 1-year

survival, which rose from 73% prior to this date, to 78% after 1994 (Fig. 11).

Causes of Death

The causes of death changed according to the post-transplantation period under consideration (Fig. 12). In the first month post-transplantation, almost 50% of deaths were due to primary graft failure. After the first month and up to the end of the first year, acute rejection and, above all, infections were the main causes of death. After the first year, the main causes were tumors and different manifestations of graft vascular disease (chronic rejection, sudden death).

DISCUSSION

The RETC is now nearly a quarter of century old and has undergone an increase in volume as a consequence of the greater number of transplantation centers, the accumulation of procedures performed and, especially, their complexity. The great strength of the RETC lies in successfully creating a registry of all heart transplantations performed in Spain since the first procedure in 1984 and in having adapted to changes in the procedure and in knowledge of transplantation over time. The continued efforts of all the Spanish programs have allowed the use of an online application to be implemented this year; this application enables RETC data to be updated in real time. This undoubtedly constitutes a very important means of improving the quality and productivity of the RETC. Sharing agreed, standardized, prospective data constitutes a research instrument and, above all, a clinical tool of immense value. This is particularly so in contexts such as heart transplantation in Spain, where implementation of the procedure is nationwide (18 centers currently have active programs) and, consequently, the volume per center is low. Obviously, only analysis of country-wide data can guarantee a minimum of consistency in the findings.

In 2012, 247 transplantations were performed—in line with figures for recent years. The falling number of transplantations since the peak reached in the late 1990s is common throughout Europe.²⁴ The causes are probably multifactorial and complex.

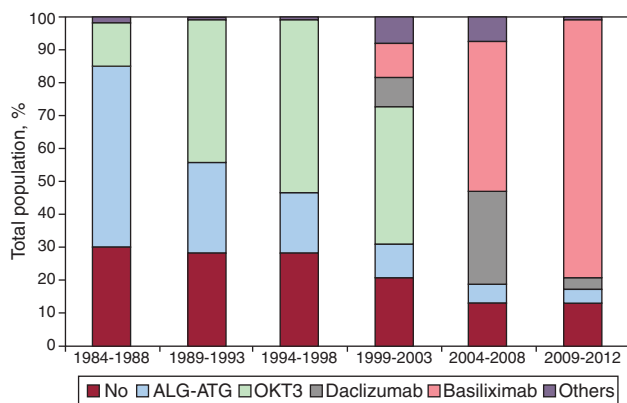


Figure 4. Induction immunosuppression drugs used. ALG-ATG, antilymphocyte and antithymocyte globulins.

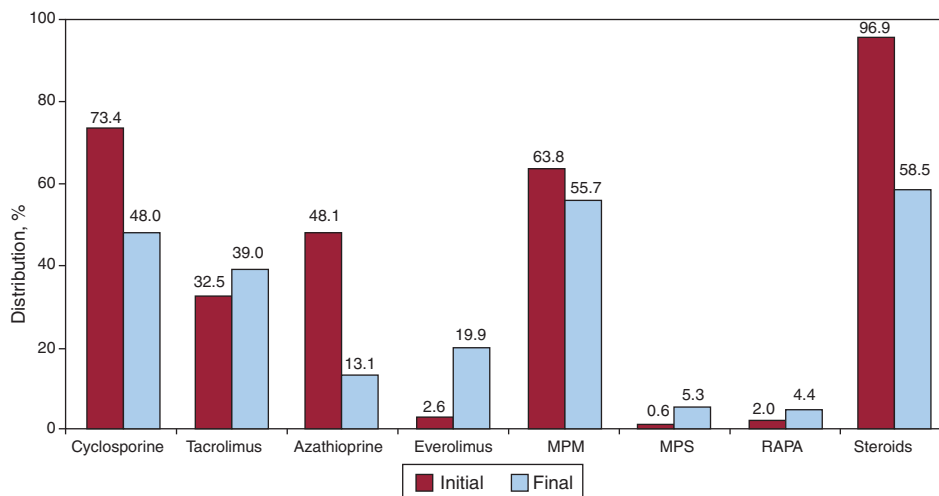


Figure 5. Maintenance immunosuppression. Variations according to drug type: at transplantation and end-of-follow-up. MPM, mycophenolate mofetil; MPS, mycophenolate sodium; RAPA, rapamycin.

Without doubt, they include the scarcity of optimal donors—principally from traffic accidents—and the improved prognosis of the most frequent heart diseases; in the last decade, drug and instrumental treatments have been consolidated and delay the need for transplantation.

Analysis of time trends in the characteristics of transplantation may shed light on changes in clinical practice over time. Firstly, data show a gradual worsening in the clinical profile of recipients. The last 5 to 10 years have seen increases in the percentage of patients who are older, have worse renal function, more insulin-dependent diabetes mellitus, and are under mechanical ventilation. All these factors are known to affect short- and long-term prognosis.²⁴ Similarly, the number of emergency procedures has increased, reaching nearly 40% in the last 4 years. We can only speculate about the causes of these trends. On the one hand, the increased experience of transplantation programs may have led to greater risk-taking with the inclusion of patients with a worse clinical profile. On the other hand, the tremendous advances in

medical and instrumental treatment of heart disease in the last 20 years have meant that patients receive prognoses similar to those for transplantation—until quite poor functional status has been reached²⁵—which generally delays their inclusion on waiting lists and the performance of transplantation.

Similarly, criteria for donation have gradually been expanded. This can be seen in the significantly older mean age of donors and the percentage of older donors (>45 years) as well as in the increase in donors who have died from a stroke, frequently associated with a greater incidence of arteriosclerosis. This trend probably reflects the struggle of transplantation programs in the face of a growing scarcity of optimal donors.

The same tendency described for recipient and donor profiles is also evident in the surgical procedure, as the gradual lengthening of ischemia time seems to indicate. Remarkably, in the last 4 years, up to 29% of recipients had >4 h of ischemia time—which is considered the limit to ensure adequate graft viability. To date, we cannot put these delays down to the gradual worsening of logistic

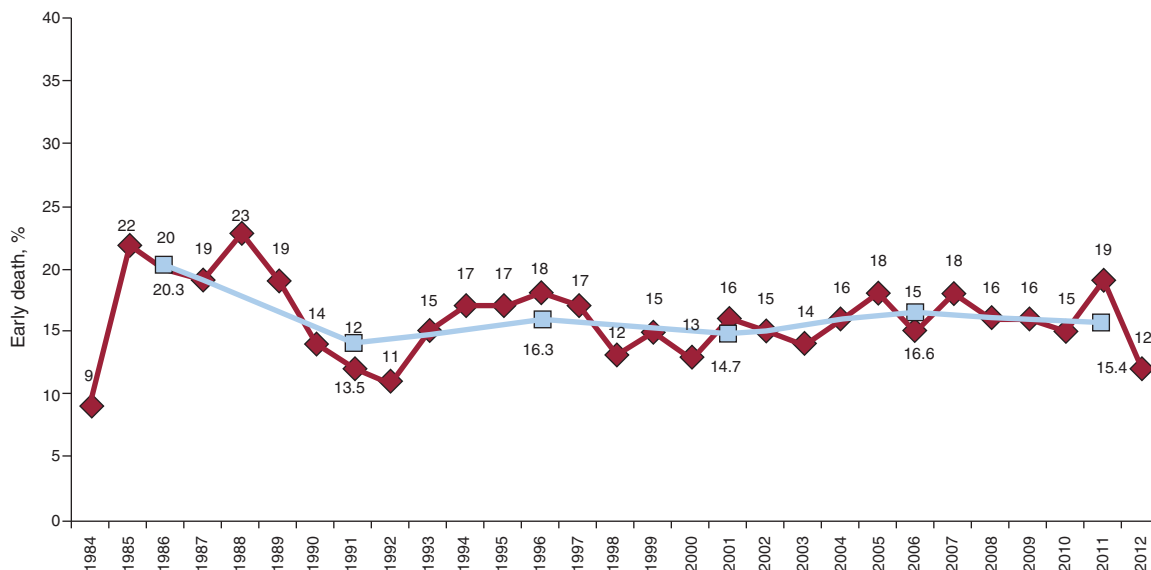


Figure 6. Year-on-year (line and red markers) and 5-year period (line and blue markers) trend in the percentage of mortality and early (≤ 30 days post-transplantation) graft loss (retransplantation).

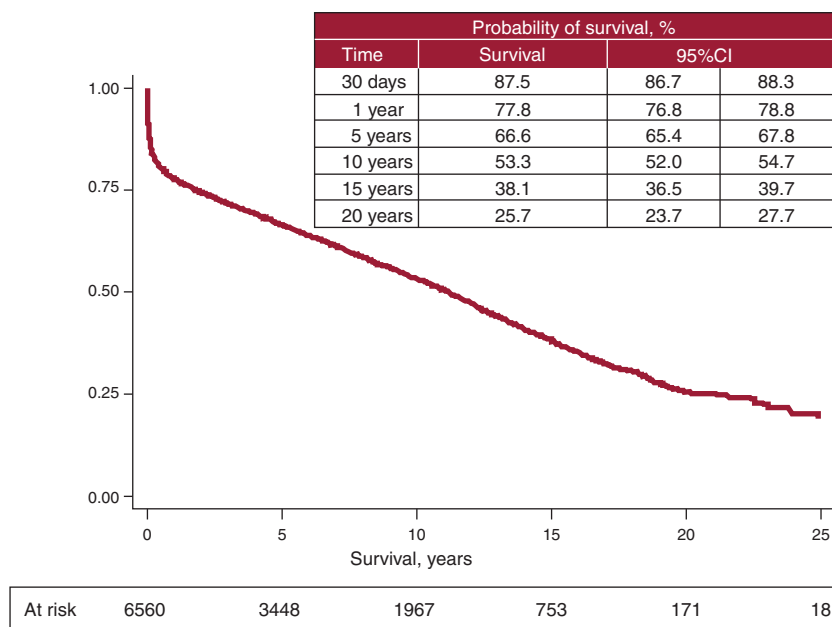


Figure 7. Actuarial survival curve (Kaplan-Meier) for the whole time series. 95%CI, 95% confidence interval.

conditions affecting procedures—at least not in general. However, this worsening could be explained by an increasingly greater willingness to accept organs from geographically distant areas—especially for urgent transplantation—and by the effect of performing transplantations on patients with medium- and long-term circulatory assist devices, which occasionally lead to less predictable surgical procedures.

Nevertheless, the general results for mortality—following the first 10 years of activity (1984-1994), which could be classified as the founding years—have remained relatively stable and compare favorably with international registry data.²⁴ Nonetheless, in general, surgical mortality has remained relatively high, making

it a clear objective for improvement. We will have to see whether the coming years confirm a positive trend in this mortality, as data for 2012 appear to suggest.

The most remarkable innovation of the last 5 years is probably the increasing use of circulatory assist devices prior to transplantation since, in 2012, these have surpassed in percentage terms the use of the traditional intraaortic counterpulsation balloon. In Spain, these devices began to be deployed much later than elsewhere, very probably due to logistic reasons, mainly—but not always—due to economic limitations. It is still too early to determine the impact of these devices both on recruiting potential transplantation recipients and the status of recipients when they

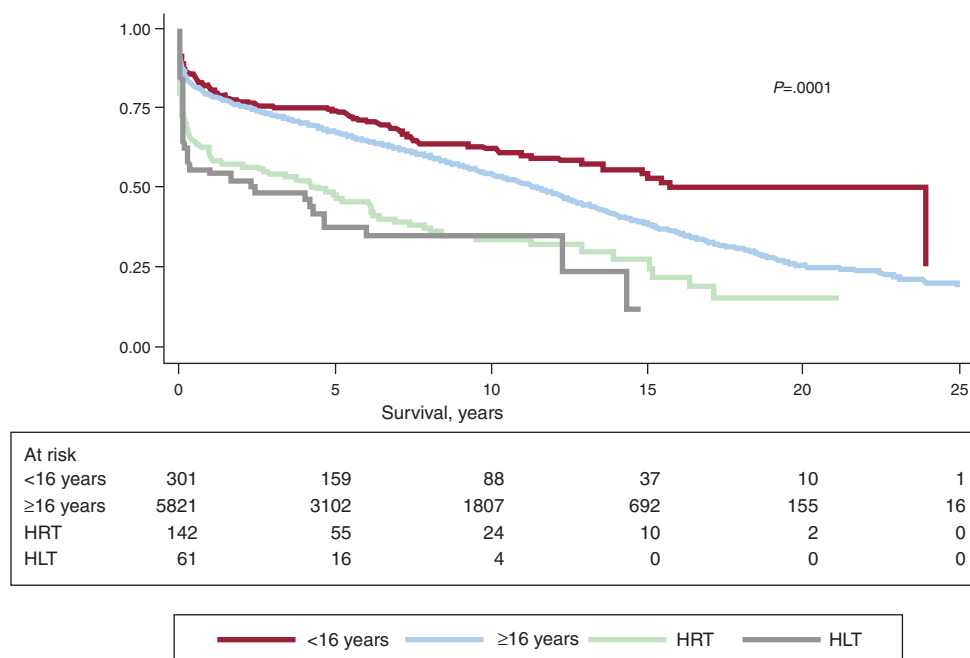


Figure 8. Comparison between survival curves of first transplantations in patients older and younger than 16 years, patients with retransplantations, and heart-lung transplantations. HLT, heart-lung transplantation; HRT, heart retransplantation.

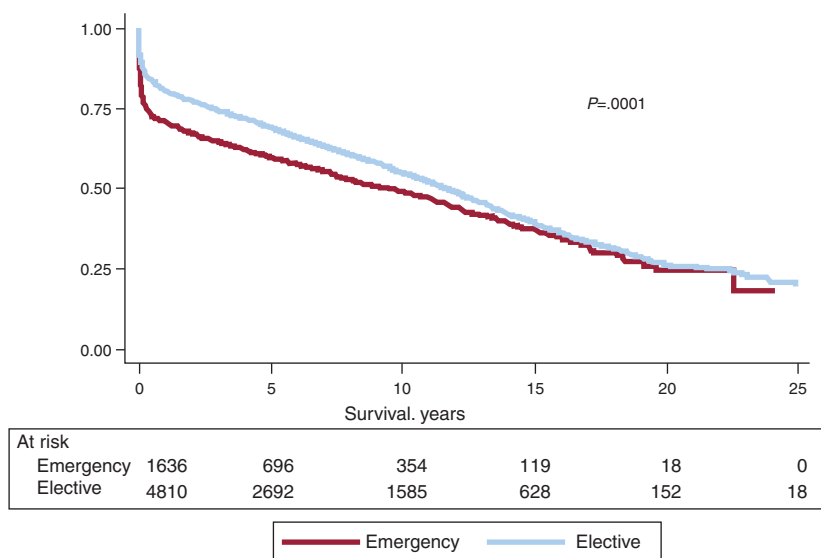


Figure 9. Comparison of survival curves between elective and emergency transplantations.

undergo the procedure and, therefore, their prognosis. Implementing these complex techniques involves a learning curve related, firstly, with an appropriate match between patient and technique, secondly, with managing these special clinical circumstances, and, thirdly, with establishing the ideal time to perform the transplantation following implementation. It is to be hoped that the individual effort and general shared knowledge derived from the transplantation centers through RETC support will lead to improved results in the coming years. Moreover, we predict that the greater use of circulatory support will lead to changes in selection criteria for emergency transplantation—an issue that is constantly changing and evolving and has significant repercussions on policy in assigning grafts.

We also detected time-scale changes in immunosuppression. Currently, induction is widely used, fundamentally with the administration of interleukin-2 inhibitors and, particularly,

basiliximab. These potent inducers allow the introduction of calcineurin inhibitors to be delayed—an increasingly widespread practice in the context of peritransplantation kidney failure. In addition, their level of clinical tolerance is excellent, which contrasts with now obsolete drugs such as OKT3. Initial immunosuppression continues to be based on traditional triple therapy, although we have found a clear change in the selection of calcineurin inhibitors toward tacrolimus and in that of anti-proliferative agent towards mycophenolate mofetil, to the detriment of cyclosporine and azathioprine, respectively. Furthermore, the use of m-TOR inhibitors (sirolimus and, above all, everolimus) has increased to reach the current total of 23% of patients, in the context of increasingly individualized immunosuppression therapy aimed at preserving renal function and preventing graft vascular disease and post-transplantation neoplasia.

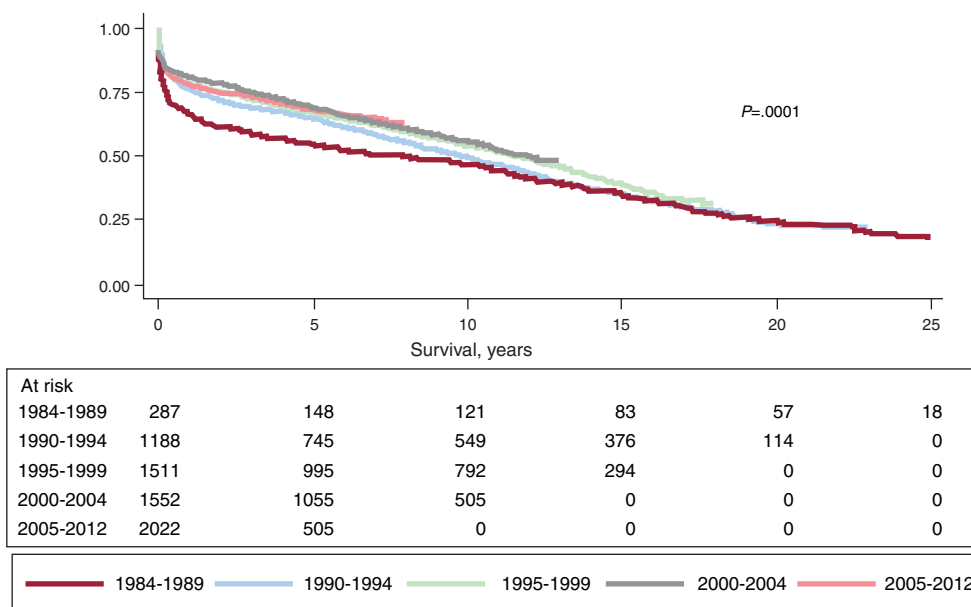


Figure 10. Comparison of survival curves for the whole sample according to the transplantation period (5-year intervals since 1984).

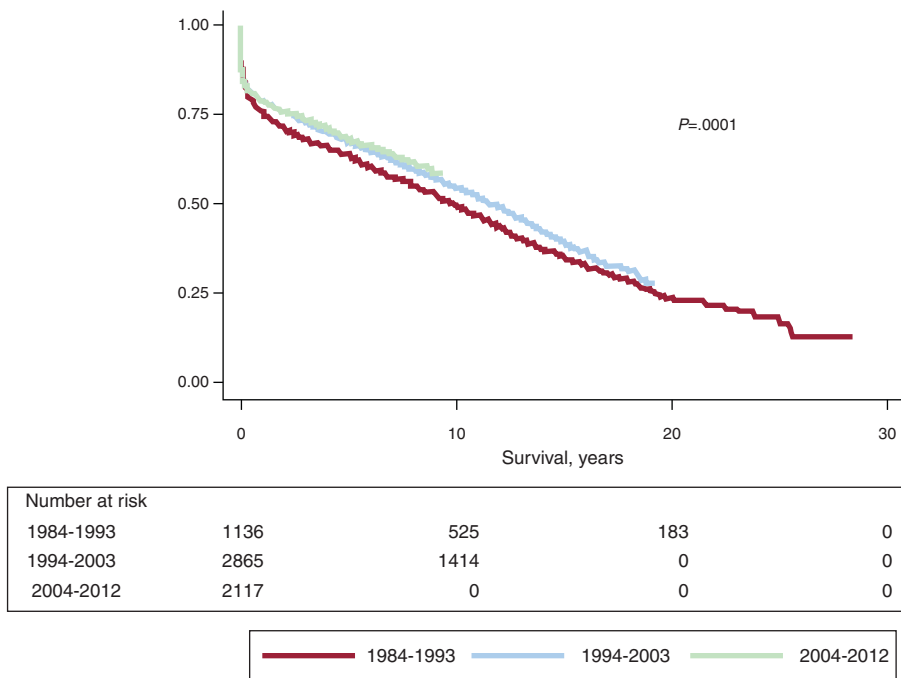


Figure 11. Comparison of survival curves for the whole sample according to the transplantation period (10-year intervals since 1984).

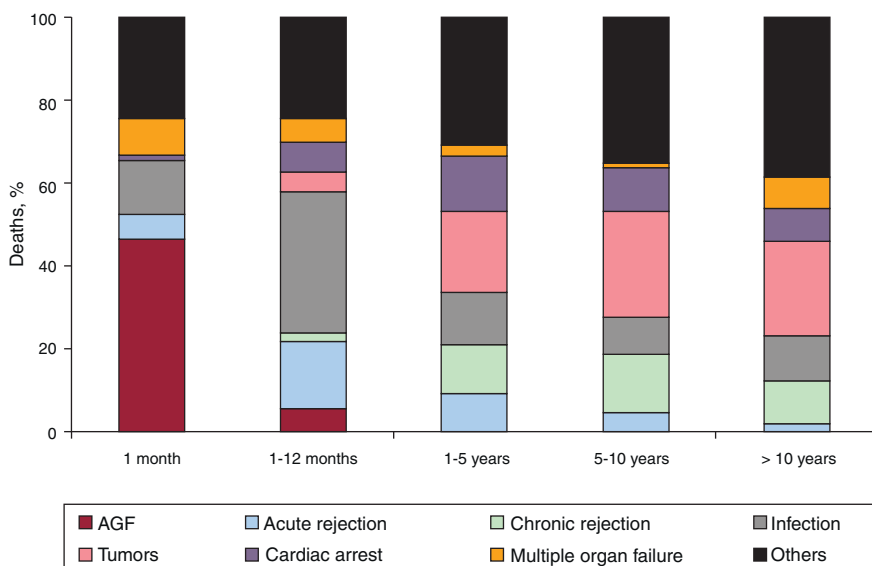


Figure 12. Causes of death by time post-transplantation. AGF, acute graft failure.

CONCLUSIONS

Heart transplantation is currently a well-established therapeutic treatment for selected patients with advanced-stage heart failure who are not candidates for other treatments. Although the clinical context in which this procedure is used has become ever more complex, the results remain within international parameters. However, potential improvements can be made in issues such as periprocedural mortality, the adequacy of immunosuppression, and long-term preventative care for major causes of mortality such as tumors, graft vascular disease, infections, and kidney failure. In the coming years, efforts must be maintained to effectively and efficiently introduce the pre- and postprocedural use of circulatory support devices into the standard management of patients suitable for heart transplantation.

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CONFLICTS OF INTEREST

F. González-Vílchez: remuneration for presentations: Astellas, Novartis, Roche, Pfizer. Expenses associated with travel, accommodation or attendance at scientific meetings: Roche, Astellas, Novartis.

APPENDIX. CONTRIBUTORS TO THE SPANISH REGISTRY ON HEART TRANSPLANTATION (1984-2012)

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