ESC HEART FAILURE
*ESC Heart Failure* 2022; **9**: 1239–1247
Published online 17 February 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13799

ORIGINAL ARTICLE

# Cardiac allograft vasculopathy and donor age affecting permanent pacemaker implantation after heart transplantation

Stefan Roest[1,2], Olivier C. Manintveld[1,2], Marit A.E. Kolff[1,2], Ferdi Akca[3], Jesse F. Veenis[1], Alina A. Constantinescu[1,2], Jasper J. Brugts[1,2], Ozcan Birim[2,3], Lennie M. van Osch-Gevers[2,4], Tamas Szili-Torok[1] and Kadir Caliskan[1,2]*

[1]*Department of Cardiology, Thorax Center, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands;* [2]*Erasmus MC Transplant Institute, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands;* [3]*Department of Cardiothoracic Surgery, Thorax Center, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands;* [4]*Department of Paediatrics, Division of Paediatric Cardiology, Erasmus MC—Sophia Children's Hospital, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands*

## Abstract

**Aims** The need for permanent pacemakers (PMs) after heart transplantation (HT) is increasing. The aim was to determine the influence of cardiac allograft vasculopathy (CAV), donor age, and other risk factors on PM implantations early and late after HT and its effect on survival.

**Methods and results** A retrospective, single-centre study was performed including HTs from 1984 to July 2018. Early PM was defined as PM implantation ≤90 days and late PM as PM > 90 days. Risk factors for PM and survival after PM were determined with (time-dependent) multivariable Cox regression. Out of 720 HTs performed, 62 were excluded (55 mortalities ≤30 days and 7 retransplantations). Of the remaining 658 patients, 95 (14%) needed a PM: 38 (6%) early and 57 (9%) late during follow-up (median 9.3 years). Early PM risk factors were donor age [hazard ratio (HR) 1.06, $P < 0.001$], ischaemic time (HR 1.01, $P < 0.001$), and in adults amiodarone use before HT (HR 2.02, $P = 0.045$). Late PM risk factors were donor age (HR 1.03, $P = 0.024$) and CAV (HR 3.59, $P < 0.001$). Late PM compromised survival (HR 2.05, $P < 0.001$), while early PM did not (HR 0.77, $P = 0.41$).

**Conclusions** Risk factors for early PM implantation were donor age, ischaemic time, and in adults amiodarone use before HT. Late PM implantation risk factors were donor age and CAV. Late PM diminished survival, which is probably a surrogate marker for underlying progressive cardiac disease.

**Keywords** Heart transplantation; Risk factors; Pacemaker implantation; Cardiac allograft vasculopathy; Donor age

*Received: 13 August 2021; Revised: 27 November 2021; Accepted: 20 December 2021*
**Correspondence to: Kadir Caliskan, Department of Cardiology, Thorax Center, Erasmus MC, University Medical Centre Rotterdam, Room Rg-431, Doctor Molewaterplein 40, PO Box 2040, 3015 GD Rotterdam, The Netherlands. Tel: +31-10-7035078; Fax: +31-10-7035333. Email: dr.kcaliskan@hotmail.com*

## Introduction

Sinus node dysfunctions (SNDs) and conduction abnormalities are relatively common early and late after orthotopic heart transplantation (HT).[1–6] Albeit in the early phase, the bradyarrhythmias are usually temporary and could be treated by intravenous isoprenaline and/or temporary external pacing, however some of these patients need a permanent pacemaker (PM) implantation.[1,6] Indications for PM implantation are mostly symptomatic bradyarrhythmias or chronotropic incompetence.[1–6]

In recent reports, it has been demonstrated that patients who received a heart from an older donor had more bradyarrhythmias and conduction disorders (SND or atrioventricular node dysfunction) after HT needing PM implantation.[2–4,7–9] Others found no correlation.[1,5] This association could partially be explained by the ischaemia time in combination with the ischaemia–reperfusion injury after transplantation, which could cause an impaired conduction in the early phase after transplantation.[6] This would be more prominent in older donors as older hearts could have less compensation mechanisms to cope with these injuries.[10] In

the last decade, because of extreme shortage of suitable heart donors, the waiting time for a HT has increased, which is why older donors are used.[11,12] Even though the donor age is rising, the long-term survival after HT is still improving.[11,12] Another reason for the increased number of PM implantations suggested in the literature is the operating technique.[4,8,9] There are two types of surgical techniques that are generally used in HTs. The first one is the biatrial technique, in which the atria of the donor are sutured to (a part of) the atria of the recipient.[13] With the second method, the bicaval technique, the left atrium of the donor is sutured to the left atrium of the recipient, while a second anastomosis is created with the superior and inferior caval vein of the recipient.[14] It has been suggested that the biatrial technique increases the risk for PM implantation early after HT, which is one of the reasons why more and more centres are implementing the bicaval technique into clinical practice.[15]

For PMs implanted longer after HT, the cause for conduction problems could be more 'common' degenerative disease of the sinus or atrioventricular node in combination with specific conditions associated with a HT such as cardiac allograft vasculopathy (CAV) and fibrosis due to rejections.[6,11] Up until now, only studies with small study populations or limited follow-up durations have been published.[1,2,4,7,9] Furthermore, most studies exclude recipients younger than 18 years old, thereby excluding the youngest donors. Additionally, most studies did not have enough events or enough information about the co-morbidities to determine whether CAV or rejections are significant risk factors for PM implantation.[2,4,9] The aim of the study was to evaluate the relationship between CAV and donor age and the need for a PM implantation after HT in a large, single-centre study with over 36 years of experience. Moreover, additional risk factors for PM implantation and the effect of PM implantation on long-term survival were investigated.

# Methods

All patients who underwent a primary HT in our centre from the start of the HT programme in 1984 until July 2018 were included in this study. When a patient had a retransplantation, only the first HT was included and the follow-up was censored at the time of the retransplantation. Furthermore, patients who died within the first month after HT were excluded from the analysis. The study was approved by the Medical Ethical Review Committee of the Erasmus MC (MEC-2017-421). The study conforms to the *Declaration of Helsinki*.

## Pacemaker protocol

In our centre, all patients received a temporary pacemaker and isoprenaline after HT to maintain a heart rate >100 b.p.m. This temporary pacemaker rate was per protocol steadily lowered from 3 days after HT with 10 b.p.m. every day until the patient had an adequate heart rate of at least 60 b.p.m. or higher with stable haemodynamics. After 10–14 days, if the heart rate was not sufficient, low oral theophylline supply was initiated in order to taper the isoprenaline intravenously. If this did not improve the heart rate appropriately within 4–6 weeks, a permanent PM implantation was planned. When theophylline was tolerated and helped with keeping the heart rate above 60 b.p.m., the patient was discharged with theophylline without the need for a PM.

## Definitions

Early PM was defined as a pacemaker that was implanted within the first 90 days after HT. A late PM was defined as a pacemaker implanted after 90 days. The indication for the PM was obtained from the patient chart at the time of PM implantation. Indications for PM are categorized into SND and atrioventricular blockage (AVB).

To determine the effect of donor age on outcomes, recipients were divided into tertiles by donor age.

Rejections were classified according to the International Society for Heart and Lung Transplantation guidelines.[16] CAV was defined according to the International Society for Heart and Lung Transplantation CAV guideline.[17] Diabetes before HT was defined as the use of glucose-lowering medication at the moment of the HT. Amiodarone use before HT was defined as the chronic use of amiodarone (>1 month) in the year before HT. Protocols on immunosuppressive regimen have been described before.[12]

## Cardiac allograft vasculopathy monitoring

CAV was monitored by performing a coronary angiography at the annual check-up of Years 1 and 4. After the fourth year, patients were screened for CAV using myocardial perfusion imaging. Whenever the scan was abnormal or there was a clinical indication for further coronary testing, an invasive coronary angiography was performed. Further information on the CAV screening has been reported before.[12] Since March 2018, coronary computed tomographies are performed instead of myocardial perfusion imaging in suitable patients.[18] Again, when the computed tomography result was abnormal, an invasive coronary angiography was performed to confirm the CAV diagnosis. In case a patient developed a bradyarrythmia, an invasive coronary angiography and an endomyocardial biopsy were performed to exclude CAV and/or rejection before PM implantation.

## Statistical analysis

When continuous variables were normally distributed, means were noted ± standard deviations. If not normally distributed, medians with the 25–75th percentile [interquartile range (IQR)] were presented. Normally distributed data were compared using Student's *t*-test or one-way ANOVA test, and non-normally distributed data were compared with the Mann–Whitney or Kruskal–Wallis test depending on the number of groups. Categorical data are presented as an absolute number with a percentage (%) and compared using $\chi^2$ or Fisher's exact test where appropriate.

Associations between predictors of (early and late) PM implantations were examined with Cox regression analysis. Patients lost to follow-up (i.e. patients whose follow-up was continued in a different transplantation centre) were considered at risk until the date of last contact. The Cox proportional hazards assumption was assessed using log–log plots. First, univariate Cox analyses were performed. Subsequently, variables with a *P*-value $<0.05$ were included in the multivariable Cox analysis. As rejections and CAV grade are both time-dependent variables, these were included into an extended Cox regression analysis as time-dependent variables. For PM predictors, all variables were collected before PM implantation or at the end of follow-up (90 days or death for early PM and death, retransplantation date, or end of follow-up in late PM). To determine predictors for late PM implantation, all patients with an early PM or follow-up duration $\leq$90 days were excluded from the analysis. Furthermore, time-dependent Cox regression was used to investigate whether a PM implantation impairs the survival after HT. To examine the progression of the donor age over time, linear regression was used.

Kaplan–Meier curves were used to compare incidences of PM-free survival stratified by donor age group and compared by log-rank test. Patients were censored at the time of death, retransplantation, lost to follow-up, or on the 1 September 2018. *P*-value $<0.05$ was considered statistically significant. Analyses were performed using statistical software SPSS, Version 25.0 (SPSS Inc., IBM Company, Chicago, IL).

# Results

In total, 720 HTs were performed in the inclusion period, of whom 62 were excluded from the analysis [55 patients died within the first month after HT (none due to sinus node or conduction disorders) and 7 retransplantations]. Of the remaining 658 patients, 183 (28%) were women. The median recipient age at HT was 49 [IQR 39–56] years old of whom 72 (11%) under the age of 18. Most patients (99%) were transplanted with a biatrial anastomosis. All baseline characteristics of the patients included in the study are demonstrated in *Table 1*. The median donor age was 32 [IQR 20–44] years. When divided into tertiles, 215 (33%) donors were $\leq$23 years old, 226 (34%) donors were between 24 and 40 years old, and 217 (33%) donors were $>$40 years old. In *Figure 1*, the distribution of donor ages per year is plotted for all HT patients (*Figure 1A*; $r^2 = 0.148$, $P < 0.001$) and solely adult recipients (*Figure 1B*; $r^2 = 0.360$, $P < 0.001$).

## Need of permanent pacemaker implantations

Outcome parameters are demonstrated in *Table 2*. The median follow-up duration after HT was 9.3 [IQR 5.0–14.8] years.

**Table 1** Baseline characteristics of HT patients stratified according to the donor age

| Parameters | Total | Donor age (≤23 years) | Donor age (24–40 years) | Donor age (>40 years) | *P*-value |
|---|---|---|---|---|---|
| Number of patients | 658 | 215 (33) | 226 (34) | 217 (33) | |
| Donor characteristics | | | | | |
| Age (years) | 32 (20–44) | 18 (15–20) | 32 (27–36) | 49 (44–55) | <0.001 |
| Female | 328 (50) | 76 (35) | 109 (48) | 143 (66) | <0.001 |
| Recipient characteristics | | | | | |
| Female | 183 (28) | 55 (26) | 53 (24) | 75 (35) | 0.02 |
| Age at HT (years) | 49 (39–56) | 45 (19–54) | 50 (39–55) | 52 (46–60) | <0.001 |
| Ischaemic CMP | 258 (39) | 71 (33) | 102 (45) | 85 (39) | 0.03 |
| Non-ischaemic CMP | 400 (61) | 144 (67) | 124 (55) | 132 (61) | 0.03 |
| Dilated CMP | 286 (72) | 101 (70) | 97 (78) | 88 (67) | 0.40 |
| Hypertrophic CMP | 39 (10) | 9 (6) | 7 (6) | 23 (17) | 0.002 |
| Congenital heart disease | 16 (4) | 9 (6) | 5 (4) | 2 (2) | 0.09 |
| Other | 59 (15) | 25 (17) | 15 (12) | 19 (14) | 0.19 |
| LVAD | 54 (8) | 12 (6) | 14 (6) | 28 (13) | 0.009 |
| Diabetes before HT | 40 (6) | 4 (2) | 13 (6) | 23 (11) | 0.001 |
| Creatinine at HT (μmol/L) | 111 (89–135) | 103 (72–131) | 110 (92–134) | 117 (97–140) | <0.001 |
| Amiodarone use before HT | 227 (35) | 63 (29) | 65 (29) | 99 (46) | <0.001 |
| Surgical data | | | | | |
| Ischaemic time (min) | 174 (146–210) | 177 (143–210) | 170 (143–210) | 178 (151–210) | 0.25 |

CMP, cardiomyopathy; HT, heart transplantation; LVAD, left ventricular assist device; SD, standard deviation.
Categorical variables are presented as numbers with (%). Normally distributed continuous variables are shown as mean ± SD. Non-normally distributed continuous variables are shown as a median with (interquartile range).

**Figure 1** Correlation between donor age and year of heart transplantation (HT) with corresponding regression line for (A) all patients or (B) adults only.

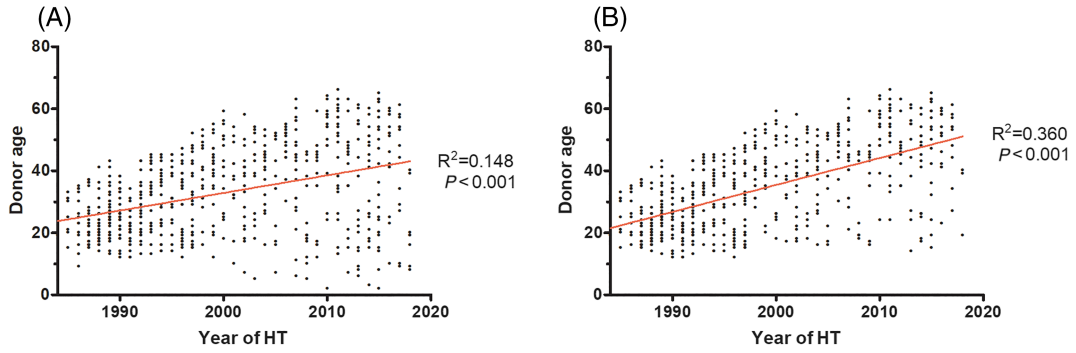



**Table 2** Long-term outcome parameters for all HT recipients stratified according to the donor age

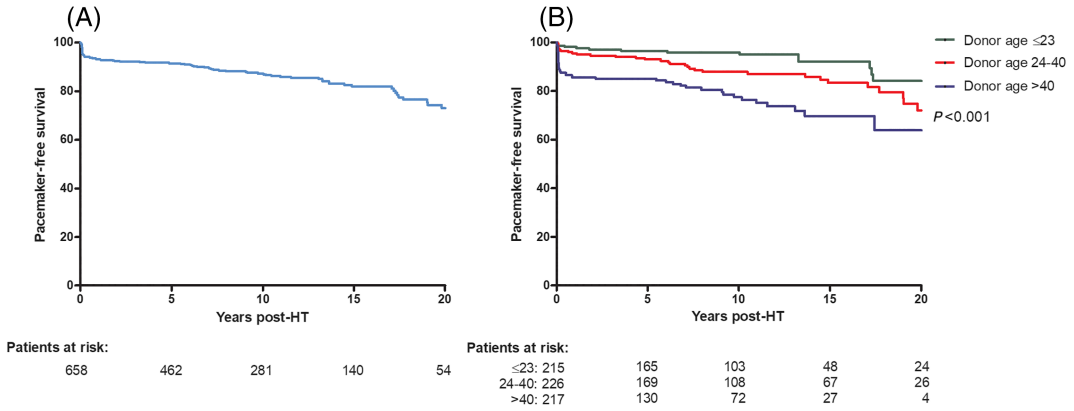
| Parameters | Total | Donor age (≤23 years) | Donor age (24–40 years) | Donor age (>40 years) | *P*-value |
|---|---|---|---|---|---|
| Number of patients | 658 | 215 | 226 | 217 | |
| Follow-up (years) | 9.3 (5.0–14.8) | 10.0 (5.5–14.9) | 10.4 (5.5–16.6) | 8.0 (3.7–12.6) | <0.001 |
| Theophylline use at discharge | 47 (7) | 9 (4) | 17 (8) | 21 (10) | 0.08 |
| PM implantation | 95 (14) | 15 (7) | 33 (15) | 47 (22) | <0.001 |
| Early PM | 38 (6) | 3 (1) | 8 (4) | 27 (12) | <0.001 |
| Late PM | 57 (9) | 12 (6) | 25 (11) | 20 (9) | 0.12 |
| PM indication | | | | | 0.29 |
| SND | 49 (52) | 6 (40) | 15 (45) | 28 (60) | |
| AVB | 46 (48) | 9 (60) | 18 (55) | 19 (40) | |
| Early SND | 30 (79) | 3 (100) | 6 (75) | 21 (78) | |
| Early AVB | 8 (21) | 0 (0) | 2 (25) | 6 (22) | |
| Late SND | 19 (33) | 3 (25) | 9 (36) | 7 (35) | |
| Late AVB | 38 (67) | 9 (75) | 16 (64) | 13 (65) | |
| Type of PM | | | | | 0.16 |
| AAI | 3 (3) | 0 (0) | 1 (3) | 2 (4) | |
| VVI | 9 (9) | 3 (20) | 5 (15) | 1 (2) | |
| DDD | 83 (87) | 12 (80) | 27 (82) | 44 (94) | |
| ICD implantation | 7 (1) | 0 (0) | 4 (2) | 3 (1) | 0.17 |
| Rejections | 1 (0–2) | 1 (0–3) | 1 (1–3) | 1 (0–2) | 0.002 |
| 0 | 180 (27) | 60 (28) | 49 (22) | 71 (33) | 0.03 |
| 1 | 180 (27) | 49 (23) | 65 (29) | 66 (30) | 0.17 |
| ≥2 | 298 (45) | 106 (49) | 112 (50) | 80 (37) | 0.01 |
| CAV grade (>1) | 153 (23) | 35 (16) | 67 (30) | 51 (24) | 0.01 |

AVB, atrioventricular block; CAV, cardiac allograft vasculopathy; HT, heart transplantation; ICD, implantable cardioverter–defibrillator; PM, permanent pacemaker; SD, standard deviation; SND, sinus node dysfunction.
Categorical variables are presented as numbers with (%). Normally distributed continuous variables are shown as mean ± SD. Non-normally distributed continuous variables are shown as a median with (interquartile range).

In total, 95 (14%) patients needed a permanent PM after HT of whom 38 (6%) received an early PM while 57 (9%) received a late PM. Of the 72 children included in this study, 14 (19%) received a PM during follow-up; 4 (29%) of these PMs were implanted early while 10 (71%) were implanted late after HT. Only 9 (13%) of the children used amiodarone before HT compared with 218 (37%) in patients >18. The median duration of the hospital stay immediately after HT was 25 [IQR 17–36] days. Patients who received an early pacemaker had a median hospital stay duration of 43 [IQR 36–53] days, compared with a median hospital stay of 24 [IQR 17–34] for patients who did not receive an early pacemaker ($P < 0.001$).

Overall pacemaker-free survival is displayed in *Figure 2A*. Patients with an older donor (>40) had a significantly shorter pacemaker-free survival than patients with a younger donor ($P < 0.001$) as displayed in *Figure 2B*. In patients with a young donor (≤23 years old), only 1% of the patients received an early PM, while this was the case in 4% of the patients with a donor between 24 and 40 and 12% of the patients with a donor >40 years old ($P < 0.001$). The frequency of late PM implantation was not statistically significantly different between groups (6% vs. 11% vs. 9%, respectively, $P = 0.12$). Median time to early PM implantation was 37 [IQR 29–41] days. Median time for late PM implantation was 7.6 [IQR 3.9–13.6]

**Figure 2** (A) The pacemaker-free survival for the whole study population. (B) The pacemaker-free survival divided into donor age categories. HT, heart transplantation.




years. Indications for PM were SND in 49 (52%) patients and AVB in 46 (48%) patients. SND was seen more frequently in patients with an early PM than patients with a late PM (79% vs. 33% respectively, $P < 0.001$). AVB was more frequently seen in patients with a late PM compared with patients with an early PM (67% vs. 21% respectively, $P < 0.001$). The most frequently implanted PMs were the DDD pacemakers (87%), followed by VVI (9%) and AAI (3%).

When the patients were divided by era (before and after 2000), there were significant differences seen between the groups (*Table 3*). Even though the number of PMs after HT was not statistically significant, early PMs were more frequent after 2000 (10% vs. 2%, $P < 0.001$) while the number of late PMs was lower (6% vs. 11%, $P = 0.009$).

## Predictors of permanent pacemaker implantation

All variables entered into the multivariable model met the Cox proportional hazard assumption. In univariate Cox regression analysis, several predictors were found for early PM implantation after HT. Donor age ($P < 0.001$), amiodarone use before HT ($P = 0.018$), and total ischaemic time ($P < 0.001$) were predictors for early PM implantation, while recipient age ($P = 0.63$) and rejections ($P = 0.12$) were not (*Table 4A*). In multivariable analysis, donor age [HR 1.06 (1.03–1.08), $P < 0.001$] and total ischaemic time [HR 1.01 (1.01–1.02), $P < 0.001$] were independent predictors for early PM implantation after HT. Amiodarone use before HT was not statistically significant [HR 1.73 (0.90–3.29), $P = 0.10$] (*Table 4A*).

**Table 3** Pacemaker incidences stratified by transplantation era

| Parameters | Total | HT < 2000 | HT ≥ 2000 | *P*-value |
|---|---|---|---|---|
| Number of patients | 658 | 342 | 316 | |
| Follow-up (years) | 9.3 (5.0–14.8) | 11.7 (7.0–18.1) | 7.2 (3.5–11.4) | <0.001 |
| Donor age | 32 (20–44) | 26 (20–35) | 42 (25–51) | <0.001 |
| Ischaemic time (min) | 174 (146–210) | 160 (135–187) | 196 (163–225) | <0.001 |
| PM implantation | 95 (14) | 44 (13) | 51 (16) | 0.23 |
| Early PM | 38 (6) | 5 (2) | 33 (10) | <0.001 |
| Late PM | 57 (9) | 39 (11) | 18 (6) | 0.009 |
| PM indication | | | | 0.02 |
| SND | 49 (52) | 17 (39) | 32 (63) | 0.01 |
| AVB | 46 (48) | 27 (61) | 19 (37) | 0.34 |
| Early SND | 30 (79) | 5 (100) | 25 (76) | <0.001 |
| Early AVB | 8 (21) | 0 (0) | 8 (24) | 0.003 |
| Late SND | 19 (33) | 12 (31) | 7 (39) | 0.32 |
| Late AVB | 38 (67) | 27 (69) | 11 (61) | 0.02 |
| Type of PM | | | | 0.03 |
| AAI | 3 (3) | 1 (2) | 2 (4) | 0.52 |
| VVI | 9 (9) | 8 (18) | 1 (2) | 0.03 |
| DDD | 83 (87) | 35 (80) | 48 (94) | 0.06 |

AVB, atrioventricular block; HT, heart transplantation; PM, permanent pacemaker; SD, standard deviation; SND, sinus node dysfunction. Categorical variables are presented as numbers with (%). Normally distributed continuous variables are shown as mean ± SD. Non-normally distributed continuous variables are shown as a median with (interquartile range).

**Table 4A** Predictors of early (≤90 days) and late (>90 days) permanent pacemaker implantation for all recipients

| Parameters | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Predictors early PM | | | | |
| Age at HT | 1.01 (0.98–1.03) | 0.63 | | |
| Donor age | 1.06 (1.04–1.09) | <0.001 | 1.06 (1.03–1.08) | <0.001 |
| Amiodarone use before HT | 2.15 (1.14–4.07) | 0.018 | 1.73 (0.90–3.29) | 0.10 |
| Total ischaemic time (min) | 1.01 (1.01–1.02) | <0.001 | 1.01 (1.01–1.02) | <0.001 |
| Rejections[a] | 0.56 (0.27–1.17) | 0.12 | | |
| Predictors late PM[b] | | | | |
| Age at HT | 0.98 (0.97–1.00) | 0.036 | 0.97 (0.95–0.99) | <0.001 |
| Donor age | 1.03 (1.01–1.05) | 0.005 | 1.04 (1.02–1.07) | 0.001 |
| Amiodarone use before HT | 1.06 (0.61–1.84) | 0.83 | | |
| Ischaemic time (min) | 1.00 (1.00–1.01) | 0.35 | | |
| Rejections[a] | 1.01 (0.54–1.87) | 0.99 | | |
| CAV Grade 2 or 3[a] | 4.30 (2.36–7.82) | <0.001 | 3.71 (2.03–6.77) | <0.001 |

CAV, cardiac allograft vasculopathy; CI, confidence interval; HR, hazard ratio; HT, heart transplantation; PM, permanent pacemaker.
[a]Number of rejection or grade of CAV before pacemaker implantation in patients with a PM.
[b]Excluding patients with an early PM.

For late PM implantation, recipient age ($P = 0.036$), donor age ($P = 0.005$), and CAV Grade 2 or 3 ($P < 0.001$) were predictors in univariate Cox analysis. On the other hand, amiodarone use before HT ($P = 0.83$), ischaemia time ($P = 0.35$), and rejections ($P = 0.99$) were not. In the multivariable analysis, recipient age [HR 0.97 (0.95–0.99), $P < 0.001$], donor age [HR 1.04 (1.02–1.07), $P = 0.001$], and CAV grade [HR 3.71 (2.03–6.77), $P < 0.001$] remained significant predictors for late PM implantation when all recipients were included. When paediatric patients (age <18 years) were excluded, donor age ($P < 0.001$), recipient age ($P < 0.001$), and amiodarone use before HT ($P = 0.045$) were independent predictors of early PM implantation in multivariable analysis (*Table 4B*). For late PM implantation, only donor age ($P = 0.024$) and CAV grade ($P < 0.001$) were independent risk factors.

## Survival after heart transplantation

The median survival in the cohort was 13.3 [IQR 12.3–14.3] years. In an extended Cox regression model, PM implantation was used as a time-dependent variable to determine whether a PM after HT impaired the survival after HT. When including all PMs after HT, there was an increased risk of mortality in patients who received a PM with a HR of 1.49 [95% confidence interval (CI) 1.09–2.04, $P = 0.014$] when corrected for recipient age, recipient sex, heart failure aetiology, renal function before HT, and diabetes before HT. When the same analysis was performed only for patients with an early PM, no significant difference was observed [HR 0.77 (95% CI 0.41–1.44), $P = 0.41$]. However, patients who received a PM late after HT had an increased risk for death [HR 2.05 (95% CI 1.43–2.93), $P < 0.001$].

**Table 4B** Predictors of early (≤90 days after HT) and late (>90 days after HT) permanent pacemaker implantation for recipients >18 years old

| Parameters | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Predictors early PM | | | | |
| Age at HT | 1.01 (0.98–1.04) | 0.60 | | |
| Donor age | 1.07 (1.04–1.10) | <0.001 | 1.06 (1.03–1.09) | <0.001 |
| Amiodarone use before HT | 2.47 (1.25–4.89) | 0.009 | 2.02 (1.02–4.03) | 0.045 |
| Total ischaemic time (min) | 1.01 (1.01–1.02) | <0.001 | 1.01 (1.01–1.02) | <0.001 |
| Rejections[a] | 0.52 (0.24–1.13) | 0.10 | | |
| Predictors late PM[b] | | | | |
| Age at HT | 0.99 (0.96–1.01) | 0.32 | | |
| Donor age | 1.04 (1.01–1.06) | 0.005 | 1.03 (1.01–1.05) | 0.024 |
| Amiodarone use before HT | 1.21 (0.67–2.17) | 0.53 | | |
| Ischaemic time (min) | 1.00 (1.00–1.01) | 0.33 | | |
| Rejections[a] | 1.15 (0.56–2.39) | 0.71 | | |
| CAV Grade 2 or 3[a] | 4.16 (2.14–8.06) | <0.001 | 3.59 (1.86–6.95) | <0.001 |

CAV, cardiac allograft vasculopathy; CI, confidence interval; HR, hazard ratio; HT, heart transplantation; PM, permanent pacemaker.
[a]Number of rejection or grade of CAV before pacemaker implantation in patients with a PM.
[b]Excluding patients with an early PM.

# Discussion

In this study, the effect of risk factors on early and late PM implantations after HT and the subsequent effect on survival were studied. The most common indication for early PM implantation was SND while AVB was more frequent in late PM implantation. Patients who had an older donor had an increased risk to have a PM implanted both early and late after HT. Furthermore, prolonged ischaemic time increased the risk for early PM implantation, while amiodarone use only did in adult recipients. Patients with an older donor heart and patients with CAV grade ≥2 had a higher risk to have a late PM implanted. Only patients who received a PM late after HT had an impaired survival.

## Incidence of permanent pacemakers

The incidence of PM implantation after HT in literature varies between 2% and 24%.[1–5,7–9,19,20] Our incidence of 14% is in accordance with this. This variation can be explained by several factors such as difference in follow-up duration, inclusion of paediatric patients, average donor age, and local policy on PM indications. In our study, the median time until late PM implantation was 7.6 years. This is significantly longer than all other studies, also due to the longer follow-up period. Even though the number of PM implantations remained stable over time, the number of early PM implantations increased while the number of late PM implantations declined. The increase in early PM implantations could be explained by the increased ischaemia time in combination with reduced resilience to ischaemia–reperfusion injury in older donors.[10] The decrease in late PM implantations is most likely due to the shorter follow-up in the recent era. Other studies with at least 70% of patients transplanted biatrially demonstrated PM incidences of 24.0% (70% biatrial),[1] 10.9% (78% biatrial),[9] and 11.5% (90.6% biatrial).[3] These incidences are comparable with our incidence, while the follow-up period is significantly shorter in two of them.[1,9] The difference in incidence could also be because bicaval HTs are associated with decreased early PM implantations.[15] However, one study with only bicavally transplanted recipients demonstrated a PM rate of 20.5%.[7] The authors claimed that due to the increasing donor age, the advantage of transplanting with the bicaval technique over the biatrial technique was diminished.

## Indication for permanent pacemakers

The main reasons for PM implantations are SND and AVB. Our results are consistent with literature that SND is more frequently seen early after HT, while AVB is more seen in the long term.[2–4] One study demonstrated more AVB as the indication for both early and late PMs; however, due to missing baseline characteristics, the reason for this cannot be determined.[20] SND early after HT can be due to ischaemia or even sinus node damage due to the surgical technique.[6] AVB late after HT can be related to degeneration due to increased donor age, myocardial ischaemia, infarction caused by CAV, and rejections.[6]

## Risk factors of permanent pacemakers

In our study, the risk factors for early PM implantation were donor age, total ischaemic time, and (in adults) amiodarone use before HT, while donor age and CAV grade were risk factors for a late PM. Several studies have demonstrated that donor age is a significant risk factor for both early and late PM implantation.[2,7–9] Possibly, the older donor hearts are more susceptible for ischaemia and reperfusion injury, which could increase the risk for early PM.[10] Furthermore, during follow-up, several factors can influence the conduction system (i.e. rejections, ischaemia due to CAV, and diabetes), which could lead to a PM implantation.[6]

The reason why age was protective for the whole study population, but not in adults, is probably due to the paediatric recipients who needed a PM long term after HT. Although in literature the incidence of PM in children after HT is low,[19] long-term studies are missing. Young recipients mostly receive hearts from young donors, decreasing the chance of a PM early after HT. However, when the years go by, CAV can develop in those hearts as well increasing the PM risk. As demonstrated in our study, CAV grade ≥2 significantly increased the risk of PM implantation. Although rarely studied, the studies that did test for CAV found no significant difference in patients with or without PM.[1,2,9] However, in contrast to other studies, we included CAV as a time-dependent variable in a multivariable model, while other studies only performed univariate tests with limited follow-up data. Furthermore, most studies had a follow-up period of approximately 6 years, which could mean that the incidence of CAV was too low to detect significant differences because 50% of patients have CAV 10 years after HT.[11]

The fact that amiodarone before HT was not a risk factor for the entire cohort but is a risk factor specifically for adults can be explained by the low use of amiodarone in children. Due to the fact that children are more often affected by cardiomyopathies and congenital cardiac abnormalities and not so much by ischaemic cardiomyopathy, the need for amiodarone use in these recipients is less before HT.[19]

Ischaemic time during transplantation was another predictor for early PM implantation. Recently, other studies have found no relationship between ischaemic time and PM implantation,[1–3,5,7,9] while it has been suggested as a potential risk factor.[6] However, most of these studies did not divide the groups into early and late PM, lacked power to perform a

multivariable analysis, or were mainly bicaval transplants. It is known that ischaemic time with the bicaval technique is longer than biatrial transplantation.[15] However, the fact that ischaemic time is increased during biatrial surgery could indicate a difficult procedure, which could increase the risk for damage to the conduction system. This in combination with the increased risk of sinus node ischaemia during the transplantation could explain why ischaemia is a risk factor for early PM implantation.[6]

### Survival after permanent pacemaker implantation

Most studies have found no survival difference between patients with or without PM,[2–4,7] while one study demonstrated an improved survival after PM implantation.[9] In contrast, one study found that patients with an early PM had the worst survival, followed by patients with no PM and the best survival in patients with a late PM.[4] Another study demonstrated no survival benefit for late PM.[2] This is in contrast to our findings, since we found no diminished survival after early PM implantation and an impaired survival for patients with a late PM. One of the issues of the other studies that look at survival is that Kaplan–Meier curves were used to compare survival (with the follow-up starting at the moment of the transplantation). However, this method can lead to the introduction of immortal time bias.[21] Patients first need to survive a certain period after HT and receive a PM during follow-up (and thus be 'immortal') before being classified as having a late PM. We believe that late PM implantation is an indicator for progressive cardiac disease (i.e. fibrosis after rejection and CAV), thus impairing the patient survival.

### Limitations

This study has several limitations. First of all, the single-centre and retrospective nature implies limitations on its own. Furthermore, the follow-up duration of patients with a donor >40 years old was shorter than patients with a younger donor. Moreover, almost all patients in our centre are transplanted biatrially, which meant we could not correct for surgical technique in relation to PM implantation risk, especially in the early post-operative phase. This also limits the wider applicability of the results to centres who (mainly) perform bicaval HT, in which a decreased need for PM is shown.

## Conclusions

In conclusion, older donor hearts significantly increased the number of patients who needed a PM after HT, as did longer transplantation ischaemic time, and adult recipients with before HT amiodarone. The development of CAV significantly increased the risk for late PM implantation. Early permanent PM implantations did not compromise survival, while late PM was associated with diminished long-term survival, probably due to the development of CAV and other comorbidities.

## Conflict of interest

None declared.

## Funding

None.

## References

1. Woo GW, Schofield RS, Pauly DF, Hill JA, Conti JB, Kron J, Klodell CT, Singh R, Aranda JM Jr. Incidence, predictors, and outcomes of cardiac pacing after cardiac transplantation: an 11-year retrospective analysis. *Transplantation* 2008; **85**: 1216–1218.
2. Jones DG, Mortsell DH, Rajaruthnam D, Hamour I, Hussain W, Markides V, Banner NR, Wong T. Permanent pacemaker implantation early and late after heart transplantation: clinical indication, risk factors and prognostic implications. *J Heart Lung Transplant* 2011; **30**: 1257–1265.
3. Wellmann P, Herrmann FE, Hagl C, Juchem G. A single center study of 1,179 heart transplant patients—factors affecting pacemaker implantation. *Pacing Clin Electrophysiol* 2017; **40**: 247–254.
4. Rivinius R, Helmschrott M, Rahm AK, Darche FF, Thomas D, Bruckner T, Doesch AO, Ehlermann P, Katus HA, Zitron E. Risk factors and survival of patients with permanent pacemaker implantation after heart transplantation. *J Thorac Dis* 2019; **11**: 5440–5452.
5. Ustunkaya T, Liang JJ, Lin AN, Shirai Y, Molina M, Owens AT, Acker MA, Bermudez CA, Santangeli P, Nazarian S, Dixit S, Marchlinski FE, Callans DJ. Clinical and procedural characteristics predicting need for chronotropic support and permanent pacing post-heart transplantation. *Heart Rhythm* 2020; **17**: 1132–1138.
6. Thajudeen A, Stecker EC, Shehata M, Patel J, Wang X, McAnulty JH Jr, Kobashigawa J, Chugh SS. Arrhythmias after heart transplantation: mechanisms and management. *J Am Heart Assoc* 2012; **1**: e001461.
7. Zieroth S, Ross H, Rao V, Delgado DH, Cusimano RJ, Thevarajah M, Cameron DA, Nanthakumar K. Permanent pacing after cardiac transplantation in the era of extended donors. *J Heart Lung Transplant* 2006; **25**: 1142–1147.
8. Mallidi HR, Bates M. Pacemaker use following heart transplantation. *Ochsner J* 2017; **17**: 20–24.
9. Cantillon DJ, Tarakji KG, Hu T, Hsu A, Smedira NG, Starling RC, Wilkoff BL, Saliba WI. Long-term outcomes and clinical predictors for pacemaker-requiring

bradyarrhythmias after cardiac transplantation: analysis of the UNOS/OPTN cardiac transplant database. *Heart Rhythm* 2010; **7**: 1567–1571.
10. Liu M, Zhang P, Chen M, Zhang W, Yu L, Yang XC, Fan Q. Aging might increase myocardial ischemia/reperfusion-induced apoptosis in humans and rats. *Age (Dordr)* 2012; **34**(3):621–632.
11. Khush KK, Cherikh WS, Chambers DC, Harhay MO, Hayes D Jr, Hsich E, Meiser B, Potena L, Robinson A, Rossano JW, Sadavarte A, Singh TP, Zuckermann A, Stehlik J, International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report—2019; focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019; **38**: 1056–1066.
12. Zijlstra LE, Constantinescu AA, Manintveld O, Birim O, Hesselink DA, van Thiel R, van Domburg R, Balk AH, Caliskan K. Improved long-term survival in Dutch heart transplant patients despite increasing donor age: the Rotterdam experience. *Transpl Int* 2015; **28**: 962–971.
13. Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. *Surg Forum* 1960; **11**: 18–19.
14. Yacoub M, Mankad P, Ledingham S. Donor procurement and surgical techniques for cardiac transplantation. *Semin Thorac Cardiovasc Surg* 1990; **2**: 153–161.
15. Zijderhand CF, Veen KM, Caliskan K, Schoonen T, Mokhles MM, Bekkers JA, Manintveld OC, Constantinescu AA, Brugts JJ, Bogers A, Takkenberg JJM. Biatrial versus bicaval orthotopic heart transplantation: a systematic review and meta-analysis. *Ann Thorac Surg* 2020; **110**: 684–691.
16. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, Andersen CB, Angelini A, Berry GJ, Burke MM, Demetris AJ, Hammond E, Itescu S, Marboe CC, McManus B, Reed EF, Reinsmoen NL, Rodriguez ER, Rose AG, Rose M, Suciu-Focia N, Zeevi A, Billingham ME. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant* 2005; **24**: 1710–1720.
17. Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, Madsen J, Parameshwar J, Starling RC, Uber PA. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *J Heart Lung Transplant* 2010; **29**: 717–727.
18. Nous FMA, Roest S, van Dijkman ED, Attrach M, Caliskan K, Brugts JJ, Nieman K, Hirsch A, Constantinescu AA, Manintveld OC, Budde RPJ. Clinical implementation of coronary computed tomography angiography for routine detection of cardiac allograft vasculopathy in heart transplant patients. *Transpl Int* 2021; **34**: 1886–1894.
19. Mylonas KS, Repanas T, Athanasiadis DI, Voulgaridou A, Sfyridis PG, Bakoyiannis C, Kapelouzou A, Avgerinos DV, Tzifa A, Kalangos A. Permanent pacemaker implantation in pediatric heart transplant recipients: a systematic review and evidence quality assessment. *Pediatr Transplant* 2020; **24**: e13698.
20. Noworolski R, Przybylowski P, Majewski J, Sadowski J, Lelakowski J. Early and late indications for implantation of cardiac pacemakers in patients after heart transplantation: a single-center experience. *Transplant Proc* 2011; **43**: 3074–3075.
21. Gleiss A, Oberbauer R, Heinze G. An unjustified benefit: immortal time bias in the analysis of time-dependent events. *Transpl Int* 2018; **31**: 125–130.