

Combined amiodarone and digitalis therapy before heart transplantation is associated with increased post-transplant mortality

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Abstract

Aims Amiodarone and digitalis are frequently used drugs in patients with heart failure. Both have separately been linked to reduced post-transplant survival, but their combined impact on mortality after HTX remains uncertain. This study investigated the effects of combined amiodarone and digitalis use before HTX on post-transplant outcomes.

Methods and results This registry study analysed 600 patients receiving HTX at Heidelberg Heart Center between 1989 and 2016. Patients were stratified by amiodarone and digitalis use before HTX. Analysis included patient characteristics, medication, echocardiographic features, heart rates, permanent pacemaker implantation, atrial fibrillation, and post-transplant survival including causes of death. One hundred eighteen patients received amiodarone before HTX (19.7%), hereof 67 patients with digitalis (56.8%) and 51 patients without digitalis before HTX (43.2%). Patients with and without amiodarone before HTX showed a similar 1 year post-transplant survival (72.0% vs. 78.4%, $P = 0.11$), but patients with combined amiodarone and digitalis before HTX had a worse 1 year post-transplant survival (64.2%, $P = 0.01$), along with a higher percentage of death due to transplant failure ($P = 0.03$). Echocardiographic analysis of these patients showed a higher percentage of an enlarged right ventricle ($P = 0.02$), left atrium ($P = 0.02$), left ventricle ($P = 0.03$), and a higher rate of reduced left ventricular ejection fraction ($P = 0.03$). Multivariate analysis indicated combined amiodarone and digitalis use before HTX as a significant risk factor for 1 year mortality after HTX (hazard ratio: 1.69; 95% confidence interval: 1.02–2.77; $P = 0.04$).

Conclusions Combined pre-transplant amiodarone and digitalis therapy is associated with increased post-transplant mortality.

Keywords Amiodarone; Digitalis; Digoxin; Digitoxin; Heart transplantation; Mortality

Received: 18 March 2020; Revised: 4 May 2020; Accepted: 14 May 2020

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Introduction

Amiodarone is a frequently used drug for the treatment of life-threatening arrhythmias in patients with end-stage heart failure (HF) awaiting heart transplantation (HTX).^{1–5} In patients with long-term use, amiodarone is extensively distributed into the body's tissues resulting in a reported half-life of about 3 months.^{6–9} As a result of this long half-life,

the cardiac allograft is exposed to a certain degree of amiodarone in the early post-transplant period.¹⁰

Although amiodarone has been used in clinical practice for many years, a recent publication of the International Society for Heart and Lung Transplantation (ISHLT) postulated an association between pre-transplant use of amiodarone and increased 1 year mortality after HTX.¹¹ As the authors state in the study limitations, the ISHLT Registry analysis included

patients with reported pre-transplant amiodarone use lacking important information about continuity, duration, dose, and indication for amiodarone therapy.¹¹ In contrast, two other large studies recently showed no reduced 1 year post-transplant survival in patients with long-term amiodarone use before HTX.^{3,5} Besides mortality, there is a controversy whether pre-transplant amiodarone use is associated with bradycardia and increased requirement for permanent pacemaker (PPM) implantation after HTX.^{4,12–14}

Patients with end-stage HF awaiting HTX often receive digitalis (digoxin/digitoxin) in combination with amiodarone. Amiodarone is known to raise serum concentrations of digitalis.^{15,16} In the light of the narrow therapeutic window of digitalis, elevated serum levels of digitalis have been linked to increased mortality.^{17,18} Moreover, digitalis therapy in patients before HTX has been reported as an independent risk factor for increased post-transplant mortality.¹⁹ However, the impact of a combined amiodarone and digitalis therapy before HTX on post-transplant mortality remains uncertain.

The aim of this study was to investigate the effects of combined amiodarone and digitalis use before HTX on post-transplant outcomes focusing on post-transplant mortality with causes of death, post-transplant echocardiographic features, early post-transplant atrial fibrillation (AF), course of heart rates, and PPM implantation after HTX.

Patients and methods

Patients

This study was performed in accordance with the ethical standards of the Declaration of Helsinki. Approval was granted by the institutional review board of Heidelberg University (ethical approval number: S-286/2015). Written informed consent was obtained from patients for inclusion in the Heidelberg HTX Registry allowing the clinical and scientific use of data. In accordance with the ethical approval, no additional written informed consent was required for this observational study as only routine clinical data were analysed.^{3,4,19–23}

All adult patients (≥ 18 years) receiving HTX at Heidelberg Heart Center, Heidelberg, Germany, between 1989 and 2016 were included in this study except for patients with repeated cardiac transplantation. Patients were initially stratified by amiodarone therapy before HTX: patients with continuous amiodarone use ≥ 90 days before HTX ('amiodarone group') and patients without continuous amiodarone use ≥ 90 days before HTX ('no amiodarone group'). Patients with intermittent amiodarone use or amiodarone therapy < 90 days before HTX were included in the no amiodarone group. Patients in the amiodarone group were further stratified into patients receiving amiodarone without digitalis therapy before HTX and patients with combined amiodarone and digitalis therapy

before HTX (digitalis use ≥ 90 days before HTX). Additionally, daily dosage (milligrams) and duration (months) of pre-transplant amiodarone and digitalis treatment were assessed. Indications for pre-transplant amiodarone use included ventricular fibrillation, ventricular tachycardia, Wolff–Parkinson–White syndrome, and AF. Indication for digitalis therapy before HTX was HF with or without AF.^{3,4}

Follow-up

Patients received standard of care by the medical team of Heidelberg Heart Center. During the initial hospital stay, patients were continuously supervised by telemetry monitoring and 12-lead electrocardiography was performed on a regular basis and in cases of suspected arrhythmias. Before discharge, 24 h Holter was routinely performed. Diagnosis of early post-transplant AF (≤ 30 days after HTX) was based upon all available records pertaining to heart rhythm in the early post-transplant period.^{3,4,19–23}

After the initial hospital stay, patients presented at our HTX outpatient clinic for follow-up. Patients were seen monthly during the first 6 months after HTX, then bimonthly until the end of the first year, and thereafter usually three to four times per year (or if clinically indicated). Routine follow-up included medical history, physical examination, 12-lead electrocardiogram, echocardiography, and routine laboratory analysis including immunosuppressive drug monitoring.^{3,4,19–23}

Post-transplant medication

Post-transplant medication including immunosuppressive drug therapy was administered in accordance to centre standard. Patients initially received an anti-thymocyte globulin-based immunosuppression induction therapy after HTX. Cyclosporine A and azathioprine were used as the initial immunosuppressive drug therapy at the beginning of the study period. From 2001 onward, azathioprine was subsequently substituted by mycophenolate mofetil, and cyclosporine A was consecutively replaced by tacrolimus from 2006 onward. Steroids (prednisolone) were tapered incrementally during the first post-transplant months and were finally discontinued 6 months after HTX (if clinically possible).^{3,4,19–23}

Statistical analysis

Data were analysed with SAS (version 9.4, SAS Institute, Cary, NC, USA) and expressed as mean \pm standard deviation or as count (n) with percentage (%). Mean difference (MD) or hazard ratio (HR) with 95% confidence interval (CI) were used as measures of association. Student's t -test was used for continuous variables and χ^2 test for categorical variables.

Kaplan–Meier estimator was employed to graphically display 1 year post-transplant survival. A *P*-value of <0.05 was considered statistically significant.^{3,4,19–23}

Substantial univariate analyses were performed to search for intergroup differences including recipient data, previous open-heart surgery, principal diagnosis for HTX, donor data, transplant sex mismatch, perioperative data, immunosuppressive drug therapy, post-transplant medication, post-transplant echocardiographic features, early post-transplant AF, course of heart rates, and PPM implantation after HTX. Causes of death within 1 year after HTX were investigated with the following categories: transplant failure, acute rejection, infection/sepsis, malignancy, and thromboembolic event/bleeding. Analysis of 1 year post-transplant mortality after HTX further included a multivariate analysis (Cox regression model) with the following five clinically relevant parameters based on a predetermined model: combined amiodarone and digitalis therapy before HTX (in total), no amiodarone use before HTX (in total), cyclosporine A use after HTX (in total), cardiac amyloidosis as principal diagnosis for HTX (in total), and ischaemic time (min). We did not include additional parameters in this multivariate analysis to avoid biased regression coefficients and to ensure a stable number of events (deceased patients) per analysed variable. Given the long study period, a sensitivity analysis was carried out to test the robustness of the study results and to investigate a possible era effect using a subgroup of patients with cyclosporine A and azathioprine as immunosuppressive drug regimen as the immunosuppressive drug therapy was switched from 2006.^{3,4,19–23}

The primary outcome of this study was mortality after HTX. Secondary outcomes included post-transplant echocardiographic features, early post-transplant AF, heart rates, and PPM implantation after HTX.

Results

Indication, duration, and daily dose of drug therapy

This study comprised a total of 600 patients: 118 patients were in the amiodarone group (19.7%) and 482 patients were in the no amiodarone group (80.3%). Patients with amiodarone use prior to HTX were further subdivided into 67 patients with additional digitalis before HTX (56.8%) and 51 patients without digitalis before HTX (43.2%).

Indications for amiodarone use before HTX covered AF in 24 patients (20.3%), Wolff–Parkinson–White syndrome in one patient (0.9%), ventricular tachycardia in 85 patients (72.0%), and ventricular fibrillation in eight patients (6.8%). In patients with combined amiodarone and digitalis therapy before HTX, 31 patients received digoxin (46.3%) and 36

patients received digitoxin (53.7%). Indications for digitalis in combination with amiodarone before HTX were HF in 33 patients (49.3%) and HF with AF in 34 patients (50.7%).

Mean duration of amiodarone therapy before HTX was 25.2 ± 26.9 months, ranging from 3 to 168 months. Mean daily amiodarone dose was 218.6 ± 75.9 mg, ranging from 100 to 600 mg per day. In patients with combined amiodarone and digitalis therapy before HTX, mean duration of digitalis therapy before HTX was 23.3 ± 20.7 months, ranging from 3 to 135 months. Of these, patients with digoxin before HTX had a mean daily dose of 0.19 ± 0.07 mg and a mean duration of intake of 26.4 ± 25.2 months, ranging from 5 to 135 months. Patients with digitoxin before HTX had a mean daily dose of 0.08 ± 0.01 mg and a mean duration of intake of 20.6 ± 15.4 months, ranging from 3 to 68 months.

Demographics and medication after heart transplantation

Patients with and without amiodarone before HTX showed no statistically significant differences in recipient data, previous open-heart surgery of the recipient, donor data, transplant sex mismatch, or perioperative data (all $P \geq 0.05$). Regarding the principal diagnosis for HTX, significantly more patients with cardiac amyloidosis were found in the no amiodarone group (45 of 482 [9.3%] vs. 3 of 118 [2.5%]; MD: 6.8%, 95% CI: 2.9–10.7%; $P = 0.01$), whereas there was no statistically significant difference between both groups with respect to ischaemic cardiomyopathy (CMP), non-ischaemic CMP, or valvular CMP (all $P \geq 0.05$). Baseline characteristics are shown in *Table 1*.

Analysis of the immunosuppressive drug regimen revealed a higher percentage of tacrolimus in patients with amiodarone before HTX (64 of 118 (54.2%) vs. 191 of 482 (39.6%); MD: 14.6%, 95% CI: 4.6–24.6%; $P < 0.01$) and accordingly a higher rate of cyclosporine A in patients without amiodarone before HTX (291 of 482 (60.4%) vs. 54 of 118 (45.8%); MD: 14.6%, 95% CI: 4.6–24.6%; $P < 0.01$). No statistically significant differences between groups could be detected regarding azathioprine or mycophenolate mofetil (both $P \geq 0.05$). Additionally, there were no statistically significant differences in the administration of acetylsalicylic acid, beta-blockers, ivabradine, calcium channel blockers, angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers, or statins (all $P \geq 0.05$). Medication after HTX is given in *Table 2*.

Primary outcome after heart transplantation

Patients with and without amiodarone before HTX showed a similar 1 year post-transplant survival in the Kaplan–Meier estimator indicating no statistically significant effect of amiodarone use before HTX on post-transplant survival (72.0% vs. 78.4%, $P = 0.11$). Further stratification of the amiodarone

Table 1 Baseline characteristics

	All (n = 600)	No amiodarone before HTX (n = 482)	Amiodarone before HTX (n = 118)	Difference	95% CI	P-value
Recipient data						
Age (years), mean ± SD	51.9 ± 10.4	51.8 ± 10.5	52.2 ± 10.2	0.4 years	−1.7 to 2.5 years	0.73
Male sex, n (%)	470 (78.3%)	375 (77.8%)	95 (80.5%)	2.7%	−5.4 to 10.8%	0.52
Body mass index (kg/m ²), mean ± SD	24.9 ± 4.0	24.7 ± 3.9	25.4 ± 4.0	0.7 kg/m ²	−0.1 to 1.5 kg/m ²	0.08
Arterial hypertension, n (%)	327 (54.5%)	258 (53.5%)	69 (58.5%)	5.0%	−5.0 to 15.0%	0.33
Dyslipidaemia, n (%)	383 (63.8%)	301 (62.4%)	82 (69.5%)	7.1%	−2.3 to 16.5%	0.15
Diabetes mellitus, n (%)	207 (34.5%)	165 (34.2%)	42 (35.6%)	1.4%	−8.2 to 11.0%	0.78
Renal insufficiency ^a , n (%)	349 (58.2%)	273 (56.6%)	76 (64.4%)	7.8%	1.9 to 17.5%	0.13
eGFR (mL/min/1.73 m ²), mean ± SD	60.1 ± 21.6	60.8 ± 21.3	57.0 ± 22.2	3.8 mL/min/ 1.73 m ²	−0.7 to 8.3 mL/min/ 1.73 m ²	0.10
Previous open-heart surgery						
Overall open-heart surgery, n (%)	169 (28.2%)	138 (28.6%)	31 (26.3%)	2.3%	−6.6 to 11.2%	0.61
CABG surgery, n (%)	76 (12.7%)	64 (13.3%)	12 (10.2%)	3.1%	−3.1 to 9.3%	0.36
Other surgery ^b , n (%)	69 (11.5%)	58 (12.0%)	11 (9.3%)	2.7%	−3.3 to 8.7%	0.41
VAD surgery, n (%)	33 (5.5%)	23 (4.8%)	10 (8.5%)	3.7%	−1.7 to 9.1%	0.11
Principal diagnosis for HTX						
Ischaemic CMP, n (%)	199 (33.2%)	156 (32.4%)	43 (36.5%)	4.1%	−5.5 to 13.7%	0.40
Non-ischaemic CMP, n (%)	319 (53.1%)	250 (51.9%)	69 (58.5%)	6.6%	−3.3 to 16.5%	0.20
Valvular heart disease, n (%)	34 (5.7%)	31 (6.4%)	3 (2.5%)	3.9%	−0.3 to 8.1%	0.10
Cardiac amyloidosis, n (%)	48 (8.0%)	45 (9.3%)	3 (2.5%)	6.8%	2.9 to 10.7%	0.01*
Donor data						
Age (years), mean ± SD	40.7 ± 13.4	40.5 ± 13.5	41.6 ± 13.2	1.1 years	−1.6 to 3.8 years	0.42
Male sex, n (%)	261 (43.5%)	211 (43.8%)	50 (42.4%)	1.4%	−8.6 to 11.4%	0.78
Body mass index (kg/m ²), mean ± SD	24.7 ± 4.0	24.6 ± 3.9	25.1 ± 4.1	0.5 kg/m ²	−0.3 to 1.3 kg/m ²	0.20
Transplant sex mismatch						
Mismatch, n (%)	266 (44.4%)	212 (44.0%)	54 (45.8%)	1.8%	−8.2 to 11.8%	0.73
Donor (m) to recipient (f), n (%)	28 (4.7%)	24 (5.0%)	4 (3.4%)	1.6%	−2.2 to 5.4%	0.46
Donor (f) to recipient (m), n (%)	238 (39.7%)	188 (39.0%)	50 (42.4%)	3.4%	−6.5 to 13.3%	0.50
Perioperative data						
Ischaemic time (min), mean ± SD	219.6 ± 67.7	218.6 ± 66.6	223.7 ± 72.0	5.1 min	−9.3 to 19.5 min	0.49
Biatlial HTX, n (%)	164 (27.3%)	135 (28.0%)	29 (24.6%)	3.4%	−5.3 to 12.1%	0.45
Bicaval HTX, n (%)	163 (27.2%)	129 (26.8%)	34 (28.8%)	2.0%	−7.0 to 11.0%	0.65
Total orthotopic HTX, n (%)	273 (45.5%)	218 (45.2%)	55 (46.6%)	1.4%	−8.6 to 11.4%	0.79

CABG, coronary artery bypass graft; CMP, cardiomyopathy; eGFR, estimated glomerular filtration rate; f, female; HTX, heart transplantation; m, male; n, number; SD, standard deviation; VAD, ventricular assist device.

^aeGFR < 60 mL/min/1.73 m².

^bCongenital, valvular, or ventricular surgery.

*Statistically significant ($P < 0.05$).

group showed a significantly lower 1 year post-transplant survival in patients with combined amiodarone and digitalis therapy before HTX (64.2%) in comparison with patients receiving amiodarone without digitalis before HTX (82.4%) or patients without amiodarone before HTX (78.4%, $P = 0.01$). Kaplan–Meier estimators are displayed in *Figures 1* and *2*.

Concerning the causes of death within 1 year after HTX, significantly more patients with combined amiodarone and digitalis therapy before HTX deceased from transplant failure (13.4%, $P = 0.03$) in comparison with patients receiving amiodarone without digitalis before HTX (0.0%) or patients without amiodarone before HTX (9.1%). Moreover, patients with combined amiodarone and digitalis therapy before HTX had a higher percentage of death due to infection/sepsis in

general ($P < 0.01$) and abdominal infections ($P = 0.01$). There was no significant difference between the three groups regarding acute rejection, malignancy, pulmonary infection, or thromboembolic event/bleeding (all $P \geq 0.05$). Causes of death within 1 year after HTX are presented in *Table 3*.

Multivariate analysis revealed a significantly increased risk for 1 year mortality in patients with combined amiodarone and digitalis therapy before HTX (HR: 1.69, 95% CI: 1.02–2.77; $P = 0.04$), whereas the other variables (no amiodarone use before HTX, cyclosporine A use after HTX, cardiac amyloidosis as principal diagnosis for HTX, and ischaemic time) showed no statistically significant effects on post-transplant mortality. Multivariate analysis for 1 year mortality after HTX is shown in *Table 4*.

Table 2 Medication after HTX

	All (n = 600)	No amiodarone before HTX (n = 482)	Amiodarone before HTX (n = 118)	Difference	95% CI	P-value
Cyclosporine A, n (%)	345 (57.5%)	291 (60.4%)	54 (45.8%)	14.6%	4.6 to 24.6%	<0.01*
Tacrolimus, n (%)	255 (42.5%)	191 (39.6%)	64 (54.2%)	14.6%	4.6 to 24.6%	<0.01*
Azathioprine, n (%)	267 (44.5%)	223 (46.3%)	44 (37.3%)	9.0%	−0.8 to 18.8%	0.08
Mycophenolate mofetil, n (%)	333 (55.5%)	259 (53.7%)	74 (62.7%)	9.0%	−0.8 to 18.8%	0.08
Steroids, n (%)	600 (100.0%)	482 (100.0%)	118 (100.0%)	0.0%	n.a.	n.a.
ASA, n (%)	57 (9.5%)	45 (9.3%)	12 (10.2%)	0.9%	−5.1 to 6.9%	0.78
Beta-blocker, n (%)	106 (17.7%)	92 (19.1%)	14 (11.9%)	7.2%	−0.4 to 14.8%	0.07
Ivabradine, n (%)	46 (7.7%)	37 (7.7%)	9 (7.6%)	0.1%	−5.3 to 5.5%	0.99
Calcium channel blocker	153 (25.5%)	126 (26.1%)	27 (22.9%)	3.2%	−5.3 to 11.7%	0.47
ACE inhibitor/ARB, n (%)	262 (43.7%)	218 (45.2%)	44 (37.3%)	7.9%	−1.9 to 17.7%	0.12
Diuretic, n (%)	600 (100.0%)	482 (100.0%)	118 (100.0%)	0.0%	n.a.	n.a.
Statin, n (%)	227 (37.8%)	183 (38.0%)	44 (37.3%)	0.7%	−9.0 to 10.4%	0.89
Gastric protection (PPI/H ₂ blocker), n (%)	600 (100.0%)	482 (100.0%)	118 (100.0%)	0.0%	n.a.	n.a.

ACE inhibitor, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; H₂ blocker, histamine receptor blocker; n, number; n.a., not applicable; PPI, proton pump inhibitor.

*Statistically significant ($P < 0.05$).

Secondary outcomes after heart transplantation

Assessment of echocardiographic features showed a lower percentage of normal sized right ventricular ($P = 0.02$), left atrial ($P = 0.02$), and left ventricular end-diastolic diameter ($P = 0.03$) along with a higher rate of reduced left ventricular ejection fraction ($P = 0.03$) in patients with combined amiodarone and digitalis therapy before HTX. No statistically significant difference between groups was observed in right atrial end-diastolic diameter, mitral regurgitation, or tricuspid regurgitation (all $P \geq 0.05$). Echocardiographic features after HTX are presented in *Table 5*.

Mean heart rates during week 1–4 after HTX, occurrences of bradycardia during week 1–4 after HTX (mean weekly

heart rate < 60 b.p.m.), or 30-day PPM implantation after HTX showed no statistically significant difference between groups (all $P \geq 0.05$). Patients without amiodarone before HTX had a higher rate of 30-day post-transplant AF (14.7%, $P = 0.03$) than patients receiving amiodarone with (4.5%) or without digitalis before HTX (7.8%). Data regarding heart rates, bradycardia, PPM implantation, and AF after HTX are given in *Table 6*.

Sensitivity analysis

A sensitivity analysis to test the robustness of the study results and to investigate a possible era effect was performed

FIGURE 1 One year survival after HTX in patients with and without amiodarone before HTX (Kaplan–Meier estimator). Patients with and without amiodarone before HTX showed a similar 1 year post-transplant survival in the Kaplan–Meier estimator indicating no statistically significant negative effect of amiodarone before HTX on post-transplant survival (72.0% vs. 78.4%, $P = 0.11$). HTX, heart transplantation. *Statistically significant ($P < 0.05$).

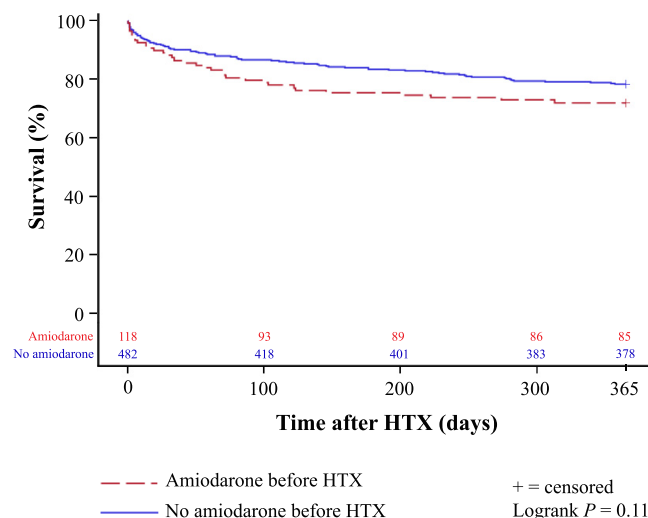
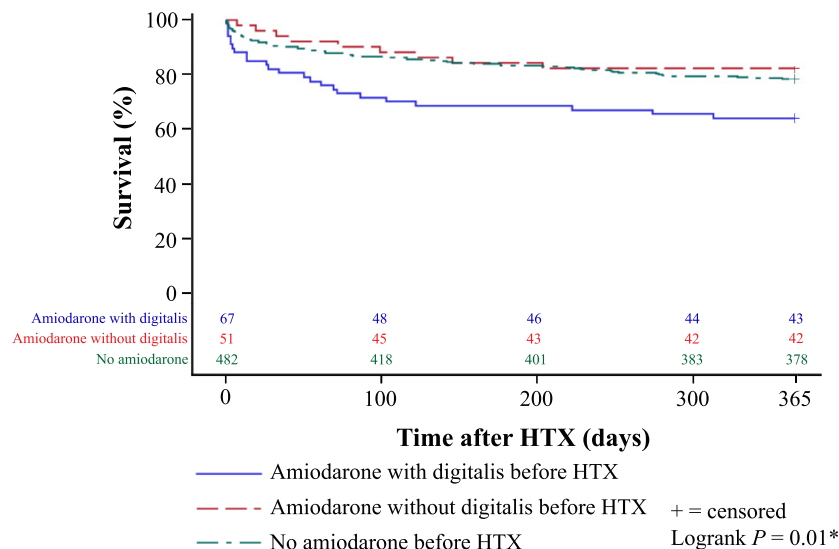


FIGURE 2 One year survival after HTX in patients receiving amiodarone with digitalis, amiodarone without digitalis, or no amiodarone before HTX (Kaplan–Meier estimator). Patients with combined amiodarone and digitalis therapy before HTX showed a worse 1 year survival after HTX (64.2%) in comparison with patients receiving amiodarone without digitalis before HTX (82.4%) or patients without amiodarone before HTX (78.4%, $P = 0.01$). HTX, heart transplantation. *Statistically significant ($P < 0.05$).



with a subgroup of patients receiving cyclosporine A and azathioprine (267 of 600 patients [44.5%]). This analysis showed similar results in terms of the primary outcome (post-transplant mortality) and the secondary outcomes (post-transplant echocardiographic features, early post-transplant AF, heart rates, and PPM implantation after HTX) confirming the robustness of the study results and minimizing the likelihood of an era effect.

Discussion

Combined amiodarone and digitalis therapy before heart transplantation

As pre-transplant use of amiodarone-associated mortality after HTX is still subject to an ongoing debate, this is the first

study to analyse the effects of combined amiodarone and digitalis use before HTX on post-transplant outcomes. We found no significant difference between patients with and without amiodarone use before HTX in 1 year post-transplant survival (72.0% vs. 78.4%, $P = 0.11$), but patients with combined amiodarone and digitalis therapy before HTX had a worse 1 year post-transplant survival (64.2%, $P = 0.01$).

Digitalis has a narrow therapeutic window, and elevated serum levels of digitalis have been associated with reduced survival.^{17,18,24} Amiodarone is a potent inhibitor of the P-glycoprotein transporter system and can induce a doubling of serum digitalis levels.^{25,26} Similar to amiodarone, dronedarone increases digitalis concentration by P-glycoprotein inhibition.^{17,27} In the PALLAS trial, which compared the effects of dronedarone versus placebo on permanent AF, 11 of 13 arrhythmic deaths in the dronedarone group occurred in patients with additional digitalis illustrating

Table 3 Causes of death within 1 year after HTX

Parameter	Patients without amiodarone (n = 482)	Patients with amiodarone but without digitalis (n = 51)	Patients with amiodarone and with digitalis (n = 67)	P-value
Transplant failure, n (%)	44 (9.1%)	0 (0.0%)	9 (13.4%)	0.03*
Acute rejection, n (%)	4 (0.8%)	0 (0.0%)	0 (0.0%)	0.61
Infection/sepsis, n (%)	45 (9.3%)	8 (15.6%)	15 (22.4%)	<0.01*
Pulmonary infection, n (%)	34 (7.0%)	6 (11.7%)	9 (13.4%)	0.13
Abdominal infection, n (%)	11 (2.3%)	2 (3.9%)	6 (9.0%)	0.01*
Malignancy, n (%)	3 (0.6%)	0 (0.0%)	0 (0.0%)	0.69
Thromboembolic event/bleeding, n (%)	8 (1.7%)	1 (2.0%)	0 (0.0%)	0.56
All causes, n (%)	104 (21.5%)	9 (17.6%)	24 (35.8%)	0.02*

HTX, heart transplantation; n, number.

*Statistically significant ($P < 0.05$).

Table 4 Multivariate analysis for 1-year mortality after HTX

Variable	Hazard Ratio	95% CI	P-value
Amiodarone and digitalis before HTX (in total)	1.69	1.02–2.77	0.04*
No amiodarone before HTX (in total)	1.32	0.86–2.03	0.20
Cyclosporine A (in total)	1.02	0.77–1.36	0.87
Cardiac amyloidosis (in total)	1.39	0.93–2.07	0.11
Ischaemic time (min)	1.00	0.99–1.01	0.30

CI, confidence interval; HTX, heart transplantation.

*Statistically significant ($P < 0.05$).

the potential impact of drug–drug interactions on arrhythmias and mortality.^{17,27,28}

Mortality and causes of death after heart transplantation

In our study, patients with combined amiodarone and digitalis therapy before HTX had a worse 1 year post-transplant survival ($P = 0.01$), along with a higher rate of death due to transplant failure ($P = 0.03$). Analysis of echocardiographic features showed a higher percentage of an enlarged right ventricle ($P = 0.02$), left atrium ($P = 0.02$), left ventricle ($P = 0.03$), and a higher rate of reduced left ventricular ejection fraction ($P = 0.03$) in these patients. Multivariate analysis revealed combined amiodarone and digitalis use before HTX as a significant risk factor for 1 year mortality after HTX (HR: 1.69; 95% CI: 1.02–2.77; $P = 0.04$).

Regarding post-transplant mortality in patients with amiodarone use before HTX, current data are inconclusive as some studies reported increased post-transplant mortality,^{11,29,30} whereas other studies found no difference.^{3,4,14,31,32} These divergent outcomes may result from a yet unconsidered variable. Patients with HF often receive digitalis in combination with amiodarone, which is known to raise serum concentrations of digitalis.^{15,16} Two modes of action should be taken into consideration when analysing post-transplant effects of digitalis therapy before HTX. First, the exposure of the cardiac allograft to the remaining serum level of digitalis (direct cardiac effects). Second, the physiological changes of digitalis-induced extracardiac alterations (sensitization of baroreceptors, modulation of smooth muscle tone, and stimulation of the central vagal nucleus) on the cardiac allograft (indirect cardiac effects). Moreover, once the effects of digitalis declined, a rebound effect may occur causing arrhythmias and fluctuation of blood pressure.¹⁹

Table 5 Echocardiographic features after HTX

Parameter	Patients without amiodarone ($n = 482$)	Patients with amiodarone but without digitalis ($n = 51$)	Patients with amiodarone and with digitalis ($n = 67$)	P-value
30-day end-diastolic diameter				
Normal RA (<35 mm), n (%)	269 (55.8%)	32 (62.7%)	31 (46.3%)	0.18
Normal LA (<40 mm), n (%)	232 (48.1%)	34 (66.7%)	28 (41.8%)	0.02*
Normal RV (<30 mm), n (%)	396 (82.2%)	48 (94.1%)	50 (74.6%)	0.02*
Normal LV (<55 mm), n (%)	444 (92.1%)	50 (98.0%)	57 (85.1%)	0.03*
30-day LVEF				
$\geq 55\%$, n (%)	435 (90.2%)	50 (98.0%)	56 (83.6%)	0.03*
<55%, n (%)	47 (9.8%)	1 (2.0%)	11 (16.4%)	
45–54%, n (%)	15 (3.1%)	1 (2.0%)	3 (4.5%)	
30–44%, n (%)	7 (1.5%)	0 (0.0%)	1 (1.5%)	
<30%, n (%)	25 (5.2%)	0 (0.0%)	7 (10.4%)	
30-day mitral regurgitation				
No, n (%)	362 (75.1%)	33 (64.7%)	53 (79.1%)	0.18
Yes, n (%)	120 (24.9%)	18 (35.3%)	14 (20.9%)	
Mild, n (%)	116 (24.1%)	18 (35.3%)	10 (14.9%)	
Moderate, n (%)	3 (0.6%)	0 (0.0%)	4 (6.0%)	
Severe, n (%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	
30-day tricuspid regurgitation				
No, n (%)	307 (63.7%)	33 (64.7%)	41 (61.2%)	0.91
Yes, n (%)	175 (36.3%)	18 (35.3%)	26 (38.8%)	
Mild, n (%)	99 (20.5%)	15 (29.4%)	13 (19.4%)	
Moderate, n (%)	48 (10.0%)	3 (5.9%)	9 (13.4%)	
Severe, n (%)	28 (5.8%)	0 (0.0%)	4 (6.0%)	

HTX, heart transplantation; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; n , number; RA, right atrium; RV, right ventricle.

*Statistically significant ($P < 0.05$).

Table 6 Heart rates, bradycardia, PPM implantation, and AF after HTX

Parameter	Patients without amiodarone (n = 482)	Patients with amiodarone but without digitalis (n = 51)	Patients with amiodarone and with digitalis (n = 67)	P-value
30-day heart rates				
Heart rate, week 1 after HTX, mean \pm SD	103.8 \pm 12.6 b.p.m.	101.5 \pm 11.4 b.p.m.	101.5 \pm 11.9 b.p.m.	0.19
Heart rate, week 2 after HTX, mean \pm SD	96.3 \pm 10.3 b.p.m.	95.6 \pm 16.2 b.p.m.	95.3 \pm 11.0 b.p.m.	0.74
Heart rate, week 3 after HTX, mean \pm SD	91.8 \pm 9.2 b.p.m.	90.1 \pm 12.0 b.p.m.	90.9 \pm 10.0 b.p.m.	0.42
Heart rate, week 4 after HTX, mean \pm SD	85.8 \pm 8.8 b.p.m.	84.2 \pm 10.7 b.p.m.	85.7 \pm 8.7 b.p.m.	0.49
30-day bradycardia				
Bradycardia ^a , week 1 after HTX, n (%)	10 (2.1%)	1 (2.0%)	1 (1.5%)	0.95
Bradycardia ^a , week 2 after HTX, n (%)	4 (0.8%)	1 (2.0%)	1 (1.5%)	0.68
Bradycardia ^a , week 3 after HTX, n (%)	5 (1.0%)	1 (2.0%)	1 (1.5%)	0.81
Bradycardia ^a , week 4 after HTX, n (%)	4 (0.8%)	1 (2.0%)	1 (1.5%)	0.68
30-day PPM implantation and AF				
30-day PPM implantation, n (%)	3 (0.6%)	1 (2.0%)	1 (1.5%)	0.50
30-day atrial fibrillation, n (%)	71 (14.7%)	4 (7.8%)	3 (4.5%)	0.03*

AF, atrial fibrillation; b.p.m., beats per minute; HTX, heart transplantation; n, number; PPM, permanent pacemaker.

^aBradycardia defined as mean weekly heart rate < 60 b.p.m.

*Statistically significant ($P < 0.05$).

Amiodarone can interfere with the immunosuppressive drug therapy by cytochrome P450 (CYP3A4) and P-glycoprotein inhibition, which can cause an increase in serum levels of cyclosporine A or tacrolimus. Therefore, close drug trough level monitoring with dosage adjustment is essential to avoid overdosing or underdosing. In addition to amiodarone, several other factors may influence serum levels of cyclosporine A or tacrolimus including age, gender, weight, glomerular filtration rate, and concomitant medication.^{1,33–37} In this study, we found no significant differences between patients with or without pre-transplant amiodarone use in dosage or drug trough levels of cyclosporine A or tacrolimus within 30 days after HTX. Moreover, we found no significant difference between both groups in terms of acute rejection as cause of death within 30 days after HTX (all $P \geq 0.05$).

Therefore, in addition to potential side effects of amiodarone, the aforementioned changes should be carefully considered to understand the consequences of combined amiodarone and digitalis therapy before HTX on post-transplant outcomes. Besides transplant failure, patients with combined amiodarone and digitalis therapy before HTX had a higher percentage of death due to infection/sepsis in general ($P < 0.01$) and abdominal infections ($P = 0.01$). Digitalis induces intestinal vasoconstriction and reduces splanchnic blood volume potentially causing mesenteric infarction, intestinal necrosis, and abdominal infection/sepsis.^{38,39}

Heart rhythm disorders after heart transplantation

Amiodarone and digitalis can have negative effects on the cardiac conduction system by decreasing heart rates (negative chronotropic effect), reducing conduction velocity

(negative dromotropic effect), and increasing cellular excitability (positive bathmotropic effect) potentially leading to lower heart rates with bradycardia, atrioventricular block, and requirement for PPM implantation.^{12,13,25,40,41} Several studies have investigated the effects of pre-transplant amiodarone on bradycardia and PPM implantation after HTX, but results are conflicting.^{4,11,13,14,30–32,42–46} An ISHLT Registry analysis by Cooper and colleagues¹¹ found a higher rate of in-hospital PPM implantation in patients with amiodarone before HTX (4.6% vs. 3.3%), but no difference in PPM implantation after HTX regarding the period from discharge to 1 year follow-up (3.5% vs. 3.3%). There are multiple reasons for heart rhythm disorders in the early period after HTX including sinoatrial node dysfunction due to surgical technique (biatrial HTX technique), reperfusion injury due to prolonged ischaemic time, cardiac denervation of the allograft with regulatory imbalances (tachycardia/bradycardia), the use of additional antiarrhythmic drugs (beta-blocker, calcium channel blocker, or ivabradine), electrolyte imbalance, and hypothyroidism, which should be addressed first, followed by heart rate stimulating agents and temporary pacing considering PPM implantation as last option.^{1,3,4,12,20,23,45,46} In our study, mean heart rates during week 1–4 after HTX, occurrences of bradycardia, and 30-day PPM implantation after HTX showed no significant difference between groups (all $P \geq 0.05$).

We observed a lower percentage of 30-day post-transplant AF in patients receiving amiodarone with (4.5%) or without digitalis before HTX (7.8%) in comparison with patients with no amiodarone before HTX (14.7%, $P = 0.03$). Lushaj and colleagues⁵ found no difference between patients with (6.5%) or without (7.1%, $P = 0.76$) amiodarone before HTX regarding post-transplant AF, which could be a result of their lower overall incidence of post-transplant AF (6.8%). A recent Cochrane meta-analysis⁴⁷ reported a higher overall incidence of AF after HTX of 10.1%, which is in line with our findings.

In summary, the aforementioned results indicate that combined amiodarone and digitalis therapy before HTX is a relevant risk factor for increased post-transplant mortality. Our findings strongly suggest that indications for combined amiodarone and digitalis therapy in patients awaiting HTX should be carefully considered and continuously re-assessed.

Study limitations

Our results were derived from a single-centre registry (Heidelberg HTX Registry). Based on the study design, findings should be treated with caution as it carries certain limitations. However, in contrast to most multicentre studies, our study provides an excellent granularity as patients received a standardized centre-specific pre-transplant, peri-transplant, and post-transplant treatment and follow-up reducing the likelihood of potential selection bias and confounders. Additionally, our study had a total of 600 patients, which is comparable in size with multicentre studies.^{3,4,19–23}

This analysis included patients receiving HTX at Heidelberg Heart Center between 1989 and 2016. Due to this long study period, a possible era effect resulting from changes in medical care may have affected post-transplant outcomes. As the initial standard immunosuppressive drug therapy was switched during the study period, a sensitivity analysis including patients with cyclosporine A and azathioprine was performed to investigate a possible era effect and to test the robustness of the study findings. This analysis revealed comparable results.^{3,4,19–23}

Serum levels of digoxin or digitoxin directly before HTX were not available. A potential association between increased post-transplant mortality and higher serum levels of digitalis could therefore not be analysed. Our results should be considered as hypothesis-generating, especially in regard to post-transplant survival as multiple factors may affect survival. Thus, our data cannot prove or disprove a causal relationship between combined amiodarone and digitalis therapy before HTX and reduced post-transplant survival but merely indicate an association. In order to confirm our findings, further large multicentre trials are required to investigate the effects of combined amiodarone and digitalis therapy before HTX on post-transplant outcomes.

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Conclusions

To our knowledge, this is the first study investigating the effects of combined amiodarone and digitalis therapy before HTX on post-transplant outcomes. There was no statistically significant difference between patients with and without amiodarone use before HTX in 1 year post-transplant survival (72.0% vs. 78.4%, $P = 0.11$), but patients with combined amiodarone and digitalis therapy before HTX had a worse 1 year post-transplant survival (64.2%, $P = 0.01$), along with a higher percentage of death due to transplant failure ($P = 0.03$). Echocardiographic analysis of these patients showed a higher percentage of an enlarged right ventricle ($P = 0.02$), left atrium ($P = 0.02$), left ventricle ($P = 0.03$), and a higher rate of reduced left ventricular ejection fraction ($P = 0.03$). Multivariate analysis indicated combined amiodarone and digitalis use before HTX as significant risk factor for 1 year mortality after HTX (HR: 1.69; 95% CI: 1.02–2.77; $P = 0.04$). In summary, combined amiodarone and digitalis therapy before HTX is associated with increased post-transplant mortality.

Acknowledgements

We thank Anna Daut, Viola Deneke, and Berthold Klein for their assistance and advice.

Conflict of interest

None declared.

Funding

This work was supported by research grants from the Faculty of Medicine, University of Heidelberg (Physician-Scientist-Program Scholarship to R. R.), by the German Cardiac Society (Research Scholarship to R. R.), by the German Society of Internal Medicine (Clinician-Scientist-Program Scholarship to A. K. R.), and by the Ministry of Science, Research and the Arts Baden-Wuerttemberg (Sonderlinie Medizin to D. T.).

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