Observational Study

Medicine

OPEN

Diltiazem as a cyclosporine A-sparing agent in heart transplantation

Benefits beyond dose reduction

Emyal Alyaydin, MD, PhD[a,*], Holger Reinecke, MD, PhD[a], Izabela Tuleta, MD, PhD[a], Juergen R. Sindermann, MD, PhD[b]

Abstract

Diltiazem (DZ) is widely prescribed in transplant recipients because of its drug-drug interactions with calcineurin inhibitors (CNI). However, these interactions have been primarily investigated in renal transplantation, and data regarding the long-term efficacy and safety of DZ in orthotopic heart transplantation (OHT) are still sparse.

Our study aimed to elucidate the extent to which the co-prescription of DZ reduces the dose required to maintain adequate blood levels of cyclosporine A (CsA) and the resulting effect on morbidity and mortality in OHT recipients.

We performed a retrospective single-center analysis of OHT recipients on a long-term immunosuppressive regimen based on CsA and mycophenolate mofetil (MMF).

The study population consisted of 95 adult OHT recipients with a mean follow-up of 15.8 ± 6.7 years. DZ was co-prescribed in 39 subjects (41.1%) and was associated with a 28.6% reduction of the mean CsA daily dose ($P < .001$). Patients on DZ had less frequent rejection episodes ($P = .002$), better renal function ($P = .009$) and a lower rate of end-stage renal disease ($P = .008$). Additionally, they developed later cardiac allograft vasculopathy (CAV). We observed no prognostic relevance of DZ co-prescription in univariate and multivariate Cox-regression analyses.

In addition to reducing the CsA dose required to maintain adequate blood through levels, DZ may have nephroprotective properties in OHT. The co-administration of DZ may decelerate the development of CAV and reduce the frequency of the rejection episodes. However, the beneficial influence on morbidity has no impact on mortality.

Abbreviations: C2 = CsA blood levels at 2 hours postdose, CAV = cardiac allograft vasculopathy, CCB = calcium channel blockers, CsA = cyclosporine A, DZ = diltiazem, ISHLT = International Society for Heart and Lung Transplantation, MMF = mycophenolate mofetil, OHT = orthotopic heart transplantation.

Keywords: cyclosporin A, diltiazem, immunosuppression, orthotopic heart transplantation, survival

1. Introduction

Since 1967 orthotopic heart transplantation (OHT) has been the ultima ratio therapy in selected patients with terminal heart failure.[1] After initial drawbacks due to graft rejection, the introduction of cyclosporine A (CsA) in the 1980s revolutionized the world of organ transplantation.[2,3] However, the improvement in survival is still limited by the side effects of immunosuppressants, which cause increased morbidity over time. Thus, alternative approaches have been suggested, such as the use of potential drug-drug interactions and identical metabolic pathways. One such consideration is the co-administration of the calcineurin inhibitor (CNI) sparing agent diltiazem (DZ) along with immunosuppression. This concept may aid in reducing costs while limiting the side effects of the immunosuppressive therapy.[4] Furthermore, previous studies revealed that DZ might reduce the hepatotoxicity and nephrotoxicity of CsA, limit the incidence and progression of cardiac allograft vasculopathy (CAV), and improve survival.[5,6] However, the clinical utilization of this concept is primarily based on investigations in a real-life setting in the field of renal transplantation.[6]

Our study aimed to examine the extent to which the co-administration of DZ can reduce morbidity and mortality in the population of patients who have undergone OHT.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The data that support the findings of this study are not publicly available due to privacy restrictions. The data are available on reasonable request from the corresponding author.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Cardiology I – Coronary and Peripheral Vascular Disease, Heart Failure, University Hospital Muenster, Muenster, Germany,
[b] Interdisciplinary Heart Failure Section, University Hospital Muenster, Muenster, Germany.

**Correspondence: Emyal Alyaydin, Department of Cardiology I – Coronary and Peripheral Vascular Disease, Heart Failure, University Hospital Muenster, Albert-Schweitzer-Campus 1, 48149 Muenster, Germany (e-mail: emyal.alyaydin@ukmuenster.de).*

How to cite this article: Alyaydin E, Reinecke H, Tuleta I, Sindermann JR. Diltiazem as a cyclosporine A-sparing agent in heart transplantation: Benefits beyond dose reduction. Medicine 2022;101:41(e31166).

Received: 2 August 2022 / Received in final form: 8 September 2022 / Accepted: 14 September 2022

http://dx.doi.org/10.1097/MD.0000000000031166

2. Methods

2.1. Study design

Our study was based on a retrospective analysis of patient data collected during the most recent routine follow-up in the outpatient clinic for terminal heart failure and heart transplantation. The overall study population consisted of 268 OHT recipients. Of these, 114 (42.5%) patients were on an immunosuppressive regimen containing an agent other than CsA. Additionally, 15 (5.6%) patients were excluded due to insufficient data, and 3 subjects (1.1%) due to heart-lung transplantation or re-OHT. In 41 (15.3%) OHT recipients, CsA was combined with azathioprine, everolimus, or prescribed as a monotherapy. The largest homogenous group on an immunosuppressive regimen based on CsA was the 1 receiving maintenance therapy with CsA and mycophenolate mofetil (MMF) (n = 95, 35.4%). We stratified the patients into 2 groups according to whether DZ was co-prescribed or not (Fig. 1). Inclusion criteria were long-term maintenance immunosuppressive therapy with CsA and MMF with/without prednisone, at least 1 year follow-up after OHT, and stable clinical condition at last presentation in the outpatient clinic.

We note that 63 patients (66.3%) were on an immunosuppressive maintenance regimen including CsA/MMF for the entire posttransplant period. The remaining 32 patients (33.7%) were either on a different immunosuppressant initially, or data regarding the therapy modality in the immediate posttransplant period were insufficient. However, the mean time span in which the immunosuppressive regimen of this cohort was CsA/MMF comprised 9.7 ± 4.7 years until the last visit.

The study was performed in compliance with the Declaration of Helsinki, and data sampling was approved by the local ethics committee (2019-021-f-S).

2.2. Laboratory and clinical examinations

The post-OHT follow-up of the study population was performed in 3-months intervals. It included patients' history, clinical examination, electrocardiogram, laboratory assessment of the liver and renal functions, cardiac enzymes, complete blood count, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP). Echocardiography was routinely performed at every other follow-up or if clinically indicated. Additional tests were conducted if necessary.

Venous blood sampling for estimation of CsA trough levels was performed at every presentation prior to the next dose so that the values represent blood levels approximately 12 hours post-dosing. All measures were expressed in ng/mL, and the target dose was based on the recommendations of the Guidelines of the International Society for Heart and Lung Transplantation (ISHLT).[3] As our study was conducted in a retrospective setting, and CsA trough levels were used to monitor the immunosuppressive therapy at our center, we cannot provide any CsA blood levels at 2 hours postdose (C2) measures. However, recent studies revealed no beneficial effects of the estimation of CsA blood levels at 2 hours postdose (C2) over trough levels (CsA trough levels [C0]) on the frequency of the rejection episodes, the incidence of hypertension, and renal parameters in heart transplantation.[7] Additionally, research in the field of renal transplantation revealed that both C0 and C2 were useful in predicting the immunosuppressant-related side effects.[8] Furthermore, the utility of C2 is yet to be proven in a maintenance setting and a long-term follow-up.[9]

CAV was defined according to the International Society for Heart and Lung Transplantation classification. We differentiated between patients with no evidence of CAV on the last invasive assessment (corresponding to ISHLT CAV_0) and patients with

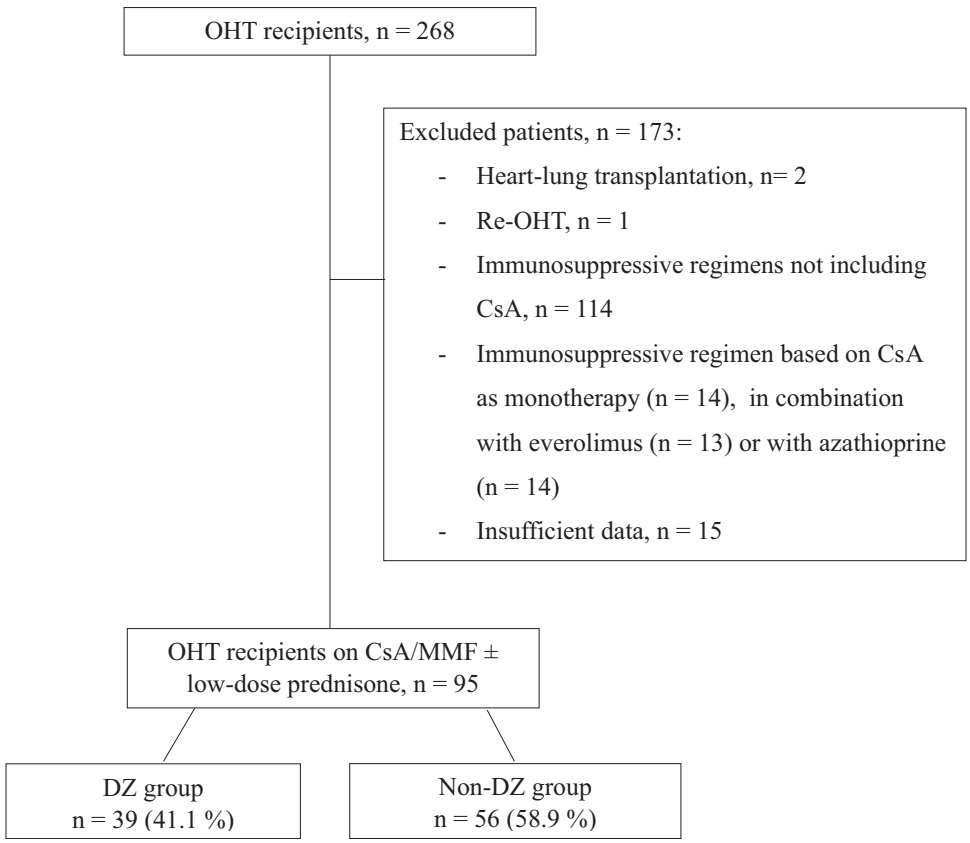

Figure 1. Flowchart of the study.CsA = cyclosporine A, DZ = diltiazem, MMF = mycophenolate mofetil, OHT = orthotopic heart transplantation.

detectable coronary lesions irrespective of the graft function or grade of angiographic involvement (≥ISHLT CAV_1).[10]

2.3. Statistical analysis

IBM SPSS statistics software was used for the performed analyses. The assessment of the continuous variables, expressed as mean ± standard deviation (mean ± SD) was performed with Student t-test. Categorical variables were reported as numbers (percentages) and examined with the chi-square test. The risk estimation was based on univariate and multivariate logistic regression analyses. The prognostic evaluation of all factors was performed using univariate and multivariate Cox-regression models. For all statistical analyses, $P < .05$ was defined as significant.

3. Results

3.1. Demographics

Our study population consisted of 95 OHT recipients with a mean follow-up of 15.8 ± 6.7 years. The mean age at the time of OHT was 47.4 ± 14.4 years. One-fourth of the population were females (n = 25, 26.3 %). DZ was a concomitant medication in 39 patients (41.1%). Males were more likely get prescribed DZ ($P = .017$), although we do not observed relevant gender-related differences in the prevalence of hypertension (n = 59, 84.3 % in male vs n = 18, 72.0% in female, $P = .234$) as well as no disparities concerning the heart rate (83.9 ± 15.4 in male vs 84.9 ± 14.6/minute in female, $P = .772$) or the systolic blood pressure (126.2 ± 17.9 in male vs 126.0 ± 18.1 mm Hg in female, $P = .975$) at the most recent presentation. We found no differences between the DZ and non-DZ groups regarding the etiology of the pretransplant heart disease or the recipient age at OHT (Table 1).

The dosing of diltiazem (DZ) was stable in most of the patients. The mean daily doses of DZ at the first evaluable follow-up and at the last presentation were 182.3 ± 69.6 mg/day and 160.8 ± 83.0 mg/day, respectively ($P = .065$). In 19 cases (48.7% of the DZ cohort), the daily dose was constant over the years.

3.2. Clinical characteristics

Patients not receiving DZ experienced more often rejection episodes in the past (OR 2.9, 95% CI 1.2–7.1, $P = .019$), although no association with rejections requiring therapy (≥2R) according to the revised classification of the ISHLT was observed (OR 2.2, 95% CI 0.8–6.3, $P = .139$).[2] The left ventricular ejection fraction was within the normal range with no significant difference. The prevalence of hypertension was similar between both groups, and there were no disparities in the estimated blood pressure values at the most recent examination. The prevalence of cancer, representing one of the most common comorbidities in patients on long-term immunosuppression, was also comparable and we observed no association of DZ with the incidence of cancer (OR 1.3, 95% CI 0.5–3.1, P .571). However, patients on DZ had a significantly better renal function, expressed as glomerular filtration rate (GFR). Additionally, DZ was associated with a lower rate of end-stage renal disease (ESRD) (OR 0.2, 95% CI 0.1–0.7, $P = .012$).

Not prescribing DZ was not associated with a higher rate of CAV in a univariate logistic regression analysis (OR 1.1, 95% CI 0.5–2.6, $P = .811$). However, patients not receiving DZ were

Table 1

Patient characteristics.

Main patient characteristics	DZ n = 39 (41.1)	Non-DZ n = 56 (58.9)	*P* value
1. Demographics			
- Age at OHT, yrs	48.4 ± 12.5	46.6 ± 15.7	.553
- Follow-up, yrs	17.4 ± 6.4	14.7 ± 6.7	.047*
- Male, n (%)	34 (87.2)	36 (64.3)	.017*
- Survivors, n (%)	25 (64.1)	36 (64.3)	1.000
2. Pretransplant heart disease			
- Ischemic cardiomyopathy, n (%)	17 (43.6)	20 (35.7)	.523
- Dilated cardiomyopathy, n (%)	19 (48.7)	25 (44.6)	.835
- Others, n (%)	3 (7.7)	11 (19.6)	.144
3. Clinical and laboratory examinations			
- NYHA ≥ 2, n (%)	28 (71.8)	46 (82.1)	.315
- Systolic BP, mm Hg	126.7 ± 18.1	125.7 ± 17.9	.785
- Diastolic BP, mm Hg	79.6 ± 8.5	80.2 ± 10.8	.779
- Heart rate, bpm	87.3 ± 13.1	81.9 ± 16.2	.089
- Rejection episodes, n (%)	10 (25.6)	28 (50.0)	.020*
- Rejections requiring therapy, n (%)	6 (15.4)	16 (28.6)	.148
- CAV, n (%)**	13 (33.3)	20 (35.7)	.831
- OHT to CAV, yrs	16.1 ± 7.4	9.4 ± 6.1	.029*
- GFR, mL/min/m²	50.7 ± 24.7	36.0 ± 27.2	.009*
- ESRD, n (%)	4 (10.3)	19 (33.9)	.007*
- OHT to ESRD, yrs	8.8 ± 6.0	19.8 ± 4.4	.002*
- Cancer, n (%)	14 (35.9)	17 (30.4)	.658
- OHT to cancer, yrs	11.2 ± 6.5	9.3 ± 5.2	.392
- Hypertension, n (%)	32 (82.1)	45 (80.4)	1.000
- NT-proBNP, pg/mL	742.0 (1168.0)	3576.0 (9228.0)	<.001*
- PCHE, U/L	7231.4 ± 1943.1	6610.3 ± 1919.0	.072
4. Echocardiographic assessment			
- LVEF, %	57.4 ± 5.6	55.4 ± 9.9	.256

BP = blood pressure, CAV = cardiac allograft vasculopathy, DZ = diltiazem, ESRD = end-stage renal disease, GFR = glomerular filtration rate, OHT = orthotopic heart transplantation, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, PCHE = pseudocholinesterase.

**≥CAV_1 according to the revised classification of the international society for heart and lung transplantation.

*$P < .05$.

more likely to develop significantly earlier CAV in a univariate logistic regression analysis (OR 8.3, 95% CI 1.0–67.5, $P = .049$ for CAV <10 years following OHT) (Table 1).

3.3. Immunosuppressive regimen

Patients were on an immunosuppressive maintenance regimen containing CsA, MMF with/without prednisone. The co-administration of DZ was associated with lower CsA dose (1.5 ± 0.6 on DZ vs 2.1 ± 0.8 mg/kg/day without DZ, $P < .001$, respectively) while achieving comparable blood trough levels (122.6 ± 46.0 on DZ vs 120.3 ± 55.1 ng/mL in the non-DZ group, $P = .0.834$, respectively). We observed no significant differences in the daily MMF dose between groups (Fig. 2). Treatment with higher doses of DZ was associated with a greater reduction in the CsA requirements ($P = .003$). However, this effect was primarily observed in doses of up to 180 mg/day, and the CsA-sparing effect was limited when higher drug doses were applied (Fig. 3). Low-dose prednisone (either 2,5 mg/day or 5 mg/day) was a co-medication in 65 patients (68.4%) without significant differences between both groups (Table 2).

3.4. Concomitant medication

Although with significant intergroup contrast, betablockers were commonly prescribed in OHT recipients, covering more than half of the DZ and three-fourths of the non-DZ groups. As expected, further differences were detected in the use of calcium channel blockers (CCB), as only 1 patient from the DZ group was on an additional CCB. In contrast, in the non-DZ group, one-fourth of the population was receiving a CCB as an antihypertensive agent. Except for 1 patient on lercanidipine, amlodipine was the drug of choice in the remaining patients. Angiotensin-converting enzyme inhibitors (ACE-inhibitors) and angiotensin II type 1 receptor antagonists (AT1-antagonists) were utilized in more than half of the overall population, without significant differences between both study groups. Diuretics were prescribed in 60% of the overall cohort with almost the same frequency. Aldosterone antagonists were only a concomitant medication in 7.4% of the population. Statins were the most commonly prescribed agents covering up to 87.4% of the overall cohort (Table 2).

3.5. Survival

We observed no significant impact of DZ use on the posttransplant survival in a univariate Cox regression analysis (HR 0.8, 95% CI 0.4–1.5, $P = .471$) or in a multivariate analysis after adjustment for the factors that are not in direct association with the use of DZ (pretransplant age and diagnosis).

4. Discussion

To our knowledge, this is the first study examining the potential benefit of DZ co-prescription in a relatively large cohort and of adult OHT recipients. The study was conducted in an observational setting but provides evidence in a very long-term follow-up. Additionally, most of the patients were on a CsA/MMF-based immunosuppression for almost the entire post-transplant period.

4.1. Gender-related differences

We did not observe relevant differences in age, pretransplant disease, and survival status between both study groups, but there were sex-related differences. While 50% of male OHT recipients were on DZ, the co-administration of a CNI-sparing agent was considered in only 20% of the females. Interestingly, there were no statistically significant sex-related disparities in the use of betablockers as a potential explanation for the limited utilization of DZ in women (n = 46, 65.7% in males vs n = 13, 52.0% in females, $P = .240$). We were unable to identify any prior research focusing on sex-related differences in the metabolism of DZ, which may result in its differing utilization.

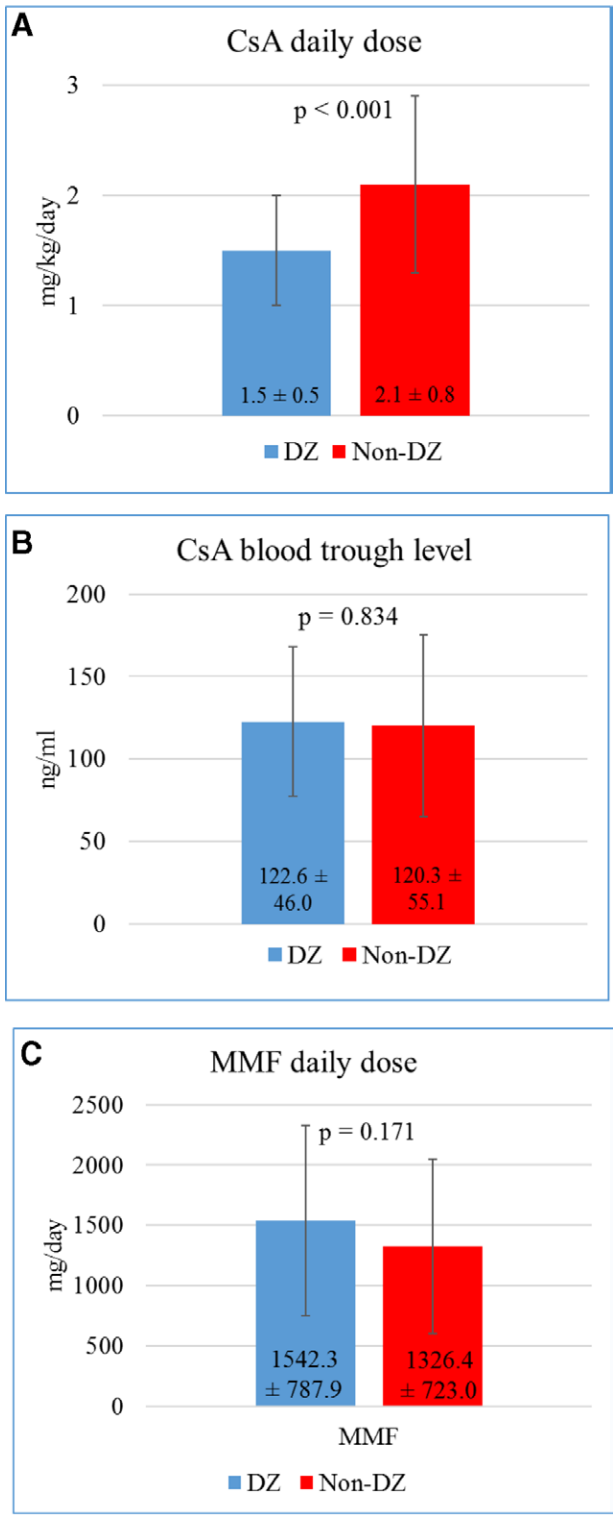

Figure 2. CsA daily dose and blood trough concentration.a) Maintenance daily dose of CsA (in mg/kg/day).b) CsA blood trough levels.c) MMF daily dose.CsA = cyclosporine A, DZ = diltiazem, MMF = mycophenolate mofetil.

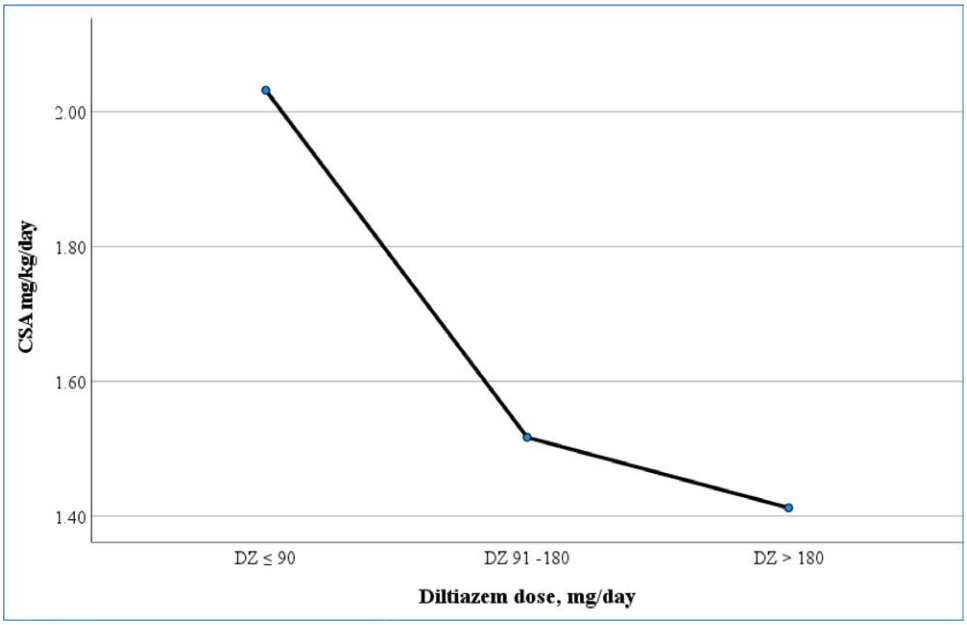

Figure 3. Association of CsA daily dose with the DZ dosage (P = .003).CsA = cyclosporine A, DZ = diltiazem.

Table 2

Concomitant medication.

Medication	DZ	Non-DZ	*P* value
Betablocker, n (%)	17 (43.6)	42 (75.0)	0.003*
ACE inhibitors/AT-antagonists, n (%)	24 (61.5)	28 (50.0)	0.300
CCB, n (%)	1 (2.6)	13 (23.2)	0.006*
Diuretics other than aldosterone antagonists, n (%)	23 (56.4)	34 (62.5)	0.671
Aldosterone antagonists, n (%)	1 (2.6)	6 (10.7)	0.234
Statins, n (%)	33 (84.6)	50 (89.3)	0.542
Prednisone, n (%)	24 (61.5)	41 (73.2)	0.266
Prednisone dose, mg	3.2 ± 2.8	3.8 ± 3.0	0.300

ACE = angiotensin-converting enzyme inhibitors, AT1-antagonists = angiotensin II type 1 receptor antagonist, CCB = calcium channel blockers, DZ = diltiazem.
*P < .05.

Additionally, a focused assessment of the incidence of cancer (P = .330), hypertension (P = .234), CAV (P = .471), ESRD (P = .597), rejection episodes (P = .353) or rejections requiring therapy (P = .583) according to the revised classification of the International Society for Heart and Lung Transplantation, showed no significant sex-related differences in potential long-term immunosuppressant related side-effects, which may explain these results. It was previously reported that males undergoing OHT have enhanced morbidity.[11] Awareness for the comorbidities may influence the clinical decision-making process and, as our results show, possibly influence the comorbidity profile in a very long-term follow-up.

4.2. CsA-sparing

We observed a significant reduction of the mean CsA daily dose associated with DZ use (28.6% reduction in the mean CsA daily dose). In contrast, the estimated blood through levels were comparable, thus confirming the CsA-sparing effect of DZ as previously reported. However, a steep decrease of the CsA dose requirements potentially resulting from the co-administration of DZ was observed primarily in patients receiving up to 180 mg/day, and the CsA-sparing effect was limited when higher doses were prescribed. This is in line with the findings of previous studies, reporting on the increase of CsA blood concentrations at initial up-titration, but no further benefits and potentially increasing side effects when higher DZ doses are used.[12]

4.3. Clinical benefit

CAV is common in long-term follow-up after OHT and may have prognostic implications.[13,14] In contrast to previous reports on the potential of DZ to reduce its progression in short-term follow-up, we found no association between DZ prescription and CAV prevalence.[5] However, CAV was diagnosed significantly earlier following transplantation in patients not receiving DZ. Thus, the almost equalized prevalence may be a consequence of the prolonged follow-up in the DZ group. Our observations indicate the potential beneficial effect of DZ in decelerating CAV development in OHT recipients, resulting in a delayed onset.[13]

In line with previous studies reporting on the potential of DZ to reduce the hepatotoxicity and nephrotoxicity of CsA in kidney transplant recipients, patients from the DZ group had a significantly better renal function and less frequent ESRD at the last follow-up.[5,6] Additionally, as observed concerning CAV, ESRD was diagnosed in a more prolonged follow-up in patients on DZ, thus indicating the nephroprotective properties of CsA-sparing.

We observed no differences in systolic left ventricular function (LVEF) of the allografts between the groups. However, the estimated NT-proBNP values were significantly elevated in patients from the non-DZ group. This may be a consequence of the more impaired renal function in this population.

Cancer is one of the most common comorbidities among patients on long-term immunosuppressive therapy. It was previously reported that the incidence of malignancies is up to 30% in 10-years follow-up and has a significant influence on patients' survival.[15,16] The overall incidence of cancer in 15-years follow-up in our population was 32.6% without significant differences between both study groups, except that we observed non-significant time-related differences with an earlier diagnosis in patients not receiving DZ.

The potential impact of CsA-sparing on the incidence of hypertension cannot be evaluated in an observational setting as it is also a common comorbidity in the pretransplant period.[11] However, the current antihypertensive therapy was optimized

over the years of continuous monitoring, and the blood pressure measurements at the most recent follow-up delivered normal results.

We observed no prognostic relevance of DZ co-prescription in a univariate Cox regression analysis and a multivariate analysis after adjusting for the pretransplant factors evaluated in our study. However, the impact on morbidity is a factor justifying its use in OHT recipients.

4.4. Additional drug-drug interactions

Dihydropyridine CCBs are commonly prescribed for the treatment of hypertension. The most frequently prescribed antihypertensive agent from this groups in our patient population was amlodipine. Lercanidipine was considered in only 1 case. Previous research focusing on the possible interactions of CCBs from this group in renal transplant recipients revealed no relevant interactions with CsA. Investigations in a real-life setting demonstrated that cyclosporine biotransformation was not altered by the concomitant administration of amlodipine.[17,18] In terms of the additional use of corticosteroids, the results of the studies to date were conflicting. However, as we observed no statistically significant differences in the frequency of their use between both study groups, potential bias related to corticosteroid use are limited in our population.[19]

4.5. Strengths and limitations

Our study provides evidence based on a very long-term follow-up in a relatively large cohort. Additionally, this is the first study investigating the potential benefit of DZ use in a real-life setting in a population of OHT recipients, as the previous evidence is derived from the field of renal transplantation. However, its observational nature is a factor limiting the utility of the study findings. Furthermore, due to data storage regulations, we had access to the information concerning the last 30 years. As a result, we have insufficient evidence regarding the pretransplant factors and the immediate posttransplant period in some patients. Additionally, as some OHT recipients considered for our study were on a long-term therapy at our center but had undergone OHT in other transplant centers, we had no detailed information on the perioperative period. Nevertheless, an asset of our study is that it is conducted in an exceptional long-term follow-up following OHT.

5. Conclusions

DZ has CsA-sparing properties and may aid in reducing the CsA-dose required to maintain adequate blood through levels. Consequently, DZ may ameliorate its side effects in the OHT recipients. We observed a positive association of DZ prescription with a better renal function, less frequent ESRD, later onset of CAV and ESRD, and less frequent rejection episodes. This evidence suggests a potential beneficial effect of DZ on patients' morbidity. However, we observed no mortality benefit in a very long-term follow-up.

Author contributions

Conceptualization: Emyal Alyaydin, Izabela Tuleta.
Data curation: Emyal Alyaydin, Juergen R. Sindermann.
Formal analysis: Emyal Alyaydin, Izabela Tuleta.
Investigation: Emyal Alyaydin, Izabela Tuleta.
Methodology: Emyal Alyaydin, Izabela Tuleta.
Project administration: Emyal Alyaydin, Holger Reinecke, Izabela Tuleta.
Resources: Emyal Alyaydin.
Software: Emyal Alyaydin.
Supervision: Holger Reinecke, Izabela Tuleta, Juergen R. Sindermann.
Validation: Holger Reinecke, Izabela Tuleta, Juergen R. Sindermann.
Visualization: Emyal Alyaydin.
Writing – original draft: Emyal Alyaydin.
Writing – review & editing: Emyal Alyaydin, Holger Reinecke, Izabela Tuleta, Juergen R. Sindermann.
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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