

Review

A Review of Systemic Hypertension in the Cardiac Transplant Population: Pathophysiology, Management, and Future Directions

Eman R. Rashed ¹, Swethika Sundaravel ²  and Juan M. Ortega-Legaspi ^{3,*} 

¹ Department of Advanced Heart Failure and Transplant, Newark Beth Israel-Robert Wood Johnson, Newark, NJ 07112, USA

² Department of Cardiovascular Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA; swethikaharini@gmail.com

³ Virtua Health Heart Failure, Cherry Hill, NJ 08034, USA

* Correspondence: jmortegalegaspi@gmail.com

Abstract

Heart transplantation is the gold standard in patients with end stage heart failure, offering vastly improved survival, mortality and quality of life. However, hypertension occurring after cardiac transplantation is a serious issue, with the incidence ranging from 50 to 80% of patients. The pathophysiology of the hypertension encompasses a more varied and unique set of causes than those identified in non-organ transplant patients, particularly related to the use of calcineurin inhibitors (CNIs) especially cyclosporine. An in-depth understanding of hypertension after heart transplantation remains a critical issue that necessitates further clarification, due to its deleterious long-term consequence such as impaired graft survival, cardiac allograft vasculopathy (CAV), and overall survival. This article provides a comprehensive review of the prevalence, risk factors, etiology, complications, and management of hypertension after heart transplantation.

Keywords: hypertension; calcineurin inhibitors; heart transplant cyclosporine; tacrolimus; corticosteroids; cardiac allograft vasculopathy; systematic literature review



Academic Editors: Matthias Thielmann and Diego Franco Jaime

Received: 1 July 2025

Revised: 24 November 2025

Accepted: 26 November 2025

Published: 8 December 2025

Citation: Rashed, E.R.; Sundaravel, S.; Ortega-Legaspi, J.M. A Review of Systemic Hypertension in the Cardiac Transplant Population: Pathophysiology, Management, and Future Directions. *Hearts* **2025**, *6*, 32. <https://doi.org/10.3390/hearts6040032>

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Heart transplantation is the gold standard of treatment in patients with end stage heart failure, offering vastly improved survival, mortality and quality of life. However, one of the most common post-transplant sequelae is hypertension. Hypertension (HTN) occurs frequently after cardiac transplantation. One study reported a prevalence of 52% at 1 year and 77% at 4 years post-transplant. Another study found a prevalence of 71.4% after 3 years post-transplant. The International Society for Heart and Lung Transplantation (ISHLT) reported 72% at 1 year and 92% at 5 years [1,2].

One of the primary pathophysiologic mechanisms which contribute to this problem is the effect of immunosuppressive agents such as calcineurin inhibitors [3,4] on the renin-angiotensin-aldosterone and sympathetic nervous systems [5], leading to sodium and fluid retention and enhanced vasoconstriction. Among CNIs, cyclosporine is more often associated with hypertension than tacrolimus, which is the most used CNI agent in the modern era of cardiac transplantation [6,7]. However, there are also alternate mechanisms of hypertension, independent of CNIs, such as failure of cardiac volume receptors to

respond to changes in loading conditions as a result of cardiac denervation after heart transplantation [8,9]. Furthermore, denervation of the transplanted heart and the consequent increase in heart rate have important implications on clinical parameters such as arterial stiffness and loss of modulation of blood pressure and heart rate during sleep [10].

The clinical implications of post-transplant hypertension are enormous, as it can lead to cardiac and renal structural alterations, and subsequent dysfunction. As delineated in Figure 1, there are special considerations for the management of post-cardiac transplant hypertension. Additionally, post-transplant hypertension plays a significant role in the onset of angiographic cardiac allograft vasculopathy (CAV). The cornerstone of management of hypertension in heart transplant recipients is reducing the dose of immunosuppression (IS) to the lowest effective dose.

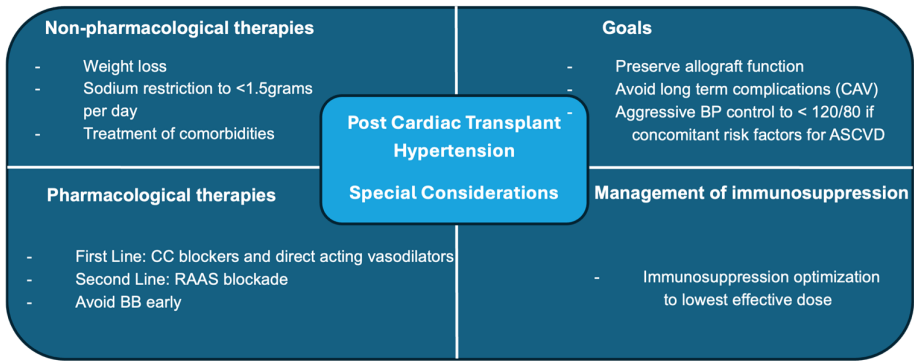


Figure 1. This figure depicts key components of post-cardiac transplant hypertension management: therapeutic strategies both pharmacological and non-pharmacological, immunosuppression optimization, and blood pressure targets.

We conducted a systematic literature review to assess the current body of knowledge on hypertension in the cardiac transplant population. The review synthesizes existing evidence on the pathophysiological mechanisms driving hypertension in transplant recipients, proposes a management framework, and highlights emerging contributors—including donor-derived factors—as well as new research avenues involving RAAS blockade, aldosterone antagonists, SGLT2 inhibitors, and renal denervation.

2. Risk Factors

In contrast to the general non-transplant hypertensive patient population, traditional risk factors, including family history of HTN, obesity, and diabetes, play a minor role in the development of post-transplant HTN [11]. Cyclosporine-induced hypertension develops regardless of the classic cardiovascular risk factors, which may exist before and after cardiac transplantation [12]. Studies have not found any correlation between body weight increase and blood pressure (BP) values. However, Olivari et al. [3,11] found that normotensive patients post-transplant had a smaller weight increase than patients who developed hypertension post-transplant, suggesting that obesity or weight gain may play an important role in the development of hypertension following cardiac transplantation. The effect of weight reduction on the BP of these patients is not known yet, but further studies on body weight reduction in this population are needed. So far, the risk factors associated with development following cardiac transplantation have not been thoroughly identified. Interestingly, while the male sex has been classically associated with non-transplant related hypertension, a study from Norway by Nygaard et. Al which looked at a total of 50 heart transplant recipients (35 males and 15 females) with an average age of 48 years, with the donor group containing 34 males and 16 females with an average age of 36 years, showed that the increases both ambulatory SBP and DBP were strongly associated

with the female donor sex [13]. This is a fascinating observation and warrants further follow-up and understanding of the contributing anatomic and physiological factors of a donor female heart to the development of hypertension after cardiac transplant.

3. Pathogenesis

The pathogenesis of hypertension in heart transplant recipients is multifactorial, complex, and unrelated to the presence of hypertension prior to transplantation (Figure 2).

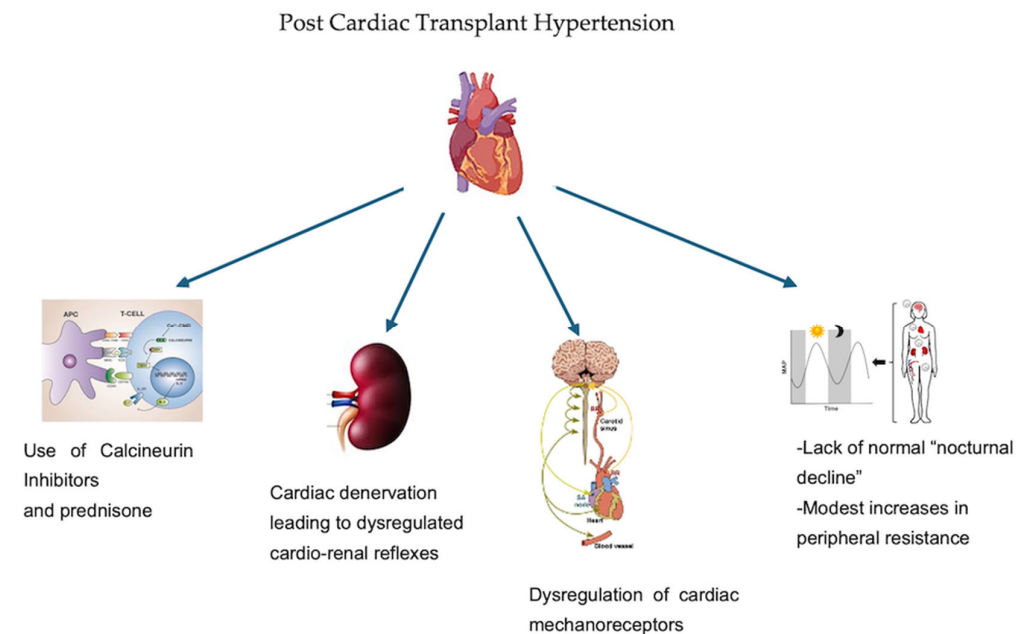


Figure 2. This figure illustrates the etiology of post-cardiac transplant hypertension: (1) Use of calcineurin inhibitors and prednisone. (2) Cardiac denervation leading to dysregulated cardio-renal reflexes. (3) Dysregulation of cardiac mechanoreceptors. (4) Lack of normal nocturnal decline in blood pressure in cardiac transplant recipients.

As mentioned, one of the common etiologies of hypertension after heart transplantation is the use of CNIs. Both cyclosporine and tacrolimus are implicated, but the incidence of hypertension with tacrolimus is reported to be lower [14,15]. The vast majority of immunosuppressive regimens include a CNI, likely combined with a corticosteroid. CNIs are known to cause hypertension in post-transplant patients through a host of mechanisms which affect blood pressure regulation, such as through the renin–angiotensin system, the sympathetic nervous system, the endothelin system, the nitric oxide system, and the production of free radicals. However, as we will further elucidate upon, hypertension in heart transplant patients is more pronounced than in other patient groups receiving cyclosporine, indicating non-CNI related mechanisms of hypertension as well [16,17].

One of the major mechanisms through which CNIs are thought to cause hypertension is through their effect on the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system. A study showed that CNIs not only induce renin production in the collecting duct but also cause increased vascular endothelial growth factor (VEGF) production, resulting in disproportional vessel growth [18]. A study by Nishiyama et al. demonstrated that in CsA-induced hypertensive rats, Angiotensin II levels are increased in both plasma and kidney [19]. Also, from a hemodynamic perspective, CsA causes intrarenal vasoconstriction, leading to a severe reduction in blood supply to nephrons, resulting in increased renin secretion. Thus, it is postulated that CNIs may trigger a vicious circle of RAAS activation [5]. CNIs impair the vasodilatory response by diminishing prostacyclin levels (PGI₂), endothelium-derived relaxing factor, and nitric oxide activity [20]. It is also

thought that CNIs reduce glomerular filtration rate and increase sodium reabsorption [21], consequently requiring greater pressure levels to maintain natriuresis, mediated in part by increased sodium chloride cotransporter (NCC) activity in the distal convoluted tubule [22]. It is likely that CNIs alter the functions of all NOS isoforms by several different mechanisms [22,23] and thus reduce NO production. This decreased NO bioavailability could lead to an inadequate vasodilation, leading to unopposed vasoconstriction, which is a main mechanism of CNI-induced alteration in organ hemodynamics, including the kidney.

While the immunosuppressive effects of corticosteroids are highly beneficial in terms of prevention and treatment of acute rejection, multiple adverse effects are associated with the use of corticosteroids. Corticosteroids are most notorious for various systemic effects such as weight gain, hormonal imbalances, salt and water retention, Cushing's disease, and hypertension [24,25]. There is substantial evidence concerning the dose-dependent relationship of corticosteroids and the risk of hypertensive crisis in organ transplant recipients [26]. The clinicians accordingly recommend minimal dosages of steroids (for example, 5 mg per day dose of prednisone) to achieve long-term immunosuppression in organ transplant recipients without increasing their risk for episodic hypertension [27].

Alterations in sympathetic nervous system activity have been suggested as a key mechanism in the development of cyclosporine-associated systemic hypertension [28]. Scherrer et al. [29] provided evidence of sympathetic overactivity in heart transplant recipients treated with cyclosporine (CsA) by recording sympathetic action potentials from the peroneal nerve using intraneural microelectrodes. Arterial pressure and sympathetic nerve activity were compared between five recipients treated with azathioprine and prednisone alone and 16 recipients treated with azathioprine, prednisone, and CsA. The CsA-treated group exhibited higher blood pressures, which were accompanied by increased sympathetic nerve activity. Notably, although norepinephrine levels in these patients were within the "normal" range, they were still approximately 50% higher than in transplant recipients not receiving CsA, thus leading to elevated sympathetic discharge and increased regional vascular resistance [30].

A calcineurin inhibitor (CNI)-independent explanation for hypertension in cardiac transplant patients centers on cardiac denervation and its effect on dysregulated cardio-renal reflexes [9]. In a normal heart, volume expansion is sensed by cardiac volume receptors, which suppress vasopressin and the renin-angiotensin-aldosterone system (RAAS) while promoting diuresis and natriuresis [31]. Animal studies in denervated dogs have shown diminished diuretic and natriuretic responses. Similarly, in heart transplant patients, renal reflexes to volume expansion are impaired, and the RAAS response is not appropriately suppressed. In a small study, Braith et al. compared blood pressure, renal, and endocrine responses to acute volume expansion in 10 heart transplant recipients and six liver transplant patients on similar cyclosporine doses versus a control group. Blood pressure increased in the heart transplant group, while urine flow and sodium excretion were blunted compared to controls [32]. They also observed abnormally elevated atrial natriuretic peptide levels in heart transplant recipients, suggesting dysregulation of cardiac mechanoreceptors that regulate hormone release [33]. It was shown that pretreatment with captopril abolished elevations in systolic and diastolic blood pressure, normalized angiotensin II and aldosterone levels, and restored urine flow and sodium excretion following saline infusion [34]. These findings have important therapeutic implications, highlighting the potential benefit of angiotensin-converting enzyme inhibitors (ACEi) and sodium restriction in managing hypertension in this population.

Another factor contributing to hypertension in heart transplant patients is the absence of the normal nocturnal decline in blood pressure, which leads to inappropriately smaller reductions in cardiac output. Modest increases in peripheral resistance have also been

observed [35]. This disrupted circadian rhythm, with the loss of the typical nighttime blood pressure fall, results in a greater 24-h hypertensive burden on the allograft. It is thought to arise from the denervated transplanted heart's inability to respond appropriately to the nocturnal increase in vagal tone and decrease in sympathetic activity. Additionally, immunosuppressive therapy may play a role, as cyclosporine and glucocorticoids can cause fluid retention and increased venous return during the night, potentially further blunting the normal nocturnal decline in cardiac output [36].

4. Diagnostic Workup of Post-Cardiac Transplant Hypertension

When hypertension is suspected, a 24 h ambulatory blood pressure monitoring (ABPM) should be performed to confirm the diagnosis of hypertension, identify non-circadian patterns of hypertension, as well as ascertain the burden of hypertension. In a study by Walker et al. [37] comparing 24 h ABPM and routine clinical BP monitoring, the incidence of hypertension was 52% in the 24 h group and 33% in the clinical BP monitoring group ($p = 0.02$). Bansal et al. showed that when ABPM was performed in 34 pediatric heart transplant recipients (PHT), mean age 14 ± 5 years, median 5.5 years post-PHT, ABPM identified masked HTN in 60% of patients, with majority being categorized as nocturnal hypertension, with abnormal circadian BP patterns found in 82% of patients. A discordance between clinic BP readings and ABPM was also seen, thus diagnosing masked hypertension; resulting in a modification of therapy [38]. In a review consisting of over 2000 renal transplant patients, ABPM reflected target organ damage (carotid intimal thickness and left ventricular wall mass) more closely than blood pressure measured in the office. It also served the dual purpose of identifying patients who exhibited nocturnal hypertension, as well as a non-circadian BP “non-dipper” which has emerged as a risk factor for cardiovascular events in kidney transplant patients [39].

The ISHLT guidelines [40] on the care of heart transplant recipients recommend the use of 24 h ambulatory blood pressure monitoring as a IIa recommendation with level of evidence C. Since transplant patients lack the normal diurnal variation in BP, the 24 h ABPM can also help ascertain the burden of hypertension [41]. Thus, ABPM is emerging as an important tool in heart transplant follow-up, especially for diagnosing masked hypertension and nocturnal BP abnormalities. Given the parallel evidence from renal transplant patients, ABPM should be strongly considered for patients with discrepant clinic vs. home BP readings, those with suspected nocturnal patterns, or individuals with immunosuppression-related hypertension or early graft vasculopathy.

A basic workup, including thyroid function, renin, aldosterone levels, and metanephrines, can be obtained to rule out other causes of hypertension, depending on the clinical scenario [42]. Other comorbidities should also be evaluated. These include overnight sleep testing for obstructive sleep apnea [43], 24 h urine protein or urine spot PCR, renal ultrasound for evaluation of renal parenchymal disease [44], complete blood count to rule out cell dyscrasias, comprehensive metabolic panel for electrolytes, renal and liver function, and hemoglobin A1c. Renal artery ultrasound should be obtained to look for renal vascular disease [45].

Once the diagnosis of hypertension is made, it is important to obtain a transthoracic echocardiogram to establish a baseline cardiac function and chamber sizes, as we know that hypertension can lead to left ventricular hypertrophy (LVH). In cardiac transplant patients, LVH can also be due to other causes, such as treatment with CNIs [46], donor-derived LVH, and chronic allograft rejection [47,48]. It is also essential to repeat echocardiograms during follow-up of treatment of hypertension, since there is clear evidence of LVH regression with treatment of hypertension [49].

5. Blood Pressure Goals

Treatment of hypertension in transplant recipients is imperative to preserve allograft function and avoid long-term complications such as CAV [50]. The BP goal for transplant recipients is not well established; however, based on recent hypertension guidelines in 2017 [51], it is safe to say that we should be targeting a BP < 130/90 or even lower to <120/80 as studied in the SPRINT trial [52], although the trial did not include any transplant patients. The hypertension guidelines recommend aggressive BP control to <120/80 in patients with concomitant risk factors for ASCVD (which in our case would include CAV), such as hyperlipidemia, smoking, diabetes, and obesity.

6. Non-Pharmacological Therapies for Treatment of Hypertension in Heart Transplant Recipients

The ACC/AHA hypertension guidelines emphasize the importance of non-pharmacological measures to target hypertension. These include weight loss in patients who are overweight or obese [53], sodium restriction to <1.5 g per day [54], DASH (Dietary Approaches to Stop Hypertension) diet [55], reduced alcohol intake and smoking cessation. Sodium restriction is particularly very important in post-cardiac transplant hypertension, which is partly mediated by enhanced sodium sensitivity and sodium retention [56,57]. The guidelines also recommend potassium supplementation to treat hypertension. However, this might be harmful in transplant patients who are at risk for hyperkalemia from other medications. Physical activity such as aerobic exercises, dynamic resistance training, and isometric resistance training have been shown to be extremely beneficial for hypertension management as elucidated by several meta-analyses [58,59].

Treatment of hypertension also includes treatment of comorbidities such as hyperlipidemia and diabetes, both of which are risk factors for hypertension in heart transplant patients. Treatment of OSA with CPAP has been shown to have beneficial effects in lowering BP [60]. Often, these patients need multiple visits to up-titrate/optimize anti-hypertensive medications to achieve the target. A study from the Cedars group by Jamero et al. [61] showed that utilizing tele-visits with nurse practitioners was a very effective tool in achieving the target BP goal in heart transplant patients within a short timeframe.

7. Anti-Hypertensive Medications in Transplant Recipients

As previously mentioned, patients with heart transplantation have an altered circadian rhythm and lose the diurnal variation in BP. Hence, the burden of hypertension is much higher compared to normal individuals [62]. In general, due to the lack of diurnal variation and lack of nighttime BP dip, expert reviews recommend twice daily dosing or nighttime dosing of anti-HTN medications to combat this problem [63,64].

7.1. Calcium Channel Blockers (CCBs)

Dihydropyridine CCBs are the most widely used anti-hypertensive medications in the early post-transplant period. They have minimal drug interactions and a simple side effect profile. The non-dihydropyridine CCBs like diltiazem and verapamil have negative inotropic effects and AV nodal blocking properties, so they are generally avoided during the early postoperative period. Diltiazem and verapamil have the added effect of boosting the levels of CNI, as it is a CYP 450 enzyme inhibitor [65], so one should be very careful in monitoring the CNI levels when a patient is initiated on these drugs. It is usually suggested to dose reduce CNIs by 20–50% [66]. CCBs are potent renal vasodilators and have the added benefit of combating CNI-induced renal vasoconstriction and thereby improving renal function [67].

Based on a large Cochrane analysis [68] performed on renal transplant recipients, the hypertension guidelines recommend the use of calcium channel blockers as first-line agents for hypertension in the renal transplant population. The RAAS blockade should be considered in patients with additional comorbidities, such as proteinuria or reduced LVEF, with caution required in those with hyperkalemia and worsening creatinine.

In a large randomized trial including 116 cyclosporin-treated heart transplant patients with HTN, Brozena et al. [69] studied the efficacy of lisinopril vs. diltiazem in the treatment of HTN. They found that both drugs were equally effective in lowering blood pressure. There was a numerically higher incidence of peripheral edema in the diltiazem group, and similarly numerically higher incidence of hypotension and hyperkalemia in the lisinopril group. Interestingly, there was a significant number of non-responders in both groups (42% in the diltiazem group and 36% in the lisinopril group), suggesting that most patients need more than one drug for the treatment of hypertension.

7.2. RAAS Blockade

As previously discussed, heart transplant recipients tend to have the inability to suppress their RAAS due to sympathetic denervation of the heart [9], leading to expansion of extracellular volume by sodium and water retention. ACEi and angiotensin receptor blockers (ARBs) are less commonly used to treat isolated post-transplant hypertension without another indication. The reason is the added nephrotoxicity by renal vasoconstriction concomitantly with CNIs [70]. A large systematic review on using ACEi in renal transplant patients [71] showed that there was a decrease in proteinuria and BP. However, they did notice a decline in GFR during short-term follow-up. A study by Hausberg et al., comparing atenolol to quinapril for treatment of HTN in renal transplant patients, showed that both medications were equally effective, and quinapril had the added benefit of renal protection by reducing albuminuria with no change in renal function [72]. As such, the guidelines recommend using RAAS blockade for hypertension in patients with concomitant CKD, proteinuria, or depressed LVEF.

7.3. Beta Blockers

Beta blockers (BB) are generally avoided in the initial period post-transplant due to the risk of bradycardia in denervated hearts and the negative inotropic effects [66]. Some specific beta blockers, such as nebivolol with intrinsic nitric oxide-mediated vasodilatory properties, are particularly attractive to treat CNI-induced hypertension from a high SVR state. Although there are no randomized controlled trials, BB can be used safely and effectively for the treatment of hypertension in heart transplant recipients [73].

7.4. Diuretics

Diuretics are commonly used in heart transplant recipients for volume optimization during the initial post-operative phase when the allograft is still stiff, recovering from cold ischemia. Loop diuretics have a modest effect on BP. A recent study by Tutakhel et al. [74] showed that thiazide diuretics are better at treating CNI-induced hypertension by promoting sodium excretion via the thiazide-sensitive sodium chloride transporters, which are upregulated by CNIs.

7.5. Vasodilators

As previously discussed, systemic vasoconstriction due to a high SVR state is one of the pathophysiological drivers of systemic hypertension in post-transplant patients [75]. Vasodilators such as alpha blockers and hydralazine are very effective in controlling HTN in this setting [76].

8. Management of Immunosuppression for Treatment of Hypertension in Heart Transplant Recipients

The cornerstone of pharmacological therapy in targeting hypertension in heart transplant recipients is reducing the dose of immunosuppression to the lowest effective dose [22]. The ISHLT guidelines recommend that immunosuppression be tailored to every individual patient to minimize the ill effects while protecting the allograft from rejection [50].

There are several studies evaluating the safety and efficacy of early steroid weaning in heart transplant patients [22,77]. All of these studies have demonstrated that early steroid weaning is feasible and safe in the first year after transplant in the contemporary era of maintenance immunosuppression using CNI and cell cycle inhibitors. Some studies did report increased incidence of biopsy-proven early rejections in the early steroid weaning group; however, the overall survival was not different [78]. An interesting trial by Yamani et al. [79] studied the outcomes on steroid-free immunosuppression after thymoglobulin induction compared to routine immunosuppression with thymoglobulin induction. They showed that both groups had similar incidences of early rejection (both groups were treated with pulse steroids during rejection). The steroid-free group had better long-term metabolic effects in terms of bone density and muscle strength. The RESTCO study [80] in the Spanish heart transplant population also showed similar results, including a statistically significant decrease in hypertension in the steroid-free group. Multiple other studies have also shown that hypertension improves after steroid weaning [81,82].

The ISHLT guidelines [50] recommend weaning immunosuppression, including CNIs, to the lowest effective dose to mitigate the potential side effects. There have been several studies evaluating the safety of reduced CNI dosing. In general, hypertension is less common with tacrolimus compared to cyclosporine, as shown in the landmark studies by Taylor et al. [6] and Kobashigawa et al. [7]. Reduction in CNI dosage to the minimal effective dose has been shown to decrease the incidence of hypertension in renal transplant patients [83]. CNI sparing regimens [84] or reduced-dose CNI in combination with proliferation signal inhibitors [85] have also shown decreased incidence of hypertension in the long run. However, one should be very cautious in changing immunosuppression early in the post-transplant period and in high-risk patients (with a history of rejections and donor-specific antibodies) by carefully weighing the risk of allograft rejections [75,86]. Of note, CNI-free regimens also improve renal function as well as lower BP [87]. A landmark study from the Mayo group also showed decreased incidence of CAV and decreased incidence of hypertension in the early sirolimus conversion group compared to the CNI group [88].

9. Novel Therapies and Existing Knowledge Gaps

ARNIs, non-steroidal MRAs, and SGLT2 inhibitors are some of the most recent BP agents that are being used in patients with heart failure. Although not primarily used for HTN management these agents lower the systemic BP as afterload-reducing agents, as well as leading to left ventricular reverse remodeling and improving the ejection fraction. SGLT2 inhibitors in particular have been shown to improve the nocturnal hypertension in patients with diabetes mellitus [89]. The EMPA-REG BP investigators trial showed significant BP lowering in addition to glycemic control in diabetic patients treated with empagliflozin [90]. A small retrospective study with 22 heart transplant patients showed that SGLT2i were both safe and effective in the management of diabetes without any infectious complications [91], although there was no significant change in the BP. Larger randomized studies are needed to evaluate the use of SGLT2i in heart transplant patients. The DAPARHT trial is currently enrolling patients with heart transplants to study the effects of dapagliflozin [92].

The BP-lowering effects of sacubitril valsartan, an angiotensin receptor-neprilysin inhibiting agent, are well known in the non-transplant population [93]; however, its use in the post-transplant population has not been well studied.

The latest addition to the armamentarium of heart failure therapies is finerenone, which is a non-steroidal mineralocorticoid antagonist. This is also an afterload reducing agent shown to have a significant effect on BP lowering in patients with CKD and type 2 DM [94]. Its use in heart transplant patients has not been studied yet. Spironolactone, which is also a mineralocorticoid antagonist, has been shown to improve BP in patients with resistant hypertension and HFpEF [95]. A small study from Romania showed that patients exposed to spironolactone early post-transplant had less rejection, although they did not evaluate the BP effects in this study [96]. The main caveat of mineralocorticoid antagonists is the hyperkalemia associated with treatment. In the post-transplant patients, this could be challenging with concomitant use of other medications, which may also cause hyperkalemia, such as TMP-SMX and tacrolimus.

Renal denervation therapy has been studied for many years as a treatment for refractory hypertension, and recently, we have three different devices that have been approved [97]. We do not have data about the efficacy and safety in post-heart-transplant patients. This therapy could be a potential option for heart transplant patients with sub-optimal BP control on multiple agents if shown to be safe.

The various pharmacological therapies are summarized in Table 1.

Table 1. Summary of different classes of anti-hypertension in cardiac transplant patients.

Drug Class	Recommendation	Benefits	Risks/Side Effects
Calcium Channel Blockers (CCBs)	Dihydropyridine CCB—first-line therapy for post-cardiac transplant hypertension	Minimal drug interactions (DHP CCB), low side effect profile, potent renal vasodilators, improve renal function	Diltiazem/verapamil: negative inotropic effect, AV nodal block—avoid in early postoperative period, boost CNI levels (CYP 450 inhibitor), need CNI dose reduction (20–50%)
RAAS blockade	Preferred agents with concomitant diabetes mellitus, proteinuria, reduced LVEF, CKD	Decrease proteinuria and BP, renal protection (quinapril)	Monitor for nephrotoxicity with use of CNIs, decline in GFR (short term), caution with hyperkalemia
Beta blockers	Second- or third-line agents preferred with concomitant arrhythmias, tremors (propranolol)	Nebivolol: nitric oxide-mediated vasodilation, treats CNI-induced hypertension	Risk of bradycardia, negative inotropic effects—avoid in the early postoperative period
Diuretics	Used for volume optimization, thiazides are better for CNI-induced HTN	Promote sodium excretion, Loop diuretics—modest BP effect, thiazides are more effective for BP	Risk of dehydration and volume loss
Vasodilators (hydralazine, alpha blockers)	Third-line agents are used when other agents are not tolerated.	Cause systemic vasodilation	Headaches, compensatory tachycardia, orthostatic hypotension.
SGLT2i	Modest BP-lowering effect—consider with concomitant diabetes mellitus and CKD.	No studies in use for BP control in heart transplant patients	Risk of UTI—need careful monitoring

10. Clinical Practice Application

The best clinical practice model combines evidence-based guidelines as discussed in the review, multidisciplinary care, and an understanding of donor-specific risk profiles

and individualized risk stratification. As previously stated, ABPM should be strongly considered for patients with discrepant clinic vs. home BP readings, those with suspected nocturnal patterns, or individuals with immunosuppression-related hypertension or early graft vasculopathy. Utilization of ancillary resources, such as dedicated transplant nurse practitioners and use of tele-visits, allows for closer monitoring and day-to-day follow-up. Risk factor assessment and stratification should be thoroughly performed and optimized. Further studies related to donor-specific risk factors are warranted. As previously discussed, the cornerstone of pharmacological therapy in targeting hypertension in heart transplant recipients is reducing the dose of immunosuppression to the lowest effective dose. Adding medications in a stepwise approach to reach a goal BP < 130/80, with calcium channel blockers being first-line agents and ACE inhibitors in the instance of proteinuria or LV dysfunction. Finally, our heart transplant recipients benefit greatly from coordinated management across medical, vascular, renal, and lifestyle domains. Consider involving a nephrologist from the early post-transplant period, especially in patients with pre-existing CKD, diabetes, high-dose CNI exposure, or persistent and uncontrolled hypertension. Lifestyle modifications such as sodium restriction, maintaining hydration, weight management, and aggressive diabetes control with early referral to our endocrinology colleagues are very important.

11. Prognosis

The implications of post-transplant hypertension are enormous regarding cardiac and renal structural alterations and subsequent dysfunction [98]. One consequence of hypertension is increased arterial stiffness, which leads to an increased risk of cardiovascular events, graft vascular disease, and increased mortality in transplantation patients [10]. It is also thought that post-transplant hypertension plays a significant role in the onset of angiographic CAV [99,100]. While CAV is multifactorial in origin, with both immune-mediated and non-immune-mediated factors contributing to the pathogenesis [101], non-immune mediated risk factors such as hyperlipidemia, hypertension, diabetes mellitus, metabolic syndrome, smoking, and obesity can predispose cardiac transplant recipients to CAV [102]. These risk factors are found in greater prevalence in solid organ transplant recipients, mainly due to the side effects of immunosuppressive medications, which can cause or worsen pre-existing metabolic disorders.

However, there have been several smaller studies suggesting that outcomes improve with treatment. One study by Schroeder et al. showed that in cardiac-transplant recipients randomized to diltiazem, there was a decreased incidence of angiographic CAV and death at five years. Similarly, it was shown that in 32 cardiac transplant recipients, intimal thickness at one year measured by intravascular ultrasound (IVUS) was significantly greater in the untreated control group than in those who received calcium channel blockers, ACE inhibitors, or both [103,104]. In a more recent study, the combined use of these agents was more effective than either drug alone at reducing IVUS indices of CAV [105], and there is further evidence that use of ACE inhibitors or angiotensin receptor blockers results in improved outcomes [7]. These findings emphasize the gravity of the fact that control of hypertension should be a priority in heart transplant recipients [106].

12. Conclusions

In summary, while heart transplantation remains the gold standard of treatment for end-stage heart failure, hypertension post-transplant is not only very common but also carries a significant burden of morbidity and mortality. Post-transplant hypertension is a complex issue with multiple proposed pathophysiologic etiologies. The first step in the management of HTN is lifestyle modification, as well as management of comorbidities

such as OSA and obesity in post-transplant recipients. The second step is the optimization of immunosuppression to the lowest effective dose, particularly with calcineurin inhibitors. When it comes to pharmacological therapies for HTN, multiple anti-hypertensive agents are available; it is imperative to choose the right agent for the individual patient using personalized medicine based on comorbidities. Larger randomized trials to evaluate the long-term effects of the various anti-HTN medications in transplant recipients, as well as the use of the latest therapies such as renal nerve denervation, and the use of ARNi, SGLT2i, and Finerenone.

13. Limitations

A limitation in our systematic literature review is that most studies involving cardiac transplant patients are single-center retrospective studies, with smaller population sizes, which limit generalizability. There are variations in study design, populations, and interventions, thus making comparisons difficult.

14. Key Points

- A 70–90% incidence of HTN in heart transplant patients attributable to CNI therapy, which cause renal vasoconstriction, stimulating the RAAS, causing sodium and fluid retention.
- Lack of normal “nocturnal decline” of blood pressure due to cardiac denervation is also an important cause.
- Confirm hypertension diagnosis in cardiac transplant patients with 24 h ambulatory BP monitoring
- Lifestyle modification as well as management of comorbidities such as OSA and obesity is essential
- Multiple anti-hypertensive agents are available; choose the right agent for the individual patient using personalized medicine based on other comorbidities.
- Non-DHP CCB are first-line to alleviate CNI-induced vasoconstriction.
- RAAS blockade should be considered in patients with co-existing CKD or proteinuria.
- Beta blockers can be safely used in heart transplant patients who are not bradycardic.
- Immunosuppression management—Wean steroids as early as safely possible, Wean CNI to the lowest effective dose individualized to each patient.
- There exist knowledge gaps—there exists no data for the latest therapies such as renal nerve denervation, ARNi, SGLT2i, Finerenone in cardiac transplant recipients.

Author Contributions: Conceptualization, E.R.R., S.S. and J.M.O.-L.; writing—original draft preparation, E.R.R. and S.S.; writing—review and editing, E.R.R., S.S. and J.M.O.-L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Lund, L.H.; Edwards, L.B.; Kucheryavaya, A.Y.; Benden, C.; Christie, J.D.; Dipchand, A.I.; Dobbels, F.; Goldfarb, S.B.; Levvey, B.J.; Meiser, B.; et al. The registry of the international society for heart and lung transplantation: Thirty-first official adult heart transplant report—2014; Focus theme: Retransplantation. *J. Heart Lung Transplant.* **2014**, *33*, 996–1008. [[CrossRef](#)]
2. Campbell, P.T.; Krim, S.R. Hypertension in cardiac transplant recipients: Tackling a new face of an old foe. *Curr. Opin. Cardiol.* **2020**, *35*, 368–375. [[CrossRef](#)]

3. Olivari, M.T.; Antolick, A.; Ring, W.S. Arterial-hypertension in heart-transplant recipients treated with triple-drug immunosuppressive therapy. *J. Heart Transplant.* **1989**, *8*, 34–39. [\[PubMed\]](#)
4. Roche, S.L.; Kaufmann, J.; Dipchand, A.I.; Kantor, P.F. Hypertension After Pediatric Heart Transplantation is Primarily Associated With Immunosuppressive Regimen. *J. Heart Lung Transplant.* **2008**, *27*, 501–507. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Hořková, L.; Málek, I.; Kopkan, L.; Kautzner, J. Pathophysiological mechanisms of calcineurin inhibitor-induced nephrotoxicity and arterial hypertension. *Physiol. Res.* **2017**, *66*, 167–180. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Taylor, D.O.; Barr, M.L.; Radovancevic, B.; Renlund, D.G.; Mentzer, R.M., Jr.; Smart, F.W.; Tolman, D.E.; Frazier, O.; Young, J.B.; VanVeldhuisen, P. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: Decreased hyperlipidemia and hypertension with tacrolimus. *J. Heart Lung Transplant.* **1999**, *18*, 336–345. [\[CrossRef\]](#)
7. Kobashigawa, J.A.; Patel, J.; Furukawa, H.; Moriguchi, J.; Yeatman, L.; Takemoto, S.; Marquez, A.; Shaw, J.; Oeser, B.; Subherwal, S.; et al. Five-year results of a randomized, single-center study of tacrolimus vs microemulsion cyclosporine in heart transplant patients. *J. Heart Lung Transplant.* **2006**, *25*, 434–439. [\[CrossRef\]](#)
8. Eisen, H.J. Hypertension in heart transplant recipients: More than just cyclosporine. *J. Am. Coll. Cardiol.* **2003**, *41*, 433–434. [\[CrossRef\]](#)
9. Braith, R.W.; Mills, R.M.; Wilcox, C.S.; Convertino, V.; Davis, G.L.; Limacher, M.C.; Wood, C. Fluid homeostasis after heart transplantation: The role of cardiac denervation. *J. Heart Lung Transplant.* **1996**, *15*, 872–880.
10. de Souza-Neto, J.D.; de Oliveira, Í.M.; Lima-Rocha, H.A.; Oliveira-Lima, J.W.; Bacal, F. Hypertension and arterial stiffness in heart transplantation patients. *Clinics* **2016**, *71*, 494–499. [\[CrossRef\]](#)
11. Gus, M.; Schiavo, N.; Da Costa, A.R. Systemic hypertension in heart transplant recipients. *Arq. Bras. Cardiol.* **1999**, *72*, 634–640. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Farge, D.; Julien, J.; Amrein, C.; Guillemain, R.; Vulser, C.; Mihaileanu, S.; Dreyfus, G.; Carpentier, A. Effect of systemic hypertension on renal function and left ventricular hypertrophy in heart transplant recipients. *J. Am. Coll. Cardiol.* **1990**, *15*, 1095–1101. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Nygaard, S.; Christensen, A.H.; Sletner, L.; Rolid, K.; Nytrøen, K.; Gullestad, L.; Fiane, A.; Thaulow, E.; Døhlen, G.; Saul, J.P.; et al. Predictors of Hypertension Development 1 Year After Heart Transplantation. *Transplantation* **2022**, *106*, 1656–1665. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Radermacher, J.; Meiners, M.; Bramlage, C.; Kliem, V.; Behrend, M.; Schlitt, H.J.; Pichlmayr, R.; Koch, K.M.; Brunkhorst, R. Pronounced renal vasoconstriction and systemic hypertension in renal transplant patients treated with cyclosporin A versus FK 506. *Transpl. Int.* **1998**, *11*, 3–10. [\[CrossRef\]](#)
15. Ye, F.; Ying-Bin, X.; Yu-Guo, W.; Hetzer, R. Tacrolimus Versus Cyclosporine Microemulsion for Heart Transplant Recipients: A Meta-analysis. *J. Heart Lung Transplant.* **2009**, *28*, 58–66. [\[CrossRef\]](#)
16. Weidle, P.J.; Vlasses, P.H. Systemic hypertension associated with cyclosporine: A review. *Drug Intell. Clin. Pharm.* **1988**, *22*, 443–451. [\[CrossRef\]](#)
17. Ozdogan, E.; Banner, N.; Fitzgerald, M.; Musumeci, F.; Khaghani, A.; Yacoub, M. Factors influencing the development of hypertension after heart transplantation. *J. Heart Transplant.* **1990**, *9*, 548–553.
18. Prókai, Á.; Csóhány, R.; Sziksz, E.; Pap, D.; Balicza-Himer, L.; Boros, S.; Magda, B.; Vannay, Á.; Kis-Petik, K.; Fekete, A.; et al. Calcineurin-inhibition Results in Upregulation of Local Renin and Subsequent Vascular Endothelial Growth Factor Production in Renal Collecting Ducts. *Transplantation* **2016**, *100*, 325–333. [\[CrossRef\]](#)
19. Nishiyama, A.; Kobori, H.; Fukui, T.; Zhang, G.-X.; Yao, L.; Rahman, M.; Hitomi, H.; Kiyomoto, H.; Shokoji, T.; Kimura, S.; et al. Role of Angiotensin II and Reactive Oxygen Species in Cyclosporine A-Dependent Hypertension. *Hypertension* **2003**, *42*, 754–760. [\[CrossRef\]](#)
20. Sudhir, K.; MacGregor, J.S.; DeMarco, T.; De Groot, C.J.; Taylor, R.N.; Chou, T.M.; Yock, P.G.; Chatterjee, K. Cyclosporine impairs release of endothelium-derived relaxing factors in epicardial and resistance coronary arteries. *Circulation* **1994**, *90*, 3018–3023. [\[CrossRef\]](#)
21. Cornu, C.; Dufays, C.; Gaillard, S.; Gueyffier, F.; Redonnet, M.; Sebbag, L.; Roussoulières, A.; Gleissner, C.A.; Groetzner, J.; Lehmkuhl, H.B.; et al. Impact of the reduction of calcineurin inhibitors on renal function in heart transplant patients: A systematic review and meta-analysis. *Br. J. Clin. Pharmacol.* **2014**, *78*, 24–32. [\[CrossRef\]](#)
22. Aparicio, L.S.; Alfie, J.; Barochiner, J.; Cuffaro, P.E.; Rada, M.; Morales, M.; Galarza, C.; Waisman, G.D. Hypertension: The Neglected Complication of Transplantation. *ISRN Hypertens.* **2013**, *2013*, 165937. [\[CrossRef\]](#)
23. Issa, N.; Kukla, A.; Ibrahim, H.N. Calcineurin inhibitor nephrotoxicity: A review and perspective of the evidence. *Am. J. Nephrol.* **2013**, *37*, 602–612. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Veenstra, D.L.; Best, J.H.; Hornberger, J.; Sullivan, S.D.; Hricik, D.E. Incidence and long-term cost of steroid-related side effects after renal transplantation. *Am. J. Kidney Dis.* **1999**, *33*, 829–839. [\[CrossRef\]](#) [\[PubMed\]](#)

25. Bonnet, G.; Coutance, G.; Van Keer, J.; Raynaud, M.; Aubert, O.; Bories, M.; Bruneval, P.; Varnous, S.; Leprince, P.; Empana, J.; et al. Determinants of trajectories of cardiac allograft vasculopathy after heart transplantation: A population based study. *Eur. Heart J.* **2020**, *41*, ehaa946–1288. [\[CrossRef\]](#)
26. Nassar, M.; Nso, N.; Lakhdar, S.; Kondaveeti, R.; Buttar, C.; Bhango, H.; Awad, M.; Sheikh, N.S.; Soliman, K.M.; Munira, M.S.; et al. New onset hypertension after transplantation. *World J. Transplant.* **2022**, *12*, 42–54. [\[CrossRef\]](#)
27. Heegaard, B.; Nelson, L.M.; Gustafsson, F. Steroid withdrawal after heart transplantation in adults. *Transpl. Int.* **2021**, *34*, 2469–2482. [\[CrossRef\]](#)
28. Ciarka, A.; Najem, B.; Cuylits, N.; Leeman, M.; Xhaet, O.; Narkiewicz, K.; Antoine, M.; Degaute, J.-P.; van de Borne, P. Effects of peripheral chemoreceptors deactivation on sympathetic activity in heart transplant recipients. *Hypertension* **2005**, *45*, 894–900. [\[CrossRef\]](#)
29. Scherrer, U.; Vissing, S.F.; Morgan, B.J.; Rollins, J.A.; Tindall, R.S.; Ring, S.; Hanson, P.; Mohanty, P.K.; Victor, R.G. Cyclosporine-Induced Sympathetic Activation and Hypertension after Heart Transplantation. *N. Engl. J. Med.* **1990**, *323*, 693–699. [\[CrossRef\]](#)
30. Rundqvist, B.; Casale, R.; Bergmann-Sverrisdottir, Y.; Friberg, P.; Mortara, A.; Elam, M. Rapid fall in sympathetic nerve hyperactivity in patients with heart failure after cardiac transplantation. *J. Card. Fail.* **1997**, *3*, 21–26. [\[CrossRef\]](#)
31. Braith, R.W.; Plunkett, M.B.; Mills, R.M. Cardiac output responses during exercise in volume-expanded heart transplant recipients. *Am. J. Cardiol.* **1998**, *81*, 1152–1156. [\[CrossRef\]](#)
32. Braith, R.W.; Mills, R.M.; Wilcox, C.S.; Davis, G.L.; Wood, C.E. Breakdown of blood pressure and body fluid homeostasis in heart transplant recipients. *J. Am. Coll. Cardiol.* **1996**, *27*, 375–383. [\[CrossRef\]](#)
33. Braith, R.W.; Wood, C.; Limacher, M.C.; Pollock, M.L.; Lowenthal, D.T.; Phillips, M.; Staples, E.D. Abnormal neuroendocrine responses during exercise in heart transplant recipients. *Circulation* **1992**, *86*, 1453–1463. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Braith, R.W.; Mills, R.M.; Wilcox, C.S.; Davis, G.L.; Hill, J.; Wood, C. High-dose angiotensin-converting enzyme inhibition restores body fluid homeostasis in heart-transplant recipients. *J. Am. Coll. Cardiol.* **2003**, *41*, 426–432. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Idema, R.N.; Van Den Meiracker, A.H.; Balk, A.H.M.M.; Bos, E.; Schalekamp, M.A.D.H.; Man In 'Tveld, A.J. Abnormal diurnal variation of blood pressure, cardiac output, and vascular resistance in cardiac transplant recipients. *Circulation* **1994**, *90*, 2797–2803. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Imai, Y.; Abe, K.; Sasaki, S.; Minami, N.; Nihei, M.; Munakata, M.; Murakami, O.; Matsue, K.; Sekino, H.; Miura, Y. Altered circadian blood pressure rhythm in patients with Cushing's syndrome. *Hypertension* **1988**, *12*, 11–19. [\[CrossRef\]](#)
37. Walker, A.H.; Locke, T.J.; Braidley, P.C.; Al-Mohammed, A. The importance of 24 hour ambulatory blood pressure monitoring after thoracic organ transplantation. *J. Heart Lung Transplant.* **2005**, *24*, 1770–1773. [\[CrossRef\]](#)
38. Bansal, N.; Raedi, W.A.; Medar, S.S.; Abraham, L.; Beddows, K.; Hsu, D.T.; Lamour, J.M.; Mahgerefteh, J. Masked Hypertension in Pediatric Heart Transplant Recipients. *Pediatr. Cardiol.* **2023**, *44*, 1003–1008. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Lipkin, G.W.; Tucker, B.; Giles, M.; Raine, A.E.G. Ambulatory blood pressure and left ventricular mass in cyclosporin- and non-cyclosporin-treated renal transplant recipients. *J. Hypertens.* **1993**, *11*, 439–442. [\[CrossRef\]](#)
40. Velleca, A.; Shullo, M.A.; Dhital, K.; Azeka, E.; Colvin, M.; DePasquale, E.; Farrero, M.; García-Guereta, L.; Jamero, G.; Khush, K.; et al. The international society of heart and lung transplantation guidelines for the care of heart transplant recipients TASK FORCE 3: Long-term Care of Heart Transplant Recipients. *J. Heart Lung Transplant.* **2010**, *29*, 914–956.
41. Haydar, A.A.; Covic, A.; Jayawardene, S.; Agharazii, M.; Smith, E.; Gordon, I.; O'sullivan, H.; Goldsmith, D.J.A. Insights from ambulatory blood pressure monitoring: Diagnosis of hypertension and diurnal blood pressure in renal transplant recipients. *Transplantation* **2004**, *77*, 849–853. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Rimoldi, S.F.; Scherrer, U.; Messerli, F.H. Secondary arterial hypertension: When, who, and how to screen? *Eur. Heart J.* **2013**, *35*, 1245–1254. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Davies, C.W.H.; Crosby, J.H.; Mullins, R.L.; Barbour, C.; Davies, R.J.O.; Stradling, J.R. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. *Thorax* **2000**, *55*, 736–740. [\[CrossRef\]](#)
44. Whaley-Connell, A.T.; Sowers, J.R.; Stevens, L.A.; McFarlane, S.I.; Shlipak, M.G.; Norris, K.C.; Chen, S.-C.; Qiu, Y.; Wang, C.; Li, S.; et al. CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Am. J. Kidney Dis.* **2008**, *51*, S13–S20. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Garovic, V.D.; Textor, S.C. Renovascular hypertension and ischemic nephropathy. *Circulation* **2005**, *112*, 1362–1374. [\[CrossRef\]](#)
46. Antunes, M.L.; Spotnitz, H.M.; Clark, M.B.; Steinhardt, M.J.; Marboe, C.C.; Smith, C.R.; Rose, E.A.; Reemtsma, K. Long-term function of human cardiac allografts assessed by two-dimensional echocardiography. *J. Thorac. Cardiovasc. Surg.* **1989**, *98*, 275–284. [\[CrossRef\]](#)
47. Ananthasubramaniam, K.; Garikapati, K.; Williams, C.T. Progressive left ventricular hypertrophy after heart transplantation: Insights and mechanisms suggested by multimodal images. *Tex. Heart Inst. J.* **2016**, *43*, 65–68. [\[CrossRef\]](#)

48. Stetson, S.J.; Perez-Verdia, A.; Mazur, W.; Farmer, J.A.; Koerner, M.M.; Weilbaecher, D.G.; Entman, M.L.; Quinones, M.A.; Noon, G.P.; Torre-Amione, G. Cardiac hypertrophy after transplantation is associated with persistent expression of tumor necrosis factor- α . *Circulation* **2001**, *104*, 676–681. [\[CrossRef\]](#)
49. Angermann, C.E.; Spes, C.H.; Willems, S.; Dominiak, P.; Kemkes, B.M.; Theisen, K. Regression of left ventricular hypertrophy in hypertensive heart transplant recipients treated with enalapril, furosemide, and verapamil. *Circulation* **1991**, *84*, 583–593. [\[CrossRef\]](#)
50. Velleca, A.; Shullo, M.A.; Dhital, K.; Azeka, E.; Colvin, M.; DePasquale, E.; Farrero, M.; García-Guereta, L.; Jamero, G.; Khush, K.; et al. The International Society for Heart and Lung Transplantation (ISHLT) Guidelines for the Care of Heart Transplant Recipients. *J. Heart Lung Transplant.* **2022**, *42*, e1–e141. [\[CrossRef\]](#)
51. Whelton, P.K.; Carey, R.M.; Aronow, W.S.; Casey, D.E., Jr.; Collins, K.J.; Dennison Himmelfarb, C.; DePalma, S.M.; Gidding, S.; Jamerson, K.A.; Jones, D.W.; et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical practice guidelines. *Hypertension* **2018**, *71*, e13–e115. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Wright, J.T.; Whelton, P.K.; Reboussin, D.M. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N. Engl. J. Med.* **2016**, *374*, 2290–2295. [\[CrossRef\]](#)
53. Whelton, P.K.; Appel, L.J.; Espeland, M.A.; Applegate, W.B.; Ettinger, W.H., Jr.; Kostis, J.B.; Kumanyika, S.; Lacy, C.R.; Johnson, K.C.; Folmar, S.; et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: A randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). *JAMA* **1998**, *279*, 839. [\[CrossRef\]](#)
54. Singer, D.R.; Markandu, N.D.; Buckley, M.G.; Miller, M.; Sagnella, G.; Lachno, D.R.; Cappuccio, F.P.; Murday, A.; Yacoub, M.H.; MacGregor, G. Blood pressure and endocrine responses to changes in dietary sodium intake in cardiac transplant recipients. Implications for the control of sodium balance. *Circulation* **1994**, *89*, 1153–1159. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Filippou, C.D.; Tsioufis, C.P.; Thomopoulos, C.G.; Mihos, C.C.; Dimitriadis, K.S.; Sotiropoulou, L.; Chrysochoou, C.; Nihoyannopoulos, P.; Tousoulis, D.M. Dietary Approaches to Stop Hypertension (DASH) Diet and Blood Pressure Reduction in Adults with and without Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Adv. Nutr.* **2020**, *11*, 1150–1160. [\[CrossRef\]](#)
56. Hoorn, E.J.; Walsh, S.B.; McCormick, J.; Fürstenberg, A.; Yang, C.-L.; Roeschel, T.; Paliege, A.; Howie, A.J.; Conley, J.; Bachmann, S.; et al. The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. *Nat. Med.* **2011**, *17*, 1304–1309. [\[CrossRef\]](#)
57. Ciresi, D.L.; Lloyd, M.A.; Sandberg, S.M.; Heublein, D.M.; Edwards, B.S. The sodium retaining effects of cyclosporine. *Kidney Int.* **1992**, *41*, 1599–1605. [\[CrossRef\]](#)
58. Cornelissen, V.A.; Smart, N.A. Exercise training for blood pressure: A systematic review and meta-analysis. *J. Am. Heart Assoc.* **2013**, *2*, e004473. [\[CrossRef\]](#)
59. Carlson, D.J.; Dieberg, G.; Hess, N.C.; Millar, P.J.; Smart, N.A. Isometric exercise training for blood pressure management: A systematic review and meta-analysis. *Mayo Clin. Proc.* **2014**, *89*, 327–334. [\[CrossRef\]](#)
60. Kapa, S.; Kuniyoshi, F.H.S.; Somers, V.K. Sleep apnea and hypertension: Interactions and implications for management. *Hypertension* **2008**, *51*, 605–608. [\[CrossRef\]](#)
61. Jamero, G.; De Leon, F.; Ackerman, M.; Welton, M.; Kissling, N.; Velleca, A.; White, M.; Czer, L.; Nikolova, A.; Kransdorf, E.; et al. NP Telehealth Blood Pressure Management in Heart Transplant Patients—A Single Center Experience. *J. Heart Lung Transplant.* **2022**, *41*, S403. [\[CrossRef\]](#)
62. Wenting, G.J.; Meiracker, A.H.V.; Simoons, M.L.; Bos, E.; Eck, H.J.R.V.; Veld, A.J.M.I.; Weimar, W.; Schalekamp, M. Circadian variation of heart rate but not of blood pressure after heart transplantation. *Transplant. Proc.* **1987**, *19*, 2554–2555. [\[PubMed\]](#)
63. Starling, R.C.; Cody, R.J. Cardiac transplant hypertension. *Am. J. Cardiol.* **1990**, *65*, 106–111. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Mangray, M.; Vella, J.P. Hypertension after kidney transplant. *Am. J. Kidney Dis.* **2011**, *57*, 331–341. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Griño, J.M.; Sabate, I.; Castela, A.M.; Alsina, J. Influence of Diltiazem on Cyclosporin Clearance. *Lancet* **1986**, *327*, 1387. [\[CrossRef\]](#)
66. Lindenfeld, J.A.; Miller, G.G.; Shakar, S.F.; Zolty, R.; Lowes, B.D.; Wolfel, E.E.; Mestroni, L.; Page, R.L.; Kobashigawa, J. Drug therapy in the heart transplant recipient—Part II: Immunosuppressive drugs. *Circulation* **2004**, *110*, 3858–3865. [\[CrossRef\]](#)
67. Mehrens, T.; Thiele, S.; Suwelack, B.; Kempkes, M.; Hohage, H. The beneficial effects of calcium channel blockers on long-term kidney transplant survival are independent of blood-pressure reduction. *Clin. Transplant.* **2000**, *14*, 257–261. [\[CrossRef\]](#)
68. Cross, N.B.; Webster, A.C.; Masson, P.; O’Connell, P.J.; Craig, J.C. Antihypertensive treatment for kidney transplant recipients. *Cochrane Database Syst. Rev.* **2009**, *2009*, CD003598. [\[CrossRef\]](#)
69. Brozena, S.C.; Johnson, M.R.; Ventura, H.; Hobbs, R.; Miller, L.; Olivari, M.T.; Clemson, B.; Bourge, R.; Quigg, R.; Mills, R.M.; et al. Effectiveness and safety of diltiazem or lisinopril in treatment of hypertension after heart transplantation Results of a prospective, randomized multicenter trial. *J. Am. Coll. Cardiol.* **1996**, *27*, 1707–1712. [\[CrossRef\]](#)

70. Tylicki, L.; Habicht, A.; Watschinger, B.; Hörl, W.H. Treatment of hypertension in renal transplant recipients. *Curr. Opin. Urol.* **2003**, *13*, 91–98. [[CrossRef](#)]
71. Hiremath, S.; Fergusson, D.; Doucette, S.; Mulay, A.V.; Knoll, G.A. Renin angiotensin system blockade in kidney transplantation: A systematic review of the evidence. *Am. J. Transplant.* **2007**, *7*, 2350–2360. [[CrossRef](#)]
72. Hausberg, M.; Barenbrock, M.; Hohage, H.; Müller, S.; Heidenreich, S.; Rahn, K.-H. ACE inhibitor versus β -blocker for the treatment of hypertension in renal allograft recipients. *Hypertension* **1999**, *33*, 862–868. [[CrossRef](#)]
73. Aftab, W.; Varadarajan, P.; Rasool, S.; Kore, A.; Pai, R.G. Beta and angiotensin blockades are associated with improved 10-year survival in renal transplant recipients. *J. Am. Heart Assoc.* **2013**, *2*, e000091. [[CrossRef](#)] [[PubMed](#)]
74. Tutakhel, O.A.Z.; Moes, A.D.; Valdez-Flores, M.A.; Kortenoeven, M.L.; Vrie, M.V.D.; Jeleń, S.; Fenton, R.; Zietse, R.; Hoenderop, J.G.J.; Hoorn, E.J.; et al. NaCl cotransporter abundance in urinary vesicles is increased by calcineurin inhibitors and predicts thiazide sensitivity. *PLoS ONE* **2017**, *12*, e0176220. [[CrossRef](#)]
75. Weir, M.R.; Burgess, E.D.; Cooper, J.E.; Fenves, A.Z.; Goldsmith, D.; McKay, D.; Mehrotra, A.; Mitsnefes, M.M.; Sica, D.A.; Taler, S.J. Assessment and management of hypertension in transplant patients. *J. Am. Soc. Nephrol.* **2015**, *26*, 1248–1260. [[CrossRef](#)] [[PubMed](#)]
76. Castela, A.M.; Ibernón, M.; Sarrias, X.; Sanz, V.; Moreso, F.; Rama, I.; Grinyó, J. Doxazosin GITS trough to peak ratio and 24-hour blood pressure monitoring in the management of hypertension in renal transplant patients. *Transplant. Proc.* **2003**, *35*, 1736–1738. [[CrossRef](#)] [[PubMed](#)]
77. Pritzker, M.R.; Lake, K.D.; Reutzel, T.J.; Hoffman, F.M.; Jorgensen, C.R.; Pederson, W.; Emery, R.W. Steroid-free maintenance immunotherapy: Minneapolis Heart Institute experience. *J. Heart Lung Transplant.* **1992**, *11 Pt 2*, 415–420.
78. Baraldo, M.; Gregoraci, G.; Livi, U. Steroid-free and steroid withdrawal protocols in heart transplantation: The review of literature. *Transpl. Int.* **2014**, *27*, 515–529. [[CrossRef](#)]
79. Yamani, M.H.; Taylor, D.O.; Czerr, J.; Haire, C.; Kring, R.; Zhou, L.; Hobbs, R.; Smedira, N.; Starling, R.C. Thymoglobulin induction and steroid avoidance in cardiac transplantation: Results of a prospective, randomized, controlled study. *Clin. Transplant.* **2008**, *22*, 76–81. [[CrossRef](#)]
80. Crespo Leiro, M.G.; Bonet, L.A.; Paniagua Martín, M.; Bueno, M.G.; Escribano, P.; Vilchez, F.G.; Lambert, J.R.; Loidi, V.B.; Gallé, E.L.; Jiménez, J.D. Steroid Withdrawal during 5 years following heart transplantation, and the relationship between steroid dosage at 1-year follow-up and complications during the next 2 years: Results from the restco study. *Transplant. Proc.* **2012**, *44*, 2631–2634. [[CrossRef](#)]
81. Baran, D.A.; Rosenfeld, C.; Zucker, M.J. Corticosteroid Weaning in Stable Heart Transplant Patients: Guidance by Serum Cortisol Level. *J. Transplant.* **2018**, *2018*, 3740395. [[CrossRef](#)]
82. Rosenbaum, D.H.; Adams, B.C.; Mitchell, J.D.; Jessen, M.E.; Paul, M.C.; Kaiser, P.A.; Pappas, P.A.; Meyer, D.M.; Wait, M.A.; Drazner, M.H.; et al. Effects of Early Steroid Withdrawal After Heart Transplantation. *Ann. Thorac. Surg.* **2006**, *82*, 637–644. [[CrossRef](#)] [[PubMed](#)]
83. Pascual, M.; Curtis, J.; Delmonico, F.L.; Farrell, M.L.; Williams, W.W.; Kalil, R.; Jones, P.; Cosimi, A.B.; Tolkoff-Rubin, N. A prospective, randomized clinical trial of cyclosporine reduction in stable patients greater than 12 months after renal transplantation. *Transplantation* **2003**, *75*, 1501–1505. [[CrossRef](#)]
84. Rostaing, L.; Massari, P.; Garcia, V.D.; Mancilla-Urrea, E.; Nainan, G.; Rial, M.d.C.; Steinberg, S.; Vincenti, F.; Shi, R.; Di Russo, G.; et al. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: A randomized phase II study. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 430–439. [[CrossRef](#)] [[PubMed](#)]
85. Ekberg, H.; Grinyó, J.; Nashan, B.; Vanrenterghem, Y.; Vincenti, F.; Voulgari, A.; Truman, M.; Nasmyth-Miller, C.; Rashford, M. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: The CAESAR study. *Am. J. Transplant.* **2007**, *7*, 560–570. [[CrossRef](#)] [[PubMed](#)]
86. Eisen, H.J.; Tuzcu, E.M.; Dorent, R.; Kobashigawa, J.; Mancini, D.; Kaeppler, H.A.V.-V.; Starling, R.C.; Sørensen, K.; Hummel, M.; Lind, J.M.; et al. Everolimus for the Prevention of Allograft Rejection and Vasculopathy in Cardiac-Transplant Recipients. *N. Engl. J. Med.* **2003**, *349*, 847–858. [[CrossRef](#)]
87. Groetzner, J.; Kaczmarek, I.; Schulz, U.; Stegemann, E.; Kaiser, K.; Wittwer, T.; Schirmer, J.; Voss, M.; Strauch, J.; Wahlers, T.; et al. Mycophenolate and Sirolimus as Calcineurin Inhibitor-Free Immunosuppression Improves Renal Function Better Than Calcineurin Inhibitor-Reduction in Late Cardiac Transplant Recipients With Chronic Renal Failure. *Transplantation* **2009**, *87*, 726–733. [[CrossRef](#)]
88. Asleh, R.; Briasoulis, A.; Kremers, W.K.; Adigun, R.; Boilson, B.A.; Pereira, N.L.; Edwards, B.S.; Clavell, A.L.; Schirger, J.A.; Rodeheffer, R.J.; et al. Long-Term Sirolimus for Primary Immunosuppression in Heart Transplant Recipients. *J. Am. Coll. Cardiol.* **2018**, *71*, 636–650. [[CrossRef](#)]
89. Kario, K.; Okada, K.; Kato, M.; Nishizawa, M.; Yoshida, T.; Asano, T.; Uchiyama, K.; Nijima, Y.; Katsuya, T.; Urata, H.; et al. 24-h blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: Results from the randomized, placebo-controlled SACRA study. *Circulation* **2019**, *139*, 2089–2097. [[CrossRef](#)]

90. Tikkanen, I.; Narko, K.; Zeller, C.; Green, A.; Salsali, A.; Broedl, U.C.; Woerle, H.J. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care* **2015**, *38*, 420–428. [\[CrossRef\]](#)
91. Cehic, M.G.; Muir, C.A.; Greenfield, J.R.; Hayward, C.; Jabbour, A.; Keogh, A.; Kotlyar, E.; Muthiah, K.; Macdonald, P.S. Efficacy and safety of empagliflozin in the management of diabetes mellitus in heart transplant recipients. *Transplant. Direct* **2019**, *5*, e450. [\[CrossRef\]](#) [\[PubMed\]](#)
92. ClinicalTrials.gov. DAPAgliflozin for Renal Protection in Heart Transplant Recipients (DAPARHT). Available online: <https://classic.clinicaltrials.gov/ct2/show/NCT05321706> (accessed on 13 March 2024).
93. De Vecchis, R.; Soreca, S.; Ariano, C. Anti-Hypertensive Effect of Sacubitril/Valsartan: A Meta-Analysis of Randomized Controlled Trials. *Cardiol. Res.* **2019**, *10*, 24–33. [\[CrossRef\]](#) [\[PubMed\]](#) [\[PubMed Central\]](#)
94. Agarwal, R.; Ruilope, L.M.; Ruiz-Hurtado, G.; Haller, H.; Schmieder, R.E.; Anker, S.D.; Filippatos, G.; Pitt, B.; Rossing, P.; Lambelet, M.; et al. Effect of finerenone on ambulatory blood pressure in chronic kidney disease in type 2 diabetes. *J. Hypertens.* **2023**, *41*, 295–302. [\[CrossRef\]](#) [\[PubMed\]](#) [\[PubMed Central\]](#)
95. Tsujimoto, T.; Kajio, H. Spironolactone Use and Improved Outcomes in Patients With Heart Failure With Preserved Ejection Fraction With Resistant Hypertension. *J. Am. Heart Assoc.* **2020**, *9*, e018827. [\[CrossRef\]](#) [\[PubMed\]](#) [\[PubMed Central\]](#)
96. Baba, D.-F.; Danilescu, A.; Suci, H.; Avram, C.; Harpa, M.M.; Stoian, M.; Moldovan, D.-A.; Huma, L.; Rusu, G.; Pal, T.; et al. The Effect of Early Spironolactone Administration on 2-Year Acute Graft Rejection in Cardiac Transplant Patients. *Biomedicines* **2025**, *13*, 1164. [\[CrossRef\]](#) [\[PubMed\]](#) [\[PubMed Central\]](#)
97. Cluett, J.L.; Blazek, O.; Brown, A.L.; East, C.; Ferdinand, K.C.; Fisher, N.D.; Ford, C.D.; Griffin, K.A.; Mena-Hurtado, C.I.; Sarathy, H.; et al. Renal Denervation for the Treatment of Hypertension: A Scientific Statement From the American Heart Association. *Hypertension* **2024**, *81*, e135–e148. [\[CrossRef\]](#) [\[PubMed\]](#)
98. Nelson, M.R.; Stepanek, J.; Cevette, M.; Covalciuc, M.; Hurst, R.T.; Tajik, A.J. Noninvasive measurement of central vascular pressures with arterial tonometry: Clinical revival of the pulse pressure waveform? *Mayo Clin. Proc.* **2010**, *85*, 460–472. [\[CrossRef\]](#)
99. Radovancevic, B.; Poindexter, S.; Birovljev, S.; Velebit, V.; Mcallister, H.; Duncan, J.; Vega, D.; Lonquist, J.; Burnett, C. Risk factors for development of accelerated coronary artery disease in cardiac transplant recipients. *Eur. J. Cardio-Thoracic Surg.* **1990**, *4*, 309–313. [\[CrossRef\]](#)
100. Hartmann, R.; Der Maur, C.A.; Toggweiler, S.; Brunner, C.; Jamshidi, P.; Mueller, X.; Tavakoli, R. Diastolic Filling Reserve Preservation Using a Semispherical Dacron Patch for Repair of Anteroapical Left Ventricular Aneurysm. *Ann. Thorac. Surg.* **2016**, *102*, e73–e75. [\[CrossRef\]](#)
101. Rahmani, M.; Cruz, R.P.; Granville, D.J.; McManus, B.M. Allograft vasculopathy versus atherosclerosis. *Circ. Res.* **2006**, *99*, 801–815. [\[CrossRef\]](#)
102. Vassalli, G.; Gallino, A.; Weis, M.; Von Scheidt, W.; Kappenberger, L.; Von Segesser, L.K.; Goy, J.-J.; Working Group Microcirculation of the European Society of Cardiology. Alloimmunity and nonimmunologic risk factors in cardiac allograft vasculopathy. *Eur. Heart J.* **2003**, *24*, 1180–1188. [\[CrossRef\]](#)
103. Mehra, M.R.; Ventura, H.O.; Chambers, R.; Collins, T.J.; Ramee, S.R.; Kates, M.A.; Smart, F.W.; Stapleton, D.D. Predictive model to assess risk for cardiac allograft vasculopathy: An intravascular ultrasound study. *J. Am. Coll. Cardiol.* **1995**, *26*, 1537–1544. [\[CrossRef\]](#)
104. Schroeder, J.S.; Gao, S.-Z.; Alderman, E.L.; Hunt, S.A.; Johnstone, I.; Boothroyd, D.B.; Wiederhold, V.; Stinson, E.B. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. *Drugs Today* **1993**, *328*, 164–170. [\[CrossRef\]](#)
105. Erinc, K.; Yamani, M.H.; Starling, R.C.; Crowe, T.; Hobbs, R.; Bott-Silverman, C.; Rincon, G.; Young, J.B.; Feng, J.; Cook, D.J.; et al. The Effect of combined angiotensin-converting enzyme inhibition and calcium antagonism on allograft coronary vasculopathy validated by intravascular ultrasound. *J. Heart Lung Transplant.* **2005**, *24*, 1033–1038. [\[CrossRef\]](#)
106. Kittleson, M.M.; Kobashigawa, J.A. Cardiac Transplantation: Current Outcomes and Contemporary Controversies. *JACC Heart Fail.* **2017**, *5*, 857–868. [\[CrossRef\]](#)

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.