# Tacrolimus Versus Ciclosporin for Immunosuppression in Cardiac Transplantation – Short to Mid-Term Renal Effects

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**Abstract:** Approximately 100 cardiac transplants are performed yearly in the UK. The choice of maintenance immunosuppression regimes, however, varies due to the dearth of evidence. Tacrolimus and ciclosporin are used most commonly. An added benefit of tacrolimus has been suggested due to reduced rejection rates and side effect profile, particularly nephrotoxicity. The results were reviewed at the Scottish National Advanced Heart Failure Service. A retrospective analysis of data from 50 patients was conducted. All patients had undergone orthotopic heart transplantation between September 2010 and June 2016. In addition to tacrolimus or ciclosporin all patients also received mycophenolate mofetil and corticosteroids. Serum creatinine levels and estimated glomerular filtration rates (eGFR) were compared at 3 monthly intervals during follow-up post-transplant. Statistical analysis was performed using Student's $t$-test for continuous variables and Chi-squared test for categorical variables. The drug regimens remained unchanged in all patients through the study period. The eGFR was significantly higher in the ciclosporin group compared to the tacrolimus group at 9 months (p=0.045) and 1 year (p=0.025). There was also a trend towards higher serum creatinine in the tacrolimus group (p=0.125 at 12 months). This study indicates there is a significant impairment of renal function in patients on tacrolimus compared to ciclosporin. Larger studies and longer follow-up is needed to denote if this impairment is sustained and irreversible.

**Keywords:** Cardiac Transplantation, Immunosuppression, Tacrolimus, Ciclosporin, Renal Function

## 1. Introduction

Cardiac transplantation (HTX) has become a well-established and acceptable treatment for advanced heart failure in the last few decades, and the procedure and post-operative management have been subject to extensive research since the 1960's. An important early limitation to success in the field of transplantation has been immunosuppression. Many different drugs have been used over the decades, but most guidelines in 2016 recommend the use of Tacrolimus (Tac) and Ciclosporin (CyA). As powerful immunosuppressants, they exhibit a variety of side effects, one of the most important ones being nephrotoxicity. The aim of this paper is to retrospectively analyze and compare the renal effects of ciclosporin and tacrolimus-based regimens in cardiac transplant patients in a Scottish heart transplant centre. This will be done by focusing on serum creatinine levels and Estimated glomerular filtration rate (eGFR) in 50 patients up to a year following transplantation.

### 1.1. History and Development of Cardiac Transplantation

Multiple decades of research and planning resulted in the first successful human cardiac transplant being performed in 1967 by Dr. Christiaan Barnard in Cape Town, South Africa [1]. Unfortunately, Dr. Barnard's patient died of pneumonia two weeks after the transplantation, highlighting the issues of immunosuppression that would prove to be an obstacle for years to come.

The initial surge in the number of transplants performed around the world in late 1960's and early 1970's slowed down when problems understanding the transplant rejection process became apparent. The patient survival rate in 1973 was 49%

at 6 months, and only 30% at 2 years [2]. In the 1980's, ciclosporin A was added to postoperative drug regimens and has been responsible for much of the progress that has been made since.

In the UK, 141 cardiac transplantations were performed between March 2015 and April 2016 (NHS, 2016) [3]. The number has stayed at approximately 100 transplantations per year for over ten years, due to a limited availability of donor hearts. The national 5-year survival rate was 72% in 2015, a testament to the great progress that has been made since the 1970's. However, problems with drug side effects and toxicity remain, and regimen guidelines are under constant scrutiny.

## 1.2. Overview of Rejection Immunology

Transplantation presents several immunological challenges, as the graft is targeted by the hosts' immune system. In cardiac transplantation, the adaptive immune response against the donor heart is initiated by the recognition of an alloantigen by a host naive T-cell [4]. The T-cell is activated through two signals – the MHC II of an antigen presenting cell (APC), presenting the alloantigen to the T-cell receptor, and a co-stimulatory APC-signal. This receptor binding causes an increase in the cytoplasmic $Ca^{2+}$ concentration, which in turn activates calcineurin. Calcineurin is a protein phosphatase and an important component in T- cell activation. It dephosphorylates $NFAT_c1$ leading to interleukin 2 transcription and autocrine stimulation of the T-cell.

When the suppression of this process is unsuccessful or insufficient the outcome will be transplant rejection. Three main categories of rejection exist – hyperacute, acute and chronic. Hyperacute rejection occurs due to preformed donor-specific antigens and is rare due to screening tests [5]. Acute and chronic rejection occur more commonly, and preventing them is where immunosuppression becomes important.

Since the beginning of 2010 around 25% of cardiac transplant recipients have had a rejection episode within one year of transplantation worldwide [6]. This is a significant proportion and highlights the importance of pharmacological research in the area.

## 1.3. Overview of Immunosuppression in Transplantation

The suppression of a transplant recipient's immune system involves complex combinations of medications which differ depending on their purpose and timing after transplantation. Induction therapy is given either before, during or directly after the operation, and may involve a variety of different drugs. Most commonly it includes monoclonal antilymphocyte antibodies such as basiliximab and alemtuzumab [7].

Maintenance therapy is the long-term immunosuppression targeting different parts of the immune system to prevent chronic rejection and cardiac allograft vasculopathy. Corticosteroids have been used throughout the history of organ transplantation and remain an essential part of many regimens [8]. However, the aim of modern regimens is to shift the immunosuppressive focus away from corticosteroids to avoid their side-effects and to add alternative drugs to manipulate different steps of T-cell activation.

Mycophenolate mofetil (MMF) and Azathioprine are antiproliferative agents used in conjunction with other drugs to prevent the proliferation and differentiation of T- and B-cells [9, 10]. They work in similar ways to purine synthesis inhibitors, but in recent years MMF has become the preferred drug for over 80% patients [6] due to better specificity [11]. M-TOR inhibitors are used similarly in conjunction with other drugs, but only in around 10% of adult patients worldwide [6]. They include Sirolimus and Everolimus and they are mostly used in cases of significant calcineurin inhibitor nephrotoxicity.

## 1.4. Ciclosporin

Ciclosporin (CyA; cyclosporine) has been used as the mainstay drug in maintenance immunosuppression ever since its first use in kidney transplantations in the 1970's, and particularly during the 1980's and early 1990's [12] [13]. It sparked interest soon after its discovery in 1970 as a less toxic and more specific alternative to the main drug of the time, Azathioprine. In 1994 a new microemulsion formulation (Neoral by Novartis) was made with improved pharmacokinetics and bioavailability, further augmenting the role ciclosporin in solid organ transplantation [14].

As a calcineurin inhibitor (CNI), CyA exerts its main immunosuppressive effect by binding to cyclophilin in lymphocytes. The complex of CyA and cyclophilin inhibits calcineurin, blocking its action on the IL-2 transcription pathway as described above. This stops T-cell proliferation and halts the transplant rejection process. CyA, however, has molecular targets in many other cells, which account for its systemic side effects, including nephrotoxicity and neurological effects [15].

## 1.5. Tacrolimus (FK-506)

Tacrolimus (TAC) is a macrolide antibiotic that has similar calcineurin inhibitor activity to ciclosporin. After its initial approval for use in graft rejection suppression in Japan in 1993 [16] it soon gained popularity worldwide. It has now become an established agent in both maintenance therapy and emergency rescue therapy, in both solid organ and bone marrow transplant recipients. Worldwide tacrolimus surpassed ciclosporin as the most used CNI in cardiac transplantation in 2004 [6].

Tacrolimus inhibits calcineurin through a different cyclophilin to that of ciclosporin, FK-506 binding protein 12 [17] [18]. It may also have apoptotic properties in T-cells, but this remains controversial. The full extent of the systemic effects of tacrolimus is not well understood, and unidentified cellular targets account for many similar side effects to those of cyclosporine. One important difference may lie in nephrotoxicity, one of the most serious side effects.

### 1.6. Post-Transplant Chronic Renal Insufficiency

In both lung and heart transplantation, kidney disease is a well-established and increasingly recognised complication [19]. As post-transplant morbidity and mortality are both affected greatly by the presence of kidney disease [20], it is important to be aware of different causes for it. Some patient characteristics have been established in large studies as risk factors for chronic renal insufficiency, including older age, female sex, diabetes and hypertension. Pre-transplant or immediate post-transplant renal insufficiency have also been found to predict long-term renal dysfunction [20] [21]. For some parameters, findings are still contradictory. These include the presence of dyslipidaemia, hepatitis C infection, and the choice of CNI agent [21].

Because the primary CNI agent in cardiac transplantation has undergone a paradigm shift worldwide, it has become increasingly important to consider renal dysfunction. Clinically, chronic kidney disease is very common in transplant recipients, and, as such, well-informed choices by doctors are essential for patient outcomes. Pathophysiologically, the effects of ciclosporin on the kidneys are better characterised than those of tacrolimus. Structural damage and functional failure have been shown to be caused by 1) activation of the renin-angiotensin-aldosterone system [22] [23], 2) renal vasoconstriction [24] [25] and 3) upregulation of TGF-β and renal fibrosis [26] [27]. This makes avoiding renal damage difficult when a CNI is involved in immunosuppression.

The aim of this paper is to evaluate the effect of two main CNI agents, tacrolimus and ciclosporin, on short- and mid-term post-cardiac transplant renal function.

# 2. Methods

### 2.1. Study Population

In total, a study population of 50 patients was analysed. It was comprised of adult patients who underwent a first-time orthotopic heart transplantation in Golden Jubilee National Hospital (Glasgow, Scotland) between September 2010 and June 2016. 24 patients were on a tacrolimus-based maintenance immunosuppression postoperatively, after it was made the principal CNI within the unit in January 2014. A comparable cohort of 26 patients on a ciclosporin-based immunosuppression was selected. Exclusion criteria included death between 2010-2016 and changes in maintenance drug regimens. No patients under the age of 18 were included.

### 2.2. Drug Regimens and Monitoring

All patients received immunosuppression according to the unit's protocol. In the immediate post-operative period, patients received rabbit-derived anti-thymocyte globulin for up to 4 days until their kidney function was adequate. Afterwards they were put on their standard regimen of a CNI, MMF and a steroid. Target CNI levels depend on time after transplantation, details of which are provided in Table

1. Drug level monitoring was performed alongside routine follow-up visits at regular time intervals. Levels were determined by a laboratory in the Queen Elizabeth University Hospital, Glasgow, using tandem mass spectrometry.

*Table 1. Target drug levels for maintenance immunosuppression after HTX in the Golden Jubilee National Hospital, Glasgow.*

| Time after transplantation | Tacrolimus (µg/L) | Time after transplantation | Ciclosporin (µg/L) |
|---|---|---|---|
| 0-3 months | 10-15 | 0-4 weeks | 240-320 |
| 3-6 months | 8-12 | 1-6 months | 160-200 |
| 6-12 months | 7-10 | 6-12 months | 130-160 |
| >12 months | 5-7 | >12 months | 64-96 |

### 2.3. Data Gathering and Analysis

All patient data used was extracted from the database of the transplant unit. Clinical notes provided all the information necessary for analysis, including demographical information. Blood creatinine levels were collected from seven different points in time; within 24h pre-operatively, within 24h post-operatively, 1, 3, 6, 9, and finally 12 months post-operatively. The laboratory also provided the Estimated glomerular filtration rates (eGFR) used, calculated using the MDRD (Modification of Diet in Renal Disease) equation. It reads as follows; $eGFR \ (mL/min/1.73 \ m^2) = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \ if \ female) \times (1.212 \ if \ Black \ Ethnicity)$

The time points were chosen per the post-operative follow-up protocol used by the unit, and they were consistent between patients.

Statistical analysis was performed using the IBM SPSS Statistics v23.0. Student's *t*-test was used to analyse differences in continuous data and the Chi-squared test was used for categorical data. The level of significance was set at *p*-value of <0.05.

# 3. Results

### 3.1. Patient Demographics

All 50 patients included in the study had appropriate clinical records and all necessary information was accessible.

*Table 2. Baseline characteristics of the two study cohorts.*

| Variable | All | Ciclosporin & MMF | Tacrolimus & MMF | P-value |
|---|---|---|---|---|
| Number of patients (%) | 50 (100) | 26 (52) | 24 (48) | |
| Sex | | | | 0.291 |
| Male | 37 (74) | 21 (81) | 16 (67) | |
| Female (%) | 13 (26) | 5 (19) | 8 (33) | |
| Age | 47±13 | 46±13 | 48±12 | 0.504 |
| Height | 171.2±8.5 | 173.8±6.9 | 171.0±10.1 | 0.340 |
| Weight | 75.0±12.1 | 76.8±11.0 | 73.6±12.7 | 0.366 |
| BMI | 25±4 | 26±4 | 26±3 | 0.568 |
| Pretransplant diagnosis | | | | 0.355 |
| Ischaemic heart disease | 15 (30) | 6 (23) | 9 (38) | |
| Dilated cardiomyopathy | 24 (48) | 14 (53) | 10 (42) | |
| Hypertrophic CM | 2 (4) | 0 | 2 (8) | |

| Variable | All | Ciclosporin & MMF | Tacrolimus & MMF | P-value |
|---|---|---|---|---|
| Left ventricular dysfunction | 4 (8) | 3 (12) | 1 (4) | |
| Other | 5 (10) | 3 (12) | 2 (8) | |

Table 2 describes patient baseline characteristics. The study cohorts are not matched, but they are comparable, and no statistically significant difference was found in the collected characteristics, including age, sex, BMI and pre-transplant diagnosis. The mean age of recipients was 47 ± 13 years, and 74% of the population were male.

### 3.2. Renal Function, Laboratory Data

Preoperatively there were no significant differences in renal function between the study cohorts based on serum creatinine and eGFR measured within 24 hours before the operation. At baseline, creatinine for CyA patients was 91±17 µg/L, and for TAC, 86±25 µg/L (*p*=0.370), both group means falling within the normal range of 60-100 µg/L. Laboratory- calculated eGFRs at baseline were 58.8±2.8 for CyA and 58.3±4.3 for TAC (*p*=0.467). This also falls close to the maximum eGFR value provided by the laboratory, which is 60. This data in presented in Table 3 below.

There was an immediate and significant change in renal function immediately postoperatively across the population, reflecting the stress on the kidneys caused by surgery and different medications – but also changes in fluid balance. Postoperative creatinine was measured within 24 hours of the operation. No significant difference was expected, as the drug regimens being compared had not started yet, and their renal effects are chronic in nature.

At one month postoperatively, there was a decrease in serum creatinine across the population, shown in Figure 1 below. Here the initial stress on the kidneys is lifted, and no long-term damage is yet present, hence kidney function rises towards normal. Over time creatinine levels steadily increased, as the chronic effects of immunosuppression began to impact kidney function. During the first year post-op, drug dosage is always carefully monitored and adjusted according to the transplant unit's target levels, patient renal function and occurrence of transplant rejection. Rejection episodes are treated with increased immunosuppression according to the unit's protocol, and sudden or significant decreases in renal function are managed by lowering the drug target levels for CNIs.

**Table 3.** *Serum creatinine levels and eGFR of the two study cohorts over time.*

| Details | Ciclosporin & MMF (n=26) (Mean ± SD) | Tacrolimus & MMF (n=24) (Mean ± SD) | *p*-value |
|---|---|---|---|
| Preoperative creatinine (µg/L) | 91 ± 17 | 86 ± 25 | 0.370 |
| Postoperative creatinine | 170 ± 71 | 153 ± 67 | 0.385 |
| Creatinine @ 1 month | 102 ± 34 | 109 ± 45 | 0.547 |
| Creatinine @ 3 months | 122 ± 37 | 126 ± 37 | 0.708 |
| Creatinine @ 6 months | 145 ± 38 | 143 ± 48 | 0.887 |
| Creatinine @ 9 months | 139 ± 46 | 166 ± 50 | 0.096 |
| Creatinine @ 12 months | 143 ± 42 | 167 ± 47 | 0.125 |
| Preoperative estimated glomerular filtration rate (eGFR) | 58.8 ± 2.8 | 58.3 ± 4.3 | 0.666 |
| Postoperative eGFR | 40.3 ± 13.4 | 43.4 ± 15.6 | 0.467 |
| eGFR @ 1 month | 56.0 ± 8.3 | 54.2 ± 11.4 | 0.528 |
| eGFR @ 3 months | 51.7 ± 10.4 | 50.0 ± 11.2 | 0.587 |
| eGFR @ 6 months | 44.1 ± 11.9 | 44.0 ± 13.1 | 0.982 |
| eGFR @ 9 months | 47.7 ± 14.4 | 38.8 ± 12.3 | **0.045** |
| eGFR @ 12 months | 44.5 ± 11.4 | 36.6 ± 9.5 | **0.025** |
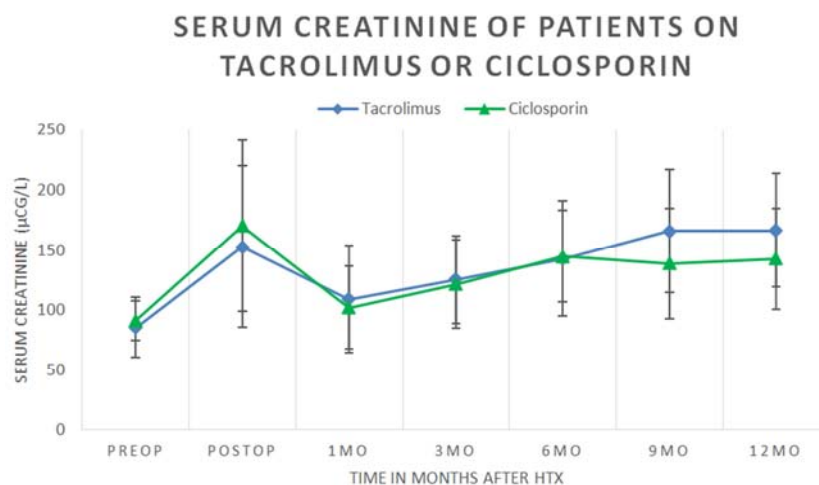


**Figure 1.** *Serum creatinine of HTX patients on ciclosporin or tacrolimus maintenance immunosuppression over time postoperatively (Mean±SD).*

The difference in mean creatinine between the cohorts shows a trend towards significance at 9 and 12 months postoperatively, with the TAC group showing higher values. Mean creatinine was 139 ± 46 at 9 and 143 ± 42 at 12 months in the CyA group. In the TAC group, they were 166 ± 50 at 9 and 167 ± 47 at 12 months (*p*=0.096 and *p*=0.125, respectively). The levels start to diverge between 6 and 9

months, reflecting chronic damage to the kidneys.

As eGFR calculation is based on serum creatinine, it showed similar changes over time. Both cohorts experienced a drop in eGFR immediately postoperatively and remained under the normal level of 60 throughout the study period.
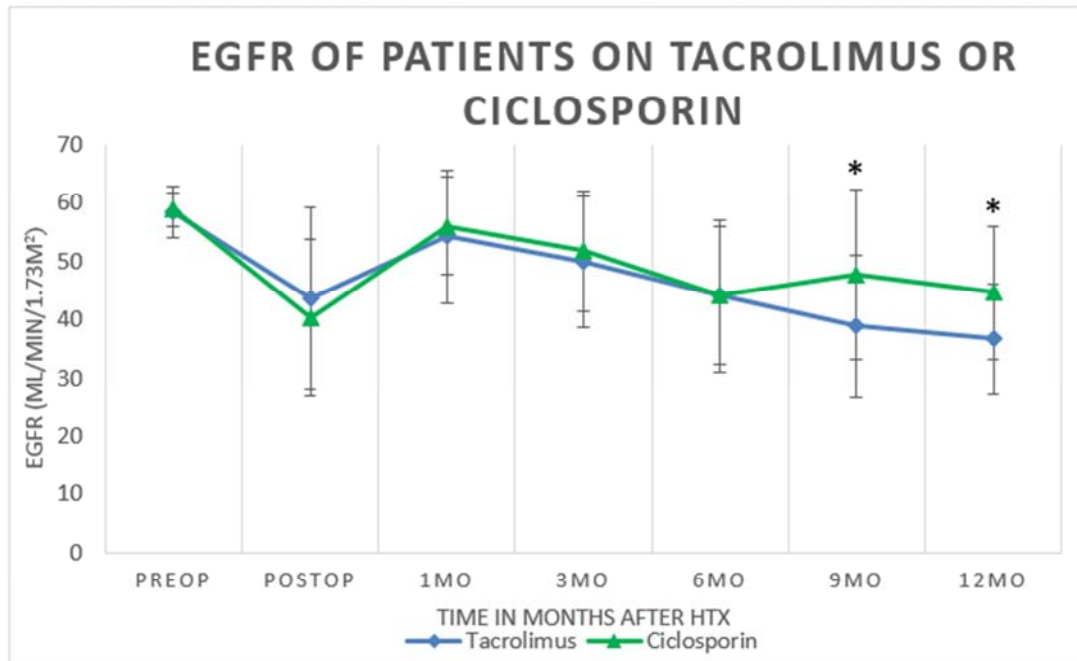


**Figure 2.** *Laboratory-calculated eGFR of HTX patients on ciclosporin or tacrolimus maintenance immunosuppression over time postoperatively (Mean±SD). At 9 and 12 months p=0.045 and p=0.025, respectively.*

At 9 and 12 months the difference in eGFR between the cohorts was statistically significant, with TAC showing worse renal function. In CyA patients, eGFR was 47.7 ± 14.4 at 9 and 44.5 ± 11.4 at 12 months. In TAC patients they were 38.8 ± 12.3 at 9 and 36.6 ± 9.5 at 12 months (*p*=0.045 and *p*=0.025, respectively).

It is also important to note that in the TAC group mean eGFR continued to decline between 1 and 12 months postoperatively, but in the CyA group, there was a temporary improvement in kidney function between 6 and 9 months.

## 4. Discussion

### 4.1. Principal Findings

This study demonstrates that mid-term renal function is worse in orthotopic heart transplant recipients treated with tacrolimus-based maintenance immunosuppression compared to those treated with ciclosporin. The difference is significant at 9 and 12 months after transplantation as measured by eGFR, and this timing fits the consensus that drug toxicity contributes to mid-term and long-term renal damage in HTX patients. The study cohorts were comparable in the beginning of the study, and many of the relevant contributors to post- transplant prognosis were taken into account -

including sex, BMI and pretransplant diagnosis. No statistically significant difference was found between the cohorts with regards to total serum creatinine over the study period.

### 4.2. Context of Research

Initially, in the early 1990's, tacrolimus was mostly used in kidney and liver transplant patients, and promising in vitro evidence prompted the move towards HTX patients [17]. The pilot study comparing the effectiveness of tacrolimus versus ciclosporin in HTX patients was a multicentre study in Europe by Reichart and colleagues [28]. It included 82 patients, all treated with azathioprine and corticosteroids, and found no difference in the effectiveness of the drugs regarding graft rejection. Reichart et al. demonstrated that tacrolimus is a viable alternative to ciclosporin, which famously revolutionised cardiac transplantation a decade before and remained the cornerstone of immunosuppressive therapy all over the world.

Another early study comparing tacrolimus and ciclosporin was carried out by David Taylor et al. in 1999 [29]. Their multicentre study included 88 patients and concluded that tacrolimus is as effective as ciclosporin in preventing rejection episodes in HTX patients, and is comparably safe.

Both studies combined CNIs with azathioprine and corticosteroids. As mentioned earlier, azathioprine has since been removed from most immunosuppressive regimens worldwide due to toxicity, so trials with different drug combinations were warranted. In these trials, follow-up time was only 12 months, so they could not draw definitive conclusions regarding survival and long-term effects.

Several further studies were conducted in the early 2000's, with different drug combinations and different focuses in data collection [31] [32] [33]. The 2004 studies were both single-centre studies with similar outcomes to previous findings. They began to use MMF in their regimens, and at that point, drug choices began to resemble what is mostly used worldwide in 2016. Wang et al found a modest difference in blood creatinine levels between TAC and CyA groups, creatinine being higher in TAC patients, but these findings lacked statistical power.

The definitive study for the use of tacrolimus combined with MMF in HTX patients was published two years later by a US-based thoracic surgeon, Jon Kobashigawa. He published the findings of his randomised trial of 343 patients after one year of follow-up. He found a significant difference in the occurrence of any treated rejection between TAC+MMF and CyA+MMF patients, establishing TAC as the better choice [34]. He, however, acknowledged that determining the superior drug is difficult as the optimal therapeutic trough blood levels had not been determined for these drugs in clinical trials. Kobashigawa found no significant difference in creatinine levels between the cohorts.

In the past ten years, more single-centre studies have been published, many with longer follow-up times [35]. Guethoff et al. published their 10-year results of 60 patients in a similar randomised trial to that of Kobashigawa's. They concluded that TAC-based regimens may be associated with fewer rejection episodes, but importantly noted no improvement in overall survival. With regards to kidney function, they found a difference in total blood creatinine to be significant at 5 years, with better kidney function in the TAC group, but this difference was no longer present at 10 years.

The data on the relative renal effects of ciclosporin and tacrolimus remains inconclusive, and many have noted no significant difference between the two drugs. Ever since the superior rejection profile of TAC was recognised more research concentrating on renal effects has been published. However, it remains a contentious issue, and new single-centre studies are still published, often with inconclusive findings. Helmschrott et al found no significant difference in the creatinine levels or eGFR between TAC and CyA groups in their 150 HTX patients but concluded that TAC is less nephrotoxic due to creatinine levels not rising as much in their cohort [36].

A 2010 meta-analysis [37] analysed 11 randomised trials to assess the differences between the drugs, but also to evaluate the strength of the current evidence for tacrolimus. These trials included a total number of 952 patients, with follow-up time ranging from 6 months to 5 years. They concluded that there is no significant difference in either survival or the effect on total serum creatinine between the drugs. Furthermore, they criticised the included trials for a high risk of bias in their results, and the inclusion of few patients with few outcomes.

### 4.3. Other Approaches to Maintaining Renal Function

Calcineurin inhibitors have a narrow therapeutic range and little correlation between trough levels and clinical response of patients [38]. This adds to the challenges faced in treating HTX patients at the clinic.

To appreciate the significance of comparing tacrolimus and ciclosporin regarding their renal effects it is important to understand the wider context of renal function maintenance in HTX patients. What other options are there, when both tacrolimus and ciclosporin seem to contribute to renal failure? M-TOR inhibitors sirolimus and everolimus are a relatively new and extensively studied option.

In 2004 and 2006 patients whose immunosuppression was converted from a CNI-based into an m-TOR inhibitor-based regimen were studied [39], [40]. In this small study, they found no significant difference in survival but found that m-TOR regimens could stop the trend of rising creatinine in HTX patients. They, therefore, recommend the use of sirolimus or everolimus in HTX patients who experience significant CNI toxicity. M-TOR inhibitors however, present multiple different issues, including problems with post-surgical wound healing [41].

In his 2007 review Dr. Bloom from the American Society of Nephrology recommends the use of eGFR, particularly calculated by the MDRD formula, as the measure of kidney function in solid organ transplant patients [19]. This is however not seen in most studies, possibly due to eGFRs not being calculated or reported by laboratories. In this current study eGFR was the only measure capable of eliciting a statistically significant difference in renal function between the cohorts.

### 4.4. Limitations of the Study

This study is retrospective in nature, which alone presents possible sources or error and bias. The data used in this study was collected from patient files, meaning there was no element of participant selection, control of drug dosage or control of confounding factors to kidney disease that are present in prospective controlled trials. Importantly not all patient information that would affect kidney function could be considered, such as history of hypertension and the use of other nephrotoxic drugs. Changes in drug regimens could be considered, and it was ensured that there were none.

This study was a single-centre study with short to mid-term follow-up of patients. Only 50 patients were included for a follow-up of 12 months, and while the results were statistically significant, a larger population and longer follow-up would be needed to denote whether renal impairment in these patients is sustained. Using data from only a single centre has its own strengths and limitations. In a single centre, all patients receive similar care, with a similar

selection for surgery, drug regimens and follow-up. In multi-centre studies, even if the included population is bigger, differences in drug regimens and follow-up may be substantial and affect the results drawn.

The use of eGFR in scientific studies is also controversial as it is only an estimate and will underestimate kidney function in some patients. Here it was provided by the laboratory, which makes it reliable but also prone to errors such as taking the race of the patient into account.

### 4.5. Implications

Knowing the renal effects of different maintenance immunosuppressants is very important as kidney failure carries high morbidity, mortality and negatively affects quality of life. However, this study does not support the notion of switching patients from tacrolimus to ciclosporin. It does not comment on the superiority of one drug over the other as for example rejection episodes and survival data collection and analysis were left out of the study.

Instead, the implications lie in informing clinicians that tacrolimus does not have the positive renal effects compared it ciclosporin that it was once thought to have. This means that more attention needs to be paid to protecting the kidneys through different means.

Based on this research the future of the pharmacological management of organ recipients lies beyond calcineurin inhibitors. Further studies should look not only at new ways to prevent rejection but also new means of reducing renal damage. Publications commenting on renal function need to make it clear to the clinicians who read them how their conclusions were reached – whether eGFR, creatinine or other variables were used and how.

## 5. Conclusion

Ciclosporin and tacrolimus remain the most important agents in the pharmacological management of heart transplant patients. Although a newer agent with a lot of promise, tacrolimus has not proven to be the solution to one of the biggest clinical issues with these patients, nephrotoxicity. Therefore, pharmacological development needs to catch up with the increasing amount and need for cardiac transplantations worldwide. A transplanted heart has the power to transform a patient's life, but the importance of functional kidneys must not be overlooked.

## Abbreviations

| APC | Antigen-presenting cell |
|-----|--------------------------|
| CNI | Calcineurin inhibitor |
| CyA | Ciclosporin |
| eGFR | Estimated glomerular filtration rate |
| HTX | Heart transplantation |
| MMF | Mycophenolate mofetil |
| TAC | Tacrolimus |

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