Everolimus immunosuppression in *de novo* heart transplant recipients: What does the evidence tell us now?

Abstract

The efficacy of everolimus with reduced cyclosporine in *de novo* heart transplant patients has been demonstrated convincingly in randomized studies. Moreover, everolimus-based immunosuppression in *de novo* heart transplant recipients has been shown in two randomized trials to reduce the increase in maximal intimal thickness based on intravascular ultrasound, indicating attenuation of cardiac allograft vasculopathy (CAV). Randomized trials of everolimus in *de novo* heart transplantation have also consistently shown reduced cytomegalovirus infection versus antimetabolite therapy. In maintenance heart transplantation, conversion from calcineurin inhibitors to everolimus has demonstrated a sustained improvement in renal function. In *de novo* patients, a renal benefit may only be achieved if there is an adequate reduction in exposure to calcineurin inhibitor therapy. Delayed introduction of everolimus may be appropriate in patients at high risk of wound healing complications, e.g. diabetic patients or patients with ventricular assist device. The current evidence base suggests that the most convincing reasons for use of everolimus from the time of heart transplantation are to slow the progression of CAV and to lower the risk of cytomegalovirus

infection. A regimen of everolimus with reduced-exposure calcineurin inhibitor and steroids in *de novo* heart transplant patients represents a welcome addition to the therapeutic armamentarium.

Keywords: everolimus, heart transplantation, mTOR inhibitor, de novo, CMV, chronic allograft vasculopathy, rejection

Introduction

The efficacy and safety of the mammalian target of rapamycin (mTOR) inhibitor everolimus in heart transplant patients has been extensively assessed in a series of trials over the last decade (1). There is a considerable body of evidence to indicate that everolimus-based immunosuppression can permit a marked reduction in exposure to cyclosporine (CsA) (1, 2), although robust evidence relating to tacrolimus reduction is still awaited. The efficacy of everolimus with reduced CsA has been convincingly demonstrated in randomized studies of *de novo* (3-6) and, to a lesser extent, maintenance (7, 8) heart transplant patients. However, its use outside the context of clinical trials remains largely restricted to maintenance patients in whom there is a reason to reduce or discontinue calcineurin inhibitor (CNI) exposure or in whom the direct antiproliferative properties of the drug are sought (3, 9). Indeed, the most frequent clinical trigger for everolimus introduction is declining renal function (7, 8, 10-21); less common indications include the development of cardiac allograft vasculopathy (CAV) (14, 17, 22), malignancy (23) and recurrent rejection (19, 20) under CNI therapy. Published experience with *de novo* use of everolimus in heart transplantation in routine clinical practice are currently relatively limited (24-29).

This article reviews the available evidence on the *de novo* use of everolimus, weighing potential issues raised in recent randomized trials with the advantages that could be expected from long-term use of everolimus-based immunosuppression in heart transplant recipients.

Methodology

Multiple searches of the PubMed database were performed with no time or language restrictions using different combinations of the terms 'everolimus', 'heart', 'cardiac', 'transplantation', 'randomized' and 'mTOR'. The proceedings of the International Society for Heart and Lung Transplantation, the American Transplant Congress and the European Society for Organ Transplantation congresses during 2010-2012 were searched for 'everolimus' or 'mTOR'.

Efficacy of everolimus in *de novo* heart transplant recipients

The immunosuppressive potency of everolimus in *de novo* heart transplant recipients was first demonstrated in a randomized study by Eisen *et al*, in which everolimus at a fixed dose of 1.5mg or 3.0mg was associated with significantly superior efficacy outcomes to azathioprine, both in combination with standard-dose CsA (30) (Table 1). Since then, following evidence from kidney (6, 31) and heart (4) transplantation showing that everolimus with reduced-exposure CsA offers equivalent efficacy to everolimus with standard-exposure CsA,

and the advantage of therapeutic drug monitoring of everolimus (32), two randomized trials have assessed the use of everolimus with reduced-exposure CsA versus mycophenolate mofetil (MMF) with standard-exposure CsA (3, 5) in *de novo* heart transplant populations. Both studies adjusted everolimus trough concentration according to pre-specified target ranges, as is now standard practice. Using an everolimus target range of 3-8ng/mL, the primary composite efficacy endpoint and the incidence of biopsy-proven acute rejection (BPAR) were similar in the everolimus and MMF treatment arms at 12 months post-transplant in each study (Table 1). Retrospective, single-center analyses using everolimus (3-8ng/mL) with reduced CsA have also reported similar efficacy to MMF with standard CsA (25, 26) or tacrolimus (27, 29), including one series of 49 patients followed up for five years post-transplant (26). Higher everolimus exposure levels in CNI-treated patients may be inadvisable in view of an increased rate of early (<3 months) deaths in the recent A2310 study among patients randomized to a target concentration range of 6-12ng/mL (3). Use of IL-2 receptor antibody induction in this setting does not appear to be associated with safety concerns (28).

Only one trial has investigated the use of mTOR inhibition within a CNI-free regimen for *de novo* heart transplant patients, in a series of 20 patients with poor kidney function at time of transplant (GFR

<30mL/min/1.73m^2) (33). All patients received steroids, six received everolimus and 14 received sirolimus; nine received induction therapy. Within the mean follow-up of 500 days, by the end of follow-up 11 patients (55%) had experienced rejection. Such an approach is unlikely to become widely adopted except possibly as a temporary regimen in patients with significant renal impairment at the time of transplant. However, a low CNI regimen with everolimus from time of transplant, followed by early CNI withdrawal (≤3 months post-transplant), may be effective. This option is being explored in the SCHEDULE study, where patients either continue or discontinue CsA from week 7 post-transplant (NCT01266148). The results of the study are awaited with interest.

Potential advantages for *de novo* use of everolimus

Inhibition of CAV

CAV affects approximately 50% of heart transplant patients within the first five years after transplantation (34) and is a significant cause of morbidity and mortality (35). It is estimated that 30% of post-transplant deaths are caused by CAV (36). CAV is exacerbated by general risk factors including dyslipidemia, diabetes and hypertension that are highly prevalent in the transplant population, but also by transplant-specific factors including donor age and gender, ischemia/reperfusion injury, allograft rejection, CMV infection and HLA mismatch (37).

CAV is characterized by endothelial injury and an exaggerated repair response, leading to diffuse intimal hyperplasia and luminal stenosis that can involve the entire coronary arterial tree. Stenotic microvasculopathy, a form of CAV that is also associated with poor prognosis (38), is typified by medial or endothelial proliferation (38). The antiproliferative effect of mTOR inhibitors, in addition to its immunosuppressive action, limits the cellular proliferation of endothelial cells and fibroblasts (37, 39, 40) and thus has the potential to ameliorate CAV. Preclinical data have confirmed that everolimus reduces vascular smooth muscle hyperplasia (41, 42) while *in vitro* exposure of human lung fibroblasts from lung transplant recipients to subtherapeutic levels of everolimus has been shown to induce a potent antiproliferative effect (37). In percutaneous coronary interventions, everolimus-eluting stents are used to reduce the risk of restenosis by harnessing everolimus-related inhibition of vascular smooth muscle cell proliferation and migration, processes which also contribute to vascular remodeling in CAV. Everolimus-eluting stents result in superior clinical outcomes versus conventional stents (43-45).

In heart transplantation, pathological evaluation of endomyocardial biopsies has shown that everolimus-based immunosuppression is associated with reduced biopsy-proven fibrosis as early as four weeks post-transplant (46). Intravascular ultrasound (IVUS) measurements

of the change in maximal intimal thickness (MIT) from baseline to one year post-transplant are predictive of cardiac events in patients with CAV (47). Two randomized studies of everolimus in *de novo* heart transplant recipients have included IVUS measurements as part of the study protocol, one with standard CsA and MMF in the control arm (3), and the other with standard CsA and azathioprine (30) (Table 2). Both studies used the change in MIT from baseline as the primary IVUS endpoint, and each showed that the increase was significantly smaller in the everolimus-treated patients, by two-fold or more. Consistent with this, the secondary endpoint of incidence of CAV (defined as ≥0.5mm increase in MIT) was significantly lower in the everolimus cohorts (3, 30). In the trial comparing fixed-dose everolimus versus azathioprine, follow-up IVUS data from 24 months post-transplant showed that the benefit was maintained, although the strict IVUS protocol limited the number of patients for whom evaluable data were available (48). Other secondary IVUS endpoints also demonstrated a significant advantage in the everolimus arms of both studies (3, 31, 48). Coronary narrowing measured by IVUS correlates with subsequent coronary events (49-51). Four-year follow-up data from the randomized trial of everolimus versus azathioprine by Eisen *et al* have indeed confirmed that the more favorable changes in MIT and incidence of CAV at one (30) and two years (48) in the everolimus treatment arm were associated with a significantly lower rate of major

adverse cardiac events versus the azathioprine group (7.9% versus 13.6%, p=0.033) (52), although the data have not been published in full. In contrast, there was no effect on CAV progression in the NOrdic Certican Trial In hEart and lung Transplantation (NOCTET) study, in which maintenance thoracic transplant patients were randomized at a mean of 5.8 years post-transplant to switch to everolimus with reduced CsA or remain on standard CsA therapy (53). A virtual histology substudy from that trial suggested that plaque composition may be adversely affected following conversion in patients who were transplanted several years previously (22).

CMV infection

Development of CMV infection is more frequent following heart transplantation compared to other types of solid organ transplant (54). The adverse clinical consequences of CMV infection following heart transplantation are well-recognized, and include increased risk of allograft rejection and infection, accelerated CAV progression and higher mortality (55, 56). Evidence from *de novo* kidney transplant populations has confirmed the incidence of CMV infection to be lower with mTOR inhibitors generally (57), and with everolimus specifically (58, 59), compared to MPA with standard-exposure CNI therapy. Similarly, randomized trials of everolimus in *de novo* heart transplantation have consistently shown a low rate of CMV infection

(3-5, 30, 60, 61) (Table 3), and comparative trials versus MMF (3, 5, 60) or azathioprine (30, 61) have each reported a significantly lower rate of CMV infection in the everolimus treatment arms (58). Indeed, the incidence of CMV infection in *de novo* heart transplant recipients receiving everolimus with reduced-dose CsA appears to be less than half that seen with MMF and standard-dose CsA (3, 60). This effect cannot be attributed solely to lower CNI exposure, since Zuckermann *et al* observed a similar rate of CMV infection with everolimus and standard CsA versus everolimus with reduced CsA (4). Results comparing everolimus to MMF were not due to differences in CMV prophylaxis between treatment groups, which were similar in both arms or in different CMV serostatus for recipients and donors (3, 61). There is evidence to suggest that mTOR is essential for CMV replication during late phases of the viral cycle (62) which could account for the inhibitor effect of everolimus on CMV infection rates. *In vitro* data indicate that mTOR acts through the mTOR complex 1 pathway to regulate memory T-cell differentiation (63), and that mTOR inhibitors exhibit immunostimulatory effects on memory CD8+ T-cells (64) that could improve the functional qualities of infection-induced memory cells.

Preservation of renal function

Evidence relating to a renal benefit of everolimus with reduced CNI

from time of heart transplantation is less convincing. The bulk of data relating to use of everolimus to minimize CNI-related nephrotoxicity and protect renal function in heart transplant recipients derives from maintenance heart transplant populations: either randomized (8, 65) and non-randomized (10, 12-14) studies of everolimus with reduced-CNI, or non-randomized trials of conversion from CNI to everolimus (11, 15-20). Encouragingly, the two randomized trials of CNI reduction in maintenance patients (8, 65) have indicated that an improvement in renal function versus controls can be achieved after introduction of everolimus in patients with GFR between 20 and 60mL/min/1.73m^2, including in patients with poor baseline function (GFR 20-29mL/min/1.73m^2), although caution was expressed over the introduction of everolimus in patients with pre-existing proteinuria (8). In contrast to experience in kidney transplantation (66), the benefit of everolimus was seen following conversion up to approximately 4 years post-transplant (8, 65). Non-randomized, single-center reports have indicated that everolimus introduction with CNI withdrawal in maintenance heart transplant patients with varying degrees of renal deterioration can significantly improve renal function with an acceptable efficacy and safety profile (11, 15, 16, 18-20). Such evidence has raised interest in *de novo* use of everolimus-based immunosuppression to reduce early CNI-related nephrotoxicity.

In *de novo* heart transplant recipients, the Phase III study in which everolimus was administered with standard-exposure CsA showed inferior renal function in the everolimus treatment arm compared to the azathioprine group (30) (Table 4). This is not unexpected in view of the known potentiation of the nephrotoxic effects of the CNI by mTOR inhibitors. More surprising was the absence of a renal benefit with CsA reduction in a trial of everolimus-treated *de novo* heart transplant patients randomized to reduced- or standard-exposure CsA (4) (Table 4). The authors pointed out that there was poor adherence to CsA exposure targets, with fewer than half the patients achieving target trough concentration. In a *post hoc* analysis that compared the change in serum creatinine from baseline to month 6 among only those patients who met the CsA exposure targets, the increase in creatinine levels was significantly smaller in the reduced-CsA arm (mean 5.5µmol/L versus 31.4µmol/L, p=0.047). Early data indicating that renal function would be superior using everolimus with reduced-CsA versus MMF with standard-exposure CsA (25) have not been borne out in two randomized trials (3, 5) (Table 4). Certain limitations of the studies may have contributed to this: the A2310 study used identical CsA ranges in the everolimus and MMF groups to month 1 post-transplant (3) while the other trial had an imbalance in renal function at baseline which favored the MMF cohort (5), and adherence to the planned reduction in CsA exposure was inadequate in both

trials. Nevertheless, current data are not fully convincing regarding a renal benefit for *de novo* heart transplant populations who are not selected on the basis of poor kidney function at time of transplant.

One single-center, single-arm prospective study in 20 *de novo* heart transplant patients with significant renal dysfunction at transplant (estimated GFR <30mL/min/1.73m^2) has described outcomes using a CNI-free *de novo* regimen comprising everolimus or sirolimus with corticosteroids, with or without induction (33). Mean (SD) estimated GFR increased dramatically, from 28 (17)mL/min/1.73m^2 preoperatively to 64 (24)mL/min/1.73m^2 at month 6, with all four patients who had previously required dialysis becoming dialysis-free. However, 55% of patients experienced rejection and 50% were eventually converted back to CNI therapy due to adverse events. While these results are of interest, it seems unlikely that everolimus-based CNI-free immunosuppression is appropriate from the time of heart transplantation unless renal function is very poor.

Everolimus and malignancy

At present, reduction of malignancy risk is not generally a reason to select *de novo* therapy with everolimus and the evidence base for prevention of post-transplant cancer remains relatively limited. Everolimus is, however, licensed for the treatment of advanced renal and breast tumors at higher doses than in post-transplant

immunosuppression, and a preventative role in transplant recipients is potentially of considerable interest. Data in heart transplantation are sparse, but mTOR inhibitors appear to reduce the rate of new malignancies and non-skin solid cancers in kidney transplant patients (67) and an observational study in heart transplantation has suggested a benefit for development of non-melanoma skin cancers (23). MTOR inhibition leads to selective upregulation of epidermal Akt1, potentially restricting the effects of tumor-associated changes on Akt1 signaling, which could represent a possible mechanism for antitumor activity in the epidermis (68). The CERTICOEUR trial (NCT00799188) is evaluating the effect of everolimus on the onset of new skin cancers in heart transplant patients with recurrent skin cancer receiving everolimus and reduced or discontinued CNI therapy versus standard CNI therapy.

Wound complications in *de novo* transplant recipients

As with all classes of immunosuppressive drugs, the mTOR inhibitors are associated with safety concerns. The most salient of these are dyslipidemia, peripheral edema, surgical wound complications, effusions, mouth ulcers and possibly proteinuria. These have been reviewed extensively elsewhere (1, 2, 69), but since wound healing and postoperative pericardial and pleural effusions are of particular interest in the *de novo* setting they are considered here. Further data

are expected from the SCHEDULE and EVERHEART studies when results become available.

Incisional site complications

Most types of immunosuppressive therapy adversely affect surgical wound healing to some extent (70) but the antiproliferative effect of mTOR inhibitors on endothelial cells, fibroblasts and smooth muscle cells and their antiangiogenic effect has led to particular awareness of healing complications with this class. It can be difficult, however, to quantify the effect of mTOR inhibition against the background of multiple general risk factors and other immunosuppressants in heart transplant populations, compounded by variations in reporting categories for wound healing complications between trials and differences in dosing regimens. A systematic review of randomized controlled trials of either sirolimus or everolimus recently concluded that the risk of wound complications is increased in patients receiving an mTOR inhibitor with CNI therapy (71), but included early trials in which large sirolimus loading doses and high exposure levels were used with standard-exposure CsA, so its relevance to modern regimens is uncertain.

The largest randomized trial to date in *de novo* heart transplants, which compared everolimus with reduced CsA versus MMF with standard CsA (3) observed no significant difference in the incidence of

sternal or non-sternal wound dehiscence between the two groups (Table 5). The Phase III trial (33) that compared everolimus at a fixed dose of 1.5mg or 3.0mg versus azathioprine, both with standard-exposure CsA, found lymphocele to be significantly more frequent with everolimus (4.8% and 4.3% versus 0.9% with azathioprine) but the overall rate of all events was low and there were no significant differences in the occurrence of wound dehiscence at the sternal site or wound complications unrelated to the site of left ventricular assist device (69). A pooled analysis of data from 1,009 heart transplant patients taking part in three trials (the Phase III trial [31], a randomized trial versus MMF [5], and a randomized trial of everolimus with two CsA exposure levels [4]) was undertaken to compare the incidence of incision-related complications (72). The overall rate of such complications was low with all immunosuppressants but highest with everolimus (everolimus 12.3%, MMF 7.2%, azathioprine 11.7%), and the difference in serious incisional complications approached significance versus MMF (everolimus 6.9%, MMF 1.2%, p=0.051). On univariate and multivariate analysis, everolimus was not significantly associated with incisional complications versus MMF (odds ratio [OR] 0.567, 95% CI 0.153-2.110, p=0.398) or versus azathioprine (OR 1.162, 95% CI 0.697-1.937, p=0.565) (72).

It is possible that the slight delay in introduction of everolimus (up to

72 hours post-transplant) in these studies (4, 5, 30), and in the more recent A2310 trial (3) may have facilitated adequate early wound healing. A longer delay until mTOR initiation (3-7 days) after heart transplantation has been suggested (2, 69) but a trial in which kidney transplant patients were randomized to immediate or delayed (4 weeks) introduction of everolimus and which included wound healing events as part of the primary endpoint showed no benefit (73). Evaluation of delayed introduction of everolimus in heart transplant recipients, or an initial low-exposure mTOR inhibitor regimen, is ongoing (74).

Pericardial and pleural effusions

Pericardial effusion is a frequent occurrence after heart transplantation, with moderately to large effusions reported in approximately a fifth of recipients (73, 75-77). Mortality and hospital stay are unaffected (75-77), although one study suggested an association between pericardial effusions and acute rejection (78). Comparative randomized trials of everolimus versus MMF (3, 5) and versus azathioprine (30) have demonstrated a higher incidence of pericardial effusions in everolimus-treated patients although, importantly, cardiac tamponade was not more frequent in any of the studies (Table 5). The ongoing EVERHEART study in a *de novo* heart transplant population includes pericardial effusion as a pre-specified

endpoint (74), and will offer robust data. The risk of pleural effusions appears to be unaffected by use of everolimus compared to MMF (Table 5).

Implications for *de novo* use of everolimus in heart transplantation

The current evidence base suggests that the most convincing reasons for use of everolimus therapy from the time of heart transplantation are (a) to slow the progression of CAV and potentially reduce cardiovascular morbidity and mortality, and (b) to lower the risk of CMV infection. It would seem appropriate to consider *de novo* everolimus-based immunosuppression in recipients of a heart from a donor with coronary artery disease, or who are undergoing retransplantation following graft loss due to CAV. A good case could be made for use of everolimus therapy in CMV-negative heart transplant patients at centers where CMV prophylaxis is not standard practice, or possibly in recipient-negative, donor-positive transplants even where prophylaxis is routine. Based on available evidence, no clear renal benefit is observed using everolimus with reduced CsA from time of transplant, although poor adherence to planned CsA exposure reductions and/or inadequate protocol-specified lowering of CsA exposure early post-transplant mean that further exploration may be justified. Currently, everolimus is usually reserved for rescue

therapy in maintenance heart transplant recipients who develop renal deterioration. However, the NOCTET study showed that pre-emptive conversion from CNI to everolimus before severe renal insufficiency develops can significantly improve renal function in heart transplant recipients, particularly when undertaken earlier post-transplant, preferably before three years (79, 80).

Everolimus with complete CNI avoidance from the day of transplant may only be appropriate in patients with very poor baseline kidney function who are at low risk for rejection (i.e. non-sensitized), and is likely to require use of induction therapy. A more cautious approach in patients with renal dysfunction may be to initiate everolimus with reduced CsA then undertake planned CNI withdrawal, a strategy that is being investigated in the ongoing MANDELA trial (NCT00862979). A similar strategy is being investigated in the SCHEDULE study, but is being applied regardless of baseline renal function.

It should be pointed out that the evidence base relating to everolimus with CNI immunosuppression in *de novo* heart transplantation relates almost exclusively to patients receiving CsA, not tacrolimus. It is relevant, however, that experience with sirolimus in combination with tacrolimus in *de novo* recipients has shown the combination to offer effective immunosuppression (81). The drug-drug interactions that occur between everolimus and CsA are less pronounced with

tacrolimus (82) but data from kidney transplantation has shown that everolimus significantly decreases tacrolimus oral bioavailability in a dose-dependent manner (83) so therapeutic drug monitoring is mandatory to prevent low tacrolimus exposure.

A target everolimus trough concentration range of 3-8ng/mL in *de novo* heart transplant recipients appears optimal when administered in combination with CNI therapy (3). Induction with a lymphocyte-depleting agent such as rabbit ATG in patients receiving an everolimus-based regimen with relatively high CsA exposure (as in the A2310 trial) should be avoided due to risk of infection-related mortality (3) unless there are compelling clinical indications. Where everolimus is initiated at the time of heart transplantation, it is not known whether delayed introduction (e.g. until wound healing is complete) would be beneficial in avoiding incisional wound healing complications. While intuitively this is an appealing option, the most recent evidence (3) does not suggest that impaired healing is a clinical concern, and data from kidney transplantation indicates no benefit in delay (68). If wound healing is a concern in high-risk patients (e.g. with high body mass index), low everolimus exposure could be a possible strategy but has not been investigated. It seems inadvisable to initiate everolimus in *de novo* heart transplant patients in whom repeat surgery is anticipated.

Other safety concerns with mTOR inhibitors are not specific to the *de novo* situation (1, 2, 64) and are not reviewed here, but it should be pointed out that *de novo* use of everolimus in patients with uncontrolled hyperlipidemia or in whom there is a clear contraindication to statin therapy would be unwise.

Conclusion

The available evidence suggests that use of everolimus in combination with reduced-dose CsA and steroids achieves outcomes which are comparable to those observed with other triple drug regimens currently used in heart transplantation. Such a combination is a therapeutic option in *de novo* heart transplantation in view of robust data showing proven non-inferiority for the prevention of acute rejection. While more research is awaited about infection rates with cytolytic induction in high-risk patients who are receiving CNI and everolimus therapy, this does not seem to be a concern in standard-risk individuals, and IL-2 receptor antibody induction is not associated with safety issues in this setting. A benefit for renal function can be achieved with everolimus-based immunosuppression if there is an adequate reduction in CNI exposure, but a persistently high level of proteinuria (>1g/day) after initiation of ACE inhibitor/angiotensin receptor blocker therapy contraindicates everolimus-based immunosuppression for *de novo* patients. Use of everolimus has been demonstrated to exert a favorable effect on certain important

complications following heart transplantation. It may slow the progression of CAV, the most limiting factor for long-term survival in heart transplant recipients, and several trials have suggested that the risk of CMV infection is reduced in patients receiving everolimus from the time of heart transplantation. It may be advisable to delay the introduction of everolimus until the wound incision has healed in patients who are at high risk of infection or healing complications.

Thus, while total avoidance of CNI therapy in *de novo* heart transplant patients receiving everolimus appears inadvisable, a regimen of everolimus with reduced-exposure CNI and steroids from the time of transplant represents a welcome addition to the therapeutic armamentarium.

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Table 1. Efficacy outcomes in prospective trials of everolimus in *de novo* heart transplant recipients

Study	Study design	Follow-up	Treatment	N	Prir Endpoint
Eisen 2012[a] (3)	Randomized Multicenter Open label	12 months	EVR 1.5mg (3-8ng/mL) Reduced CsA Steroids ± Induction	282	SHLT grade ≥3A BPAR, acute rejec associated with hemodynamic compromise, graft oss/retransplant, death, or loss to follow-up
			MMF Standard CsA Steroids ± Induction	271	
Zuckermann 2011 (4)	Randomized Multicenter Open label	6 months	EVR (3-8ng/mL) Reduced CsA ± Induction	99	SHLT grade ≥3A BPAR, acute rejec associated with hemodynamic compromise, graft oss/retransplant, death, or loss to follow-up
			EVR Standard CsA ± Induction	100	
Lehmkuhl 2009 (5)	Randomized Multicenter Open label	12 months	EVR (3-8ng/mL) Reduced CsA Steroids ± Induction	92	SHLT grade ≥3A BPAR, acute rejec associated with hemodynamic compromise, graft oss/retransplant, death, or loss to follow-up
			MMF Standard CsA Steroids ± Induction	84	
Eisen 2003 (30)	Randomized Multicenter Double blind	12 months	EVR 1.5mg (fixed dose) CsA Steroids ± Induction	209	ISHLT grade ≥3A (2R) BPAR, acute rejection associat with hemodynam compromise, graf loss/retransplant, death, or loss to follow-up
			EVR 3.0mg CsA Steroids ± Induction	211	
			Aza Standard CsA Steroids ± Induction	214	

Aza, azathioprine; BPAR, biopsy-proven acute rejection; CsA, cyclosporine; EVR, everolimus; ISHLT, International Society for Heart & Lung Transplant; MMF, mycophenolate mofetil; NI, non-inferiority

[a] Data from a discontinued third treatment arm (everolimus 3.0mg) are not shown

[b] ISHLT grade ≥3A (2R)

[c] Primary efficacy endpoint was at 6 months; proportion of patients reaching composite endpoint at 12 months was 41.6% in the EVR 1.5mg group (p=0.02), 32.2% in the EVR 3.0mg group (p<0.001) vs 52.8% in the azathioprine group

[d] At 12 months

Table 2. Intravascular ultrasound (IVUS) outcomes in randomized trials of *de novo* heart transplant patients receiving everolimus

Study	Study design	IVUS	Treatment	n/N[c]	Prin
					Mean
Eisen 2012[a] (3)	Randomized Multicenter Open label	Baseline[b] 12 months	EVR 1.5mg (3-8ng/mL) Reduced CsA Steroids ± Induction	88/282	0.03 (
			MMF Standard CsA Steroids ± Induction	101/271	0.07 (
Eisen 2003 (30) Vigano 2007 (48)	Randomized Multicenter Double blind	Baseline[b] 12 months	EVR 1.5mg (fixed dose) CsA Steroids ± Induction	70/209	0.0
			EVR 3.0mg CsA Steroids ± Induction	69/211	0.0
			Aza Standard CsA Steroids ± Induction	72/214	0.1
		Baseline[b] 24 months	EVR 1.5mg (fixed dose) CsA Steroids ± Induction	–f	0.0
			EVR 3.0mg CsA Steroids ± Induction	–f	0.0
			Aza Standard CsA Steroids ± Induction	–f	0.1

Aza, azathioprine; CsA, cyclosporine; EVR, everolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid

[a] Data from a discontinued third treatment arm (everolimus 3.0mg) are not

shown

[b] Within six weeks of transplantation

[c] Patients with evaluable IVUS data / total number of patients

[d] Mean change in MIT from baseline to IVUS follow-up (12 or 24 months)

[e] Cardiac allograft vasculopathy, defined as ≥0.5mm increase in MIT in ≥1 matched slides

Table 3. CMV infection rates in randomized trials of everolimus in *de novo* heart transplant recipients

Study	Study design	Follow-up	Treatment	N	Endpoint (definition)
Eisen 2012 (3)	Randomized Multicenter Open label[a]	12 and 24 months	EVR 1.5mg Reduced CsA Steroids ± Induction	279	Laboratory documentation of CMV infection (antigenemia-positive or PCR positive) at month 12
			MMF Standard CsA Steroids ± Induction	268	
Zuckermann 2011 (4)	Randomized Multicenter Open label	6 months	EVR Reduced CsA ± Induction	99	CMV infection (positive antigenemia and/or PCR and/or seroconversion without signs and/or symptoms)
			EVR Standard CsA ± Induction	100	
Lehmkuhl 2009 (5) Viganò 2010 (60)	Randomized Multicenter Open label	12 months	EVR Reduced CsA Steroids ± Induction	92	CMV event of any type (reported as adverse event, CMV infection, laboratory evidence, CMV syndrome or CMV disease)
			MMF Standard CsA Steroids ± Induction	84	
Eisen 2003 (30) Hill 2007 (61)	Randomized Multicenter Double blind	12 months	EVR 1.5 mg CsA Steroids ± Induction	209	CMV infection in D+/R- group with CMV prophylaxis
			EVR 3.0 mg CsA Steroids ± Induction	211	
			Azathioprine CsA Steroids ± Induction	214	

BPAR, biopsy-proven acute rejection; CMV, cytomegalovirus; CsA,

cyclosporine; EVR, everolimus; MMF, mycophenolate mofetil; D, donor; R, recipient; PCR, polymerase chain reaction

[a] Data from a discontinued third treatment arm (everolimus 3.0mg) are not shown

Table 4. Renal function in randomized trials of everolimus in *de novo* heart transplant recipients

Study	Study design	Follow-up	Treatment	N	Endpoint	Mean (SD
Eisen 2012 (3)	Randomized Multicenter Open label[a]	12 and 24 months	EVR 1.5mg Reduced CsA Steroids ± Induction	279	eGFR at month 12 ($mL/min/1{\cdot}73m^2$)	59.4 (22.8
			MMF Standard CsA Steroids ± Induction	268		64.7 (28.1
Zuckermann 2011 (4)	Randomized Multicenter Open label	6 months	EVR Reduced CsA ± Induction	99	eGFR (MDRD) at month 6 ($mL/min/1.73m^2$)	59.0 (23.2)
			EVR Standard CsA ± Induction	100		59.5 (48.2)
Lehmkuhl 2009 (5)	Randomized Multicenter Open label	12 months	EVR Reduced CsA Steroids ± Induction	92	Calculated creatinine clearance (Cockcroft-Gault) (mL/min) at 12 months	68.7 (27.7)
			MMF Standard CsA Steroids ± Induction	84		71.8 (29.8)
Eisen 2003 (30)	Randomized Multicenter Double blind	12 months	EVR 1.5mg CsA Steroids ± Induction	209	Serum creatinine at month 12 (µmol/L)	168[d]
			EVR 3.0mg CsA Steroids ± Induction	211		172[d]
			Azathioprine CsA Steroids ± Induction	214		141[d]

Aza, azathioprine; CsA, cyclosporine; eGFR, estimated GFR; EVR, everolimus; MDRD, Modification of Diet in Renal Disease; MMF, mycophenolate mofetil

[a] Data from a discontinued third treatment arm (everolimus 3.0mg) are not shown

[b] The difference in eGFR at month 12 was -5.6mL/min/1.73m^2, 97.5% confidence interval -10·9, -0·2 i.e. the lower limit of the confidence interval was below the non-inferiority margin of -10mL/min/1·73m^2 (p=0·030 for non-inferiority test; p=0·019 for no-difference test)

[c] Predefined analyses to account for missing month 6 creatinine values showed significantly lower mean serum creatinine in the reduced CsA vs. the standard CsA group (127.3 vs. 145.9 µmol/L, p=0.023, last observation carried forward).

[d] Median values

Table 5. Incidence of incisional complications and effusions in prospective trials of everolimus versus MPA in *de novo* heart transplant recipients

Study	Study design	Follow-up	Treatment	N	Incisional complications (%)	P
Eisen 2012[a] (3)	Randomized Multicenter Open label	12 months	EVR 1.5mg (3-8ng/mL) Reduced CsA Steroids ± Induction	282	24.4, 13.3[b]	
			MMF Standard CsA Steroids ± Induction	271	19.4, 13.1[b]	
Lehmkuhl 2009 (5)	Randomized Multicenter Open label	12 months	EVR (3-8ng/mL) Reduced CsA Steroids ± Induction	92	[c]	
			MMF Standard CsA Steroids ± Induction	84	[c]	
Eisen 2003 (30) Zuckermann (69)	Randomized Multicenter Double blind	12 months	EVR 1.5mg (fixed dose) CsA Steroids ± Induction	209	4.8, 1.4[d]	P< lym
			EVR 3.0mg CsA Steroids ± Induction	211	4.3, 2.4[d]	
			Azathioprine CsA Steroids ± Induction	214	0.9, 0.9[d]	

Aza, azathioprine; CsA, cyclosporine; EVR, everolimus; MMF, mycophenolate mofetil

[a] Data from a discontinued third treatment arm (everolimus 3.0mg) are

not shown

[b] Sternal & non-sternal would healing event, as defined by the investigator

[c] No data on incisional complications provided other than wound infections (everolimus 6.6%, MMF 8.6%)

[d] Lymphocele, wound dehiscence at sternal site