NHS England

Evidence Review:

Everolimus for prevention of organ rejection following heart transplantation

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Contents

1. Introduction

Allogeneic cardiac transplantation is the transfer of the heart organ from a donor to the host patient. Following the procedure, patients will need immunosuppressants to suppress their immune system and prevent it from attacking and rejecting the heart. These immunosuppressants put the patients at risk of infection and adverse drug effects.

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that exerts an immunosuppressive effect by inhibiting the proliferation, and thus clonal expansion, of antigen-activated T cells. Everolimus causes immunosuppression via different pathways to other treatments, and has been proposed as an alternative immunosuppressant treatment to prevent organ rejection and kidney dysfunction in patients at immunological risk following an allogeneic cardiac transplant.

2. Summary of results

Following a heart transplant (HT), calcineurin inhibitors (CNIs), such as cyclosporine or tacrolimus, are administered in order to reduce the risk of graft loss or acute rejection. CNI exposure is considered to play a key role in renal damage that can cause long term fatal renal failure, although renal failure is not the most common cause of death following HT. Mortality in the first year post-HT is primarily caused by graft failure and infection. Mortality from malignancy and cardiac allograft vasculopathy (CAV) predominates in subsequent years. To improve survival rates and reduce side effects, antiproliferation agents, such as azathioprine and mycophenolate mofetil (MMF), can be used in combination with CNIs. CNIs form the backbone of immunosuppression but are part of a standard triple therapy regimen together with an antimetabolite (MMF or azathioprine) and steroids.

The proliferation signal inhibitors sirolimus or everolimus can be used an alternative to antiproliferation agents i.e. in combination with CNI or as an alternative to CNIs in combination with an antiproliferative agent (e.g. renal sparing strategy). Hence the clinical efficacy and specific advantages of everolimus can be measured in terms of the efficacy in reducing organ rejection or death, impact on renal function, rates of adverse effects (in particular CMV infections), in addition to the treatment and prevention of CAV.

This literature review was aimed at identifying the current evidence for everolimus post cardiac transplant, specifically to answer the following questions:
1. Is everolimus, in combination with other drugs, clinically effective in preventing organ rejection and adverse effects post cardiac transplant?
2. Does everolimus, in combination with other drugs, offer specific advantages in terms of organ rejection and adverse effects?
3. Is everolimus a cost-effective treatment option for preventing organ rejection and adverse effects post cardiac transplant?

This review found:
• There is level 1 evidence that everolimus, and a reduced cyclosporine dose, is not inferior to MMF and superior to azathioprine in preventing organ rejection. However, everolimus alone is inferior to treatments with cyclosporine.
• There is level 1 evidence that everolimus helps to prevent CAV, but there is no evidence that it is effective against established CAV.
• There is level 1 evidence that everolimus is associated with a reduced CMV infection rate, compared with azathioprine and MMF.
• The evidence that everolimus and a reduced CNI dose results in an improved renal function is conflicted and is likely to be sensitive to the precise details of the CNI dose.
• There is level 1 evidence that everolimus treatment strategies are associated with a reduced risk of leukopenia, but an increased risk of pneumonia and pericardial effusion, when compared with MMF treatments. Overall, during treatment with everolimus a higher number of serious non-fatal adverse events are recorded.

1a. Clinical effectiveness of everolimus in preventing organ rejection post cardiac transplant

The principle outcome for measuring the clinical effectiveness in preventing organ rejection is the rate of biopsy proven acute rejection (BPAR), graded according to international society of heart and lung transplants grading (ISHLT) systems. It is also possible to look at rates of graft loss, death or a composite endpoint (defined as BPAR≥3A, graft loss or death).

• There is level 1 evidence, from 1 large RCT (n=553) with 24 month follow up, that 1.5 mg/day of everolimus with a reduced cyclosporine dose has a statistically similar acute rejection rate to 3 g/day of MMF with a standard cyclosporine dose (24% vs 27%) (Eisen et al., 2013).
• There is level 1 evidence, from 1 large RCT (n=634) with 24 months follow up, that a treatment of everolimus (1.5mg/day) has a lower rate of acute rejections (BPAR≥3A) than a treatment of Azathioprine (34.9% vs 48.1%, p=0.005), with both treatments using a standard cyclosporine dose. The acute rejection rate improved further with 3.0mg/day of everolimus (22.7%). However, subsequent trials with 3.0mg/day of everolimus were halted by the data monitoring committee due to a perceived high mortality rate. The rates of graft loss and death were statistically similar (Vigano et al., 2007).
• A smaller RCT (n=115) found that a treatment schedule including everolimus and MMF, in which the use of CNIs was withdrawn after 7-11 weeks, led to an increase in the acute rejection rate, compared with the use of MMF and cyclosporine (43% vs 15%, p<0.01), (Arora et al., 2015). This result was in agreement with a level 2+ cohort study that found the acute rejection rate for everolimus with a reduced cyclosporine dose was lower than everolimus with no cyclosporine (Gonzalez-Vilchez et al., 2014).

1b. Clinical effectiveness of everolimus in preventing and treating CAV post cardiac transplant

While the rate of CAV is sometimes recorded, it is more productive to measure the impact of treatment schedules on CAV by using an intravascular ultrasound to measure the change, from baseline value, in the coronary maximal intimal thickness (ΔMIT). An incidence of CAV is often defined as ΔMIT ≥ 0.5mm. Other metrics, such as the change in atheroma volume and intimal area, typically mirror the ΔMIT results.

The same two large RCTs and one small RCT all found respectively that 1.5 mg/day everolimus resulted in:
• A ΔMIT=0.07mm compared with azathioprine, ΔMIT=0.15mm, p=0.014, after 24 months. (Vigano et al., 2007)
• A ΔMIT=0.03mm compared with MMF, ΔMIT=0.07mm, p<0.001, after 12 months (Eisen et al., 2013).
• A ΔMIT=0.03mm compared with MMF, ΔMIT=0.08mm, p=0.02, after 12 months (Arora et al., 2015).
This resulted in rates of CAV for everolimus of between (12%-33%) vs. (27% - 58%) for azathioprine and MMF treatments.

However, this was based on using everolimus from the first month post-HT, to prevent CAV. A different RCT (n=111) examined the impact of everolimus on patients, an average of 5.8 years post-HT, who had established CAV (mean baseline MIT = 0.56mm). Both the everolimus and MMF arm found no impact on the CAV, ΔMIT=0.0±0.04mm and ΔMIT=0.04±0.04mm respectively (Arora et at., 2011). Likewise, a retrospective cohort study (n=143) found that everolimus and MMF had no impact on MIT between 1 year post HT and 5 year post HT (Masetti et al., 2013).

1c. Clinical effectiveness of everolimus in preventing CMV infection post cardiac transplant

There is level 1 evidence that everolimus is associated with a lower incidence of CMV infection. There is good agreement from four RCTs (Eisen et al., 2013 n=553 plus three combined in a meta-analysis in Kobashigawa et al., 2013, n=1009) and one large cohort study (Durante-Mangoni et al., 2015, n=378). It is found that the CMV infection rate, when the treatment strategy is using everolimus is between 3-9%. Whereas when azathioprine or MMF is used, this rises to between 19-33%.

2a. Advantages of everolimus, in combination with other drugs, in terms of nephrotoxicity

Renal function can be assessed using creatine clearance or measured/estimated glomerular filtration rates (m/eGFR), all based on creatine concentrations. Although, it was argued in (Stypmann et al., 2015) that deterioration in renal function can occur prior to an increase in serum creatine level. Hence they argue for using Neutrophil gelatinase-associated lipocalin (NGAL) levels.
• During a large RCT (n=553), eGFR was found to indicate that 1.5mg/day of everolimus with a reduced cyclosporine dose was inferior to MMF and a standard dose of cyclosporine (a mean change from baseline of eGFR of -0.67 mL/min/1.73 m^2 vs 1.6 mL/min/1.73 m^2). However, closer examination revealed that this difference occurred in the first 3 months post HT, when both treatments had similar cyclosporine doses (Eisen et al., 2013).
• A small RCT (n=115), which used everolimus and no cyclosporine after week 11 compared with MMF and cyclosporine, found that the everolimus arm had a significantly higher mGFR (79.8 mL/min/1.73 m^2 vs 61.5 mL/min/1.73 m^2, p<0.001) after 12 months. Although the same trial reported a higher rate of acute rejections for

the everolimus arm (Andreassen et al., 2014).
• Two further RCTs and a Cohort study (n=176, n=70 & n=121) compared everolimus with a reduced cyclosporine dose and MMF with a standard cyclosporine dose. After 12 months no difference in the creatine clearance levels was found in the two RCTs. Although, the everolimus arm had lower levels, but the sample size stopped this from being statistically significant (Lehmkuhl et al., 2009; Bara et al., 2013). The cohort study found plasma and urine NGAL levels significantly lower in the everolimus cohort (p<0.001), favouring the everolimus treatment strategy (Stypmann et al., 2015).

2b. Advantages of everolimus, in combination with other drugs, in terms of adverse effects

In addition to CMV infection there were a large number of additional adverse effects reported during these trials. The majority had similar rates between the respective treatment strategies, but it is worth commenting on the differences. In particular:
• (Eisen et al., 2013 and Lehmkuhl et al., 2009) both reported that everolimus treatment strategies had a lower rate of Leukopenia than MMF, (13-16% vs 26-30%, p=0.011).
• (Eisen et al., 2013) reported that everolimus was associated with higher rates of pericardial effusion than MMF (44% vs 29%, p<0.001).
• Overall patients treated with everolimus had more nonfatal serious adverse events than those treated with MMF (74.2% vs 61.2%), (Eisen et al., 2013).
• (Vigano et al., 2007) reported that treatment with everolimus resulted in higher rate of pneumonia than azathioprine (13.9% vs 2.8% p<0.001).

3. Cost effectiveness of everolimus in preventing organ rejection and adverse effects post cardiac transplant

Two studies were found that looked at the cost effectiveness of everolimus treatments. The first compared the total cost of everolimus and azathioprine, with both treatments aiming for standard doses of cyclosporine. The study found that everolimus was marginally more expensive, $72,065 vs $70, 815 (£47,910 v £47,079) . This difference was primarily due to increased hospitalisation costs and secondarily due to increased concomitant medication costs, although there were savings made on the cyclosporine costs (Radeva et al., 2005). The second study was based on the German health care model and looked at the incremental cost of everolimus and MMF verses azathioprine divided by the reduction in efficacy failure (the incremental cost effectiveness ratio ICER). The study favoured everolimus over MMF with an ICER of 24,457 Euros vs 29,912 Euros (£17,593 v £21,516), although the study doesn't appear to include hospitalisation costs (Annemans et al., 2007).

3. Research questions

1. Is Everolimus, in combination with other drugs, clinically effective in preventing organ rejection and adverse effects post cardiac transplant?

2. Does everolimus, in combination with other drugs, offer specific advantages in terms of organ rejection and adverse effects?

3. Is everolimus a cost-effective treatment option for preventing organ rejection and adverse effects post cardiac transplant?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1-	Systematic + Meta Analysis	Total of 1009 patients	Everolimus (1.5mg/day & 3mg/day) with both standard and reduced dose of Cyclosporine	Clinical effectiveness of the intervention compared to existing interventions	Any adverse event (AE) and serious adverse event (SAE).	Pooled everolimus (n=710): AE 12.3% SAE 6.9% MMF (n=83): AE 7.2% SAE 1.2% Azathioprine (n=214): AE 11.7% SAE 4.2%	-	-	Zuckermann, Andreas; Arizon, Jose M.; Dong, Gaohong; Eisen, Howard J.; Kobashigawa, Jon; Lehmkuhl, Hans; Ross, Heather; Pelligrini, Carlo; Wang, Shoei-Shen; Barten, Markus J.. Impact of de novo everolimus-based immunosuppression on incisional complications in heart transplantation. Transplantation. 2011.	-	-	This systematic review pooled the results, on the numbers of adverse events from incisional complications, from three studies, two RCTs and one cohort study. The main finding of the paper was that the rates of adverse events, for patients being treated with everolimus, were low but numerically higher than those being treated by MMF and azathioprine. Although these differences are not statistically significant. Primary concern about such results is the combination of multiple doses of everolimus and cyclosporine, although the break down by trials are also included in the paper.

1-	Systematic	634, 553, 143, 111 patients over four studies.	Everolimus 0.75mg twice/day, 1.5mg twice/day with standard or reduced doses of cyclosporine, see trial paper for details.	Clinical effectiveness of the intervention compared to existing interventions	Change in coronary maximal intimal thickness (ΔMIT)	ΔMIT was significantly lower with everolimus than azathioprine at 6 months, p=0.02 (0.75mg arm) and p=0.002 (1.5mg arm). Rates of CAV (defined as ΔMIT > 0.5 mm) lower with everolimus (12.5%) than with (26.7%) p=0.018.	-	-	Hollis, Ian B.; Reed, Brent N.; Moranville, Michael P.. Medication management of cardiac allograft vasculopathy after heart transplantation. Pharmacotherapy. 2015.	One RCT (NOCTET) focused on patients with existing CAV, with 111 patients, found no significant difference between everolimus (with reduced CNI dose) and regular CNI dose. Warning exist that high doses of everolimus (1.5mg twice/day), in first 3 months after HT, increase risk of infection. Recommended to be used from post 6 months with lower initial doses.	-	This systematic review is intended to give an overview of the possible treatments for Cardiac Allograft Vasculopathy (CAV) and evidence for the efficacy of different treatments. The study reviews four studies on everolimus, without meta-analysis, (Vigano et al. 2007, Kobashigawa et al., 2013; Andressen et al., 2014; Arora et al., 2011; Masetti et al., 2013) all included in more detail in this review. Review concludes that proliferation signal inhibitors (including everolimus and sirolimus) 'demonstrate a unique ability to attenuate CAV, especially when initiated before development', although less beneficial when used further along disease process. Only Sirolimus has evidence for efficacy in treatment of CAV, albeit based on smaller studies.
1+	RCT	115 patients	Everolimus 0.75mg twice/day with 75-175 ng/mL cyclosporine up until week 7, with Mycophenolate mofetil (MMF) 1500-2000 mg/day after week 7 cyclosporine discontinued and MMF 1000 mg/day	Clinical effectiveness of the intervention compared to existing interventions	measured Glomerular Filtration Rate (mGFR) at 12 months.	mGFR everolimus 79.8 ± 17.7 mL/min/1.73 m^2 cyclosporine 61.5 ± 19.6 mL/min/1.73 m^2 p<0.001	Acute rejection rate in 12 months. Change in coronary maximal intimal thickness (ΔMIT) Rate of CAV at 12 months Adverse events	Acute rejection rate: 76.9% everolimus vs 66.1% cyclosporine ΔMIT: 0.03 mm everolimus vs 0.08mm cyclosporine, but mean initial MIT values were smaller in everolimus 0.52 mm vs 0.56 mm Rate of CAV: 50% everolimus vs 65% cyclosporine Adverse events rates for (everolimus vs cyclosporine): hypertension (17.9% vs. 33.9%), edema (28.6% vs 18.6%), leukopenia (19.6% vs 22%), pleural effusion (23.2% vs 13.6%)	Andreassen, A. K.; Andersson, B.; Gustafsson, F.; Eiskjaer, H.; Radegran, G.; Gude, E.; Jansson, K.; Solbu, D.; Sigurdardottir, V.; Arora, S.; Dellgren, G.; Gullestad, L.; SCHEDULE Investigators. Everolimus initiation and early calcineurin inhibitor withdrawal in heart transplant recipients: a randomized trial. Am. J. Transplant.. 2014.	-	-	This RCT was primarily designed to determine the benefit to renal functions of Everolimus over Calcineurin inhibitors (CNI). The study found that the Everolimus arm had a statistically significant higher mGFR than the Cyclosporine. It also found a lower incidence of CAV (50% vs 64.6% for Cyclosporine). However, it also found that the incidence of 12 month biopsy proven acute rejection after 7-11 weeks was more frequent with Everolimus. Also change in coronary maximal intimal thickness was smaller in the Everolimus arm. There were similar levels of adverse events in the two arms. This study provides clinical evidence to the assertion that CNIs achieve low rates of acute rejection and improved short term survival rates, but suffer from higher risk of morbid chronic renal failure within first 5 years.

1+	RCT	553 patients	arm 1: everolimus 1.5 mg/day cyclosporine 200-350 ng/mL (0-2 months), 100-250 ng/mL (2-3 months), 100-200 ng/mL (3-5 months), 75-150 ng/mL (5-7 months), 50-100 ng/mL (7-24 months)	Clinical effectiveness of the intervention compared to existing interventions	Change in coronary maximal intimal thickness (ΔMIT) measured with intravascular ultrasound (IVUS)	ΔMIT : 0.03 ± 0.05 mm everolimus vs. 0.07 ± 0.11 mm MMF Incidence of CAV (ΔMIT > 0.5mm) 12.5% everolimus vs. 26.7% MMF p=0.018. amongst patients subgroups BPAR > 2 : ΔMIT : 0.04 ± 0.06 mm everolimus vs. 0.06 ± 0.09 mm MMF BPAR > 2R : ΔMIT : 0.02 ± 0.05 mm everolimus vs. 0.07 ± 0.12 mm MMF	Incidence of cytomegalo virus (CMV) infections	CMV infections: 8.2% (everolimus) vs 20.5% (MMF) BPAR > 2R: 18% (everolimus) vs 25% (MMF)	Kobashigawa, Jon A.; Pauly, Daniel F.; Starling, Randall C.; Eisen, Howard; Ross, Heather; Wang, Shoei-Shen; Cantin, Bernard; Hill, James A.; Lopez, Patricia; Dong, Gaohong; Nicholls, Stephen J.; A2310 IVUS Substudy Investigators. Cardiac allograft vasculopathy by intravascular ultrasound in heart transplant patients: substudy from the Everolimus versus mycophenolate mofetil randomized, multicenter trial. JACC Heart Fail. 2013.	Evaluable IVUS data available for 35% of patients. Demographics different for patients who underwent IVUS. A 3.0mg/day everolimus arm (with same reduced CyS dose) was discontinued due to a higher mortality rate.	-	This large RCT compares 1.5 mg/day of Everolimus with 3.0 mg/day MMF and found overall Everolimus was more effective in restricting progression of intimal thickening and preventing CAV. Everolimus also had lower levels of CMV infections in both CMV syndrome (1.4% Everolimus vs. 6.7% MMF), CMV disease (1.8% Everolimus vs. 3.7% MMF) and overall infections (8.2% vs 20.5%). Primary result mean change in MIT was 0.03 mm (Everolimus) vs 0.07 mm (MMF) and subsequently lower rates of CAV (12.5% vs 26.7% for MMF).
1-	RCT	70 patients	0.75 mg everolimus twice/day with cyclosporine (CsA) reduced to target level 35-65 ng/mL	Clinical effectiveness of the intervention compared to existing interventions	Serum Creatine levels (SCr) as a measure of renal function at 6 months.	MMF seem favourable on renal functions when assessed by SCr. LS mean difference in SCr 0.27mg/dL, with everolimus having higher levels. P value of everolimus being superior (non-inferior) was 0.019 (0.5713).	Adverse events	Gastrointestinal disorders (44.4% everolimus vs. 35.3% MMF) General disorders (41.7% everolimus vs. 29.4% MMF) Diarrhoea (11.1% everolimus vs. 17.4% MMF) Cardiac disorders (5.6% vs. 14.7%)	Bara, C.; Dengler, T.; Hack, M. A.; Ladenburger, S.; Lehmkuhl, H. B.. A 1-year randomized controlled study of everolimus versus mycophenolate mofetil with reduced-dose cyclosporine in maintenance heart transplant recipients. Transplant. Proc.. 2013.	-	-	This RCT set out to demonstrate the non-inferiority of Everolimus with reduced CsA doses to MMF in improving renal functions measured using serum creatinine levels (SCr). The study considered patients with baseline levels 1.7 mg/dL < SCr < 3.5 mg/dL and found MMF to be marginally superior. They conclude Everolimus could not be shown to be non-inferior to MMF, but CsA levels can be safely reduced for Everolimus. Primary concern with this study is the size of the sample (n=70).

1++	RCT	721 patients	1.5 mg/day everolimus with cyclosporine (CsA) reduced to fall from (200-350 ng/mL) to (50-100 ng/mL) plus steroids	Clinical effectiveness of the intervention compared to existing interventions	Incidence of Biopsy-proven acute rejection (BPAR) grade > 3A (ISHLT grade) Change in coronary maximal intimal thickness (ΔMIT) measured with intravascular ultrasound (IVUS), leading to incidence of CAV (ΔMIT > 0.5mm)	BPAR: 35.1% everolimus vs 33.6% MMF at 12 month 39.4% everolimus vs 41.3% MMF at 24 month i.e. non-inferior ΔMIT: 0.03 ± 0.05 mm everolimus vs 0.07 ± 0.11 mm MMF at 12 month Incidence of CAV: 12.5% everolimus vs 26.7% MMF at 12 month p=0.018	Mortality rate Estimated Glomerular Filtration Rate (eGFR) Adverse events	Mortality rate: 7.8% everolimus vs 4.8% MMF at 12 month 10.6% everolimus vs 9.2% MMF at 24 month; Mean (SD) eGFR: 59.4(22.8) mL/min/1.73 m^2 everolimus vs. 64.7(28.1) mL/min/1.73 m^2 MMF at 12 months 59.5(22.4) mL/min/1.73 m^2 everolimus vs. 64.5(23.8) mL/min/1.73 m^2 MMF at 24 months; Adverse events at 24 months: Majority had statistically similar rates between everolimus and MMF except: - Leukopenia 13% everolimus vs 25.7% MMF RR 0.52 - Pericardial effusions 44.1% everolimus vs 29.5% MMF RR 1.5 - Neutropenia 17.9% everolimus vs 40.3% MMF RR 0.44 -Viral infections 14.7% everolimus vs 31.7% MMF RR 0.46 -Of which CMV 7.2% everolimus vs 21.6% MMF RR 0.33	Eisen, H. J.; Kobashigawa, J.; Starling, R. C.; Pauly, D. F.; Kfoury, A.; Ross, H.; Wang, S.-S.; Cantin, B.; Van Bakel, A.; Ewald, G.; Hirt, S.; Lehmkuhl, H.; Keogh, A.; Rinaldi, M.; Potena, L.; Zuckermann, A.; Dong, G.; Cornu-Artis, C.; Lopez, P.. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. Am. J. Transplant.. 2013.	A 3.0mg/day everolimus arm (with same reduced CyS dose) was discontinued in 2008 due to recommendation by data monitoring committee, due to a higher mortality rate.	-	This large RCT compared Everolimus with 1.5 mg/day and reduced Cyclosporine doses against MMF 3 g/day. The main findings of the study are: -Everolimus non-inferior to MMF in preventing composite efficacy failure (BPAR). -Everolimus reduced intimal proliferation measured using ultra-sound (IVUS) -Everolimus reduced rate of CMV infections and some other adverse effects but not pericardial effusion which had an increased rate. -Mortality rate higher for Everolimus at 12 months but equivalent at 24 months. Possible concern about skew in data arising from which patients were deemed fit for IVUS (32% Everolimus vs 37% for MMF).

1+	Systematic	Total of 1009 patients over 3 trials: B253 (n=634), A2403 (n=199) and A2411 (n=176)	Cyclosporine (CsA) trough level target dose is reduced with time after HT. B253: Everolimus 1.5mg/day, CsA 200-400 ng/mL Everolimus 3.0mg/day, CsA 200-400 ng/mL A2403: (SD-CsA): Everolimus 1.5mg/day, CsA 600-1400 ng/mL (RD-CsA): Everolimus 1.5mg/day, CsA 300-1400 ng/mL A2411: Everolimus 1.5mg/day, CsA 350-75 ng/mL	Clinical effectiveness of the intervention compared to existing interventions	CMV infection rate, CMV disease rate	CMV infection rate: B253: 1.5mg/day everolimus 7.7%, 3.0mg/day everolimus 7.6%, Azathioprine 20.6% A2403: Everolimus (SD-CsA) 3.0%, Everolimus (RD-CsA) 7% A2411: Everolimus 7.7%, MMF 32% CMV disease rate: B253: 1.5mg/day everolimus 3.4%, 3.0mg/day everolimus 3.3%, Azathioprine 8.4% A2403: Everolimus (SD-CsA) 2.0%, Everolimus (RD-CsA) 1% A2411: Everolimus 2.2%, MMF 8.4%	Further breakdown of infection rates by whether the donor/ recipient tested positive for CMV.	No statistically significant difference in rates of donor infection between different treatments, but significant differences in rates or recipient infection.	Kobashigawa, J.; Ross, H.; Bara, C.; Delgado, J. F.; Dengler, T.; Lehmkuhl, H. B.; Wang, S.-S.; Dong, G.; Witte, S.; Junge, G.; Potena, L.. Everolimus is associated with a reduced incidence of cytomegalovirus infection following de novo cardiac transplantation. Transpl Infect Dis. 2013.	-	-	This systematic review combines the results of three RCTs with the focus of looking at CMV infection. Although the three studies measure the CMV infection rate at different times, there is still good agreement that Everolimus with differing CsA doses reduces the risk of CMV infection.
1-	RCT	34 patients	0.5 mg/day and cyclosporine reduced to 50-90 ng/ml.	Clinical effectiveness of the intervention compared to existing interventions	Creatine Clearance (CrCl)	CrCl (ml/min): Mean at Baseline = 44.6±10.6 (MMF) vs 43.5±9.1 (everolimus) Mean at 3 year = 56.5±15.1 (MMF) vs 46.4±13.6 (everolimus)	Low density lipoprotein cholesterol (LDL) Adverse events	Statistically similar levels of LDL. Lower infection rate for everolimus (29% vs 43% MMF) but not statistically significant due to sample size p=0.4. Other adverse events had similar rates.	Potena, Luciano; Prestinenzi, Paola; Bianchi, Isidoro G.; Masetti, Marco; Romani, Paolo; Magnani, Gaia; Fallani, Francesco; Coccolo, Fabio; Russo, Antonio; Ponticelli, Claudio; Rapezzi, Claudio; Grigioni, Francesco; Branzi, Angelo. Cyclosporine lowering with everolimus versus mycophenolate mofetil in heart transplant recipients: long-term follow-up of the SHIRAKISS randomized, prospective study. J. Heart Lung Transplant.. 2012.	-	-	This small RCT compared Everolimus and MMF over a three year period. The principle limitation of this study was the sample size (n=34) and hence many of the results of the paper are not on strong statistical grounds. Nonetheless the paper does examine long term renal damage using creatine clearance (CrCL) rather than ultrasound. In particular it found, after 3 years, lower levels of CrCl in the everolimus arm (46.4±13.6 vs 56.5±15.1 MMF, p=0.06). The sample size was too restrictive to reliably assess the rate of adverse effects after 3 years.

1+	RCT	111 patients	Everolimus mean dose 1.2±0.5 mg/day with reduced Cyclosporine	Clinical effectiveness of the intervention compared to existing interventions	Change in maximal intimal thickness (MIT)	Mean baseline MIT: 0.57±0.25 mm (everolimus) vs 0.56±0.31 mm (control) Mean 12 month MIT: 0.61±0.27 mm (everolimus) vs 0.58±0.31 mm (control) Mean change in MIT: 0.04±0.10 mm (everolimus) vs 0.02±0.05 mm (control)	Nominal change in percentage atheroma volume after 12 months (PAV). Nominal change in total atheroma volume after 12 months (TAV).	PAV: 2.6±5.6 % (everolimus) vs 1.8±2.9 % (control) TAV: 6.6±21.5 mm^3 (everolimus) vs 13.8±22.2 mm^3 (control)	Arora, Satish; Ueland, Thor; Wennerblom, Bertil; Sigurdadottir, Vilborg; Eiskjær, Hans; Bøtker, Hans E.; Ekmehag, Bjorn; Jansson, Kjell; Mortensen, Svend-Aage; Saunamaki, Kari; Simonsen, Svein; Gude, Einar; Bendz, Bjørn; Solbu, Dag; Aukrust, Pål; Gullestad, Lars. Effect of everolimus introduction on cardiac allograft vasculopathy--results of a randomized, multicenter trial. Transplantation. 2011.	-	-	This RCT is a useful, but underpowered study of the efficacy of Everolimus amongst patients with established CAV. The study took patients a few years after the heart transplant (mean 5.8±4.3 years), who had established CAV (baseline MIT: 0.57±0.25 mm (Everolimus) vs 0.56±0.31 mm (control)) and randomised them to receive either Everolimus, MMF or Azathioprine. The study found a change from baseline MIT of 0.04±0.10 mm (Everolimus) vs 0.02±0.05 mm (control) and similar results for atheroma volume. The principle problem with this study is the sample size (n=111), 48 for Everolimus and 63 for control. Nonetheless the study does give evidence that indicates Everolimus, MMF and Azathioprine are not effective at treating established CAV.
1+	RCT	176 patients	1.5 mg/day Everolimus with target trough level of 3-8 ng/mL with standard cyclosporine dose tapering to (100-250 ng/mL)	Clinical effectiveness of the intervention compared to existing interventions	Creatine Clearance (CrCl)	CrCl at 6 months: 65.4±24.7 mL/mm (everolimus) vs 72.2±26.2 mL/mm (MMF) CrCl at 12 months: 72.5±27.9 mL/mm (everolimus) vs 76.8±32.1 mL/mm (MMF)	Incidence of Biopsy-proven acute rejection (BPAR) grade > 3A (ISHLT grade) CMV events.	BPAR rate at 6 months: 19.6% (everolimus) vs 27.4% (MMF) p=0.003 for non inferiority. BPAR rate at 12 months: 22.8% (everolimus) vs 29.8% (MMF) p=0.005 for non inferiority. Total CMV infections after 12 months: 8.8% (everolimus) vs 32.5% (MMF) p<0.001.	Viganò, M.; Dengler, T.; Mattei, M. F.; Poncelet, A.; Vanhaecke, J.; Vermes, E.; Kleinloog, R.; Li, Y.; Gezahegen, Y.; Delgado, J. F.; RAD A2411 Study Investigators. Lower incidence of cytomegalovirus infection with everolimus versus mycophenolate mofetil in de novo cardiac transplant recipients: a randomized, multicenter study. Transpl Infect Dis. 2010.	-	-	This RCT did a 12 month comparison between Everolimus and MMF over 176 patients. It used creatinine clearance to test efficacy with respect to renal functions. Its primary results are: - Everolimus and MMF had similar results for renal function. - Everolimus and MMF had similar results for BPAR>3A rates. - Everolimus had statistically significant lower rate of CMV infections.

1+	RCT	176 patients	1.5 mg/day Everolimus with target trough level of 3-8 ng/mL with standard cyclosporine dose tapering to (100-250 ng/mL)	Clinical effectiveness of the intervention compared to existing interventions	Creatine Clearance (CrCl)	CrCl at 6 months: 65.4±24.7 mL/mm (everolimus) vs 72.2±26.2 mL/mm (MMF) CrCl at 12 months: 72.5±27.9 mL/mm (everolimus) vs 76.8±32.1 mL/mm (MMF)	In addition to BPAR, also adverse events.	After 12 months, the adverse events that demonstrated different rates between two arms were: -Leukopenia: 16.5% (everolimus) vs 30.1% (MMF) -Pericardial effusion: 35.3% (everolimus) vs 25.3% (MMF) -Pleural effusion: 24.2% (everolimus) vs 13.3% (MMF) -Diarrhoea: 16.5% (everolimus) vs 24.1% (MMF) -Nausea: 15.4% (everolimus) vs 24.1% (MMF) -Viral infections: 17.6% (everolimus) vs 25.3% (MMF) -CMV infections: 4.4% (everolimus) vs 16.9% (MMF)	Lehmkuhl, Hans B.; Arizon, José; Viganò, Mario; Almenar, Luis; Gerosa, Gino; Maccherini, Massimo; Varnous, Shaida; Musumeci, Francesco; Hexham, J. Mark; Mange, Kevin C.; Livi, Ugolino; 2411 Study Investigators. Everolimus with reduced cyclosporine versus MMF with standard cyclosporine in de novo heart transplant recipients. Transplantation. 2009.	-	-	This paper present the same study as presented in (Vigano et al., 2010) with the same results. The only difference is this paper includes additional details concerning adverse effects. The only two statistically significant differences in adverse events were in Leukopenia (p=0.047) and CMV infections (p=0.011), where Everolimus had lower rates than MMF.
1+	RCT	634 patients	arm1: 1.5 mg/day everolimus arm2: 3 mg/day everolimus both with standard cyclosporine dose tapering towards trough levels 100ng/mL	Clinical effectiveness of the intervention compared to existing interventions	Rate of CMV infection, syndrome and organ involvement.	Total incidence of CMV infections (read from figure 2, paper breaks results down by donor/recipient status): With Prophylaxis: 8% (1.5 mg/day everolimus) vs 9% (3.0 mg/day everolimus) vs 22% (azathioprine) Without Prophylaxis: 12% (1.5 mg/day everolimus) vs 9% (3.0 mg/day everolimus) vs 24% (azathioprine) All patients: 9% (1.5 mg/day everolimus) vs 9% (3.0 mg/day everolimus) vs 23% (azathioprine)	-	-	Hill, James A.; Hummel, Manfred; Starling, Randall C.; Kobashigawa, Jon A.; Perrone, Sergio V.; Arizón, Josè M.; Simonsen, Svein; Abeywickrama, Kamal H.; Bara, Christoph. A lower incidence of cytomegalovirus infection in de novo heart transplant recipients randomized to everolimus. Transplantation. 2007.	Administration of CMV prophylaxis determined by site and not protocol driven.	-	This study is a re-analysis of study B256 (Kobashigawa et al., 2013) with the express purpose of testing rates of CMV infection, incidence of CMV prophylaxis use, laboratory evidence for CMV, presence of CMV syndrome and CMV disease organ involvement. The paper makes a careful breakdown of the results by the CMV status of both the donor and recipient. Subsequently the sample sizes in the subgroups are small, meaning the individual results are often not statistically significant. However, in the high risk sub group in which both donor and recipient are CMV positive, the Everolimus group had significantly lower levels of CMV disease. The paper concludes that Everolimus is associated with lower rates of CMV infection, syndrome and organ involvement.

1+	RCT	634 patients	arm1: 1.5 mg/day everolimus arm2: 3 mg/day everolimus both with standard cyclosporine dose tapering towards trough levels 100ng/mL	Clinical effectiveness of the intervention compared to existing interventions	Composite efficacy end-points defined as either: - Acute rejection ISHLT grade >3A (BPAR > 3A) - Acute rejection associated with HDC (HDC) - Graft loss - Death	Composite End Points at 24 months: 45.9% (everolimus 1.5 mg) vs 36.0% (everolimus 3.0 mg) vs 57.5% (azathioprine) BPAR>3A: 34.9% (everolimus 1.5 mg) vs 22.7% (everolimus 3.0 mg) vs 48.1% (azathioprine) Death: Not statistically different: 10.0% (everolimus 1.5 mg) vs 13.7% (everolimus 3.0 mg) vs 11.25% (azathioprine) HDC and Graft loss also display no statistical differences between arms	Infection rates	All Infections: 76.6% (everolimus 1.5 mg) vs 80.1% (everolimus 3.0 mg) vs 72.0% (azathioprine) Pneumonia: 13.9% (everolimus 1.5 mg) vs 9.5% (everolimus 3.0 mg) vs 2.8% (azathioprine) CMV: 7.2% (everolimus 1.5 mg) vs 7.1% (everolimus 3.0 mg) vs 21.0% (azathioprine) Upper respiratory tract, urinary tract and Herpes infections had statistically similar rates	Viganò, Mario; Tuzcu, Murat; Benza, Raymond; Boissonnat, Pascale; Haverich, Axel; Hill, James; Laufer, Guenther; Love, Robert; Parameshwar, Jayan; Pulpón, Luis Alonso; Renlund, Dale; Abeywickrama, Kamal; Cretin, Nathalie; Starling, Randall C.; Eisen, Howard J.; RAD B253 Study Group. Prevention of acute rejection and allograft vasculopathy by everolimus in cardiac transplants recipients: a 24-month analysis. J. Heart Lung Transplant.. 2007.	-	-	This study is a re-analysis of study B256 (Kobashigawa et al., 2013). Its main result is that the number patients reaching a composite efficacy end-point was significantly lower with Everolimus than Azathioprine. This was largely driven by a reduced rate of acute rejections (ISHLT grade > 3A). It also found that Everolimus had a reduced rate of CMV, but a higher rate of pneumonia.
1-	RCT	634 patients	arm1: 1.5 mg/day everolimus arm2: 3 mg/day everolimus both with standard cyclosporine dose tapering towards trough levels 100ng/mL	Clinical effectiveness of the intervention compared to existing interventions	Biopsy-proven acute rejection rate (BPAR) grade > 3A	BPAR results quoted in (Vigano et al., 2007)	Change in coronary maximal intimal thickness (ΔMIT) measured with intravascular ultrasound (IVUS), in addition to change in intimal area, change in intimal volume.	ΔMIT : 0.07mm (everolimus 1.5 mg) vs 0.06mm (everolimus 3.0 mg) vs 0.15mm (azathioprine)	Eisen, Howard. Long-term cardiovascular risk in transplantation--insights from the use of everolimus in heart transplantation. Nephrol. Dial. Transplant.. 2006.	-	-	This study presents the results of (Vigano et al., 2007) and (Kobashigawa et al., 2013). No new results.

1-	RCT	54 patients	0.75 mg, 2.5 mg and 5 mg either once or twice a day (6 cohorts)	Safety of the intervention	Adverse events	Similar levels of adverse events in placebo and everolimus arms. Overall rate of infections higher in everolimus arm (43%) than placebo arm (20%). One patient died who had received 10 mg everolimus.	Pharmacokinetics	Not relevant to PICO	Budde, K.; Fritsche, L.; Waiser, J.; Glander, P.; Slowinski, T.; Neumayer, H.-H.; RADW 102 Renal Transplant Study Group. Pharmacokinetics of the immunosuppressant everolimus in maintenance renal transplant patients. Eur. J. Med. Res.. 2005.	-	-	This small and early RCT was primarily designed to test the safety of different doses. While the paper does examine adverse events, due to the sample size these results are irrelevant in light of more recent results from larger RCTs.
-	RCT	634 patients	arm1: 1.5 mg/day everolimus arm2: 3 mg/day everolimus both with standard cyclosporine dose tapering towards trough levels 100ng/mL	Cost effectiveness	Total costs ($)	Everolimus (1.5mg): $72,065 vs Everolimus (3mg): $72,631 vs Azathioprine $70,815	-	-	Radeva, Jasmina I.; Reed, Shelby D.; Kaló, Zoltán; Kauf, Teresa L.; Cantu, Edward; Cretin, Nathalie; Schulman, Kevin A.. Economic evaluation of everolimus vs. azathioprine at one year after de novo heart transplantation. Clin Transplant. 2005.	-	-	This study was concerned with the cost effectiveness analysis of the B256. It found that Everolimus is marginally more expensive than Azathioprine (1.8% for 1.5mg and 2.6% for 3mg). This is largely due to increased costs for hospitalisation and concomitant medications, although there are savings coming from the reduced Cyclosporine costs despite the trial not use intentionally using reduced Cyclosporine doses. This was based on a 1 year period and costs were estimated according to the costs of the centres where the treatments took place.
1-	RCT	634 patients	arm1: 1.5 mg/day everolimus arm2: 3 mg/day everolimus both with standard cyclosporine dose tapering towards trough levels 100ng/mL	Safety of the intervention	Trough level concentrations (Cmin)	Average Cmin: Everolimus (1.5mg): 5.2 ± 3.8 ng/ml vs Everolimus (3mg): 9.4 ± 6.3 ng/ml	-	-	Kovarik, John M.; Eisen, Howard; Dorent, Richard; Mancini, Donna; Vigano, Mario; Rouilly, Marisel; Hsu, Chyi-Hung; Rordorf, Christiane. Everolimus in de novo cardiac transplantation: pharmacokinetics, therapeutic range, and influence on cyclosporine exposure. J. Heart Lung Transplant.. 2003.	-	-	This paper is largely concerned with the pharmacokinetics of Everolimus. It does make a comparison of adverse events against concentrations, but is largely concerned with fixing the dose and hence of little relevance to the PICO.

1-	RCT	634 patients	arm1: 1.5 mg/day everolimus arm2: 3 mg/day everolimus both with standard cyclosporine dose tapering towards trough levels 100ng/mL	Clinical effectiveness of the intervention compared to existing interventions	Composite efficacy end-points defined as either: - Acute rejection ISHLT grade >3A (BPAR > 3A) - Graft loss - Death	Patients who reached primary composite efficacy endpoint at six months: 46.7% (azathioprine), 36.4% (everolimus 1.5mg), 27% (everolimus 3.0mg); Endpoint reached at 12 months: 52.8% (azathioprine), 41.6% (everolimus 1.5mg, p=0.02), 32.2% (everolimus 3.0mg, p<0.001)	Safety and adverse events; Change in maximal intimal thickness (MIT)	Rates of Death: 8.4% (azathioprine), 9.1% (everolimus 1.5mg), 11.4% (everolimus 3.0mg); ΔMIT: 0.10mm (azathioprine), 0.04mm (everolimus 1.5mg, p=0.01), 0.03mm (everolimus 3.0mg, p=0.003); Statistically similar levels of adverse events, with the exception of viral infection (driven by reduced CMV rates): 31.3% (azathioprine), 14.8% (everolimus 1.5mg), 17.1% (everolimus 3.0mg)	Eisen, Howard J.; Tuzcu, E. Murat; Dorent, Richard; Kobashigawa, Jon; Mancini, Donna; Valantine-von Kaeppler, Hannah A.; Starling, Randall C.; Sørensen, Keld; Hummel, Manfred; Lind, Joan M.; Abeywickrama, Kamal H.; Bernhardt, Peter; RAD B253 Study Group. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N. Engl. J. Med.. 2003.	-	-	This RCT presents the results from the B253 trial, which have been included in numerous other studies. Many of the results have been quoted in other studies, however this paper provides the rates at 12 months, compared with for example (Vigano et al., 2007) which provides the rates at 24 months. The conclusions are largely the same.

1+	RCT	115 patients	Everolimus 0.75mg twice/day with 75-175 ng/mL cyclosporine up until week 7, with Mycophenolate mofetil (MMF) 1500-2000 mg/day after week 7 cyclosporine discontinued and MMF 1000 mg/day	Clinical effectiveness of the intervention compared to existing interventions	Change in coronary maximal intimal thickness (ΔMIT); Nominal change in percentage atheroma volume after 12 months (PAV); Nominal change in total atheroma volume after 12 months (TAV).	ΔMIT: 0.03±0.06 mm (everolimus) vs 0.08±0.12 mm (MMF) PAV: 1.3±2.3 % (everolimus) vs 4.2±5.0 % (MMF) TAV: 1.1±19.2 mm^3 (everolimus) vs 13.8±28.0 mm^3 (MMF)	BPAR acute rejection > 2R	(BPAR rejection rate >2R): 76.6% (everolimus) vs 62.5% (MMF)	Arora, S.; Andreassen, A. K.; Andersson, B.; Gustafsson, F.; Eiskjaer, H.; Bøtker, H. E.; Rådegran, G.; Gude, E.; Ioanes, D.; Solbu, D.; Sigurdardottir, V.; Dellgren, G.; Erikstad, I.; Solberg, O. G.; Ueland, T.; Aukrust, P.; Gullestad, L.; SCHEDULE (SCandinavian HEart transplant everolimus De novo stUdy with earLy calcineurin inhibitors avoidancE) Investigators. The Effect of Everolimus Initiation and Calcineurin Inhibitor Elimination on Cardiac Allograft Vasculopathy in De Novo Recipients: One-Year Results of a Scandinavian Randomized Trial. Am. J. Transplant.. 2015.	-	-	This RCT was an additional analysis of the study discussed in (Andreassen et al., 2014). It primarily focussed on including the analysis of the intravascular ultrasound. It found, in agreement with other studies, that the Everolimus arm had statistically significant reductions in the change in intimal thickness and atheroma volume. They found that these differences continue when they consider the patient sub groups of with donor disease vs without donor disease and patients with no BPAR rejections vs one or more rejections. Principle concern with this sub-group analysis is the sample size, total 115 patients such that sub groups were between 7 and 41 patients.
1-	RCT	78 patients	Everolimus mean dose 1.2±0.5 mg/day with reduced Cyclosporine	Clinical effectiveness of the intervention compared to existing interventions	Nominal change in intima volume (ΔIV) Change in Percentage Plaque volume index (%PVI)	ΔIV: 16 ± 38 mm^3 (everolimus n=30) vs. 12 ± 32 mm^3 (control n=48) p=0.75. Change in %PVI: 1.9 ± 3.8 % (everolimus n=30) vs. 1.6 ± 3.9 % (control n=48) p=0.65.	Change in calcified tissue components. Change in Necrotic tissue components.	Change in calcified tissue components (%): 2.4 ± 4.0 % (everolimus n=30) vs. 0.3 ± 3.1 % (control n=48) p=0.02. Change in necrotic tissue components (%): 6.5 ± 8.5 % (everolimus n=30) vs. 1.1 ± 8.6 % (control n=48) p=0.01.	Arora, S.; Erikstad, I.; Ueland, T.; Sigurdardottir, V.; Ekmehag, B.; Jansson, K.; Eiskjaer, H.; Bøtker, H. E.; Mortensen, S.-A.; Saunamaki, K.; Gude, E.; Ragnarsson, A.; Solbu, D.; Aukrust, P.; Gullestad, L.. Virtual histology assessment of cardiac allograft vasculopathy following introduction of everolimus--results of a multicenter trial. Am. J. Transplant.. 2012.	-	-	Virtual histology is a new technique that uses back scattered RF signals during the IVUS to provide an assessment of plaque and intimal wall composition. This can be used to assess the risk of adverse cardiac events, although this is a new technique and further studies are need to quantify the clinical significance of the results. Nonetheless this study use virtual histology to retrospectively study the IVUS of patients being treated with Everolimus and either MMF or Azathioprine in the NOCTET trial. The study found no difference, in the change in intimal volume and plaque index, between the Everolimus arm and the control arm. However, it was found that the Everolimus arm had a greater increase in the calcified components and necrotic components in the intimal wall. No studies exist that confirm the clinical significance of such changes in the CAV composition.

2-	RCT	634 patients	arm1: 1.5 mg/day everolimus arm2: 3 mg/day everolimus both with standard cyclosporine dose tapering towards trough levels 100ng/mL	Clinical effectiveness of the intervention compared to existing interventions	Exposure efficacy modelling	That the risk of BPAR > 3A was approximately equivalent for trough levels of everolimus of 3-8 ng/mL and trough levels > 8 ng/mL. This risk is lower than that of azathioprine, which is equivalent to trough levels of everolimus of <3 ng/mL.	Pharmacokinetics Exposure Safety modelling	The pharmacokinetics analysis is of no relevance to the PICO. The probability of patients having creatine levels > 200 µm/L is strongly correlated with trough cyclosporine concentration.	Starling, Randall C.; Hare, Joshua M.; Hauptman, Paul; McCurry, Kenneth R.; Mayer, Hartmut W.; Kovarik, John M.; Schmidli, Heinz. Therapeutic drug monitoring for everolimus in heart transplant recipients based on exposure-effect modeling. Am. J. Transplant.. 2004.	-	-	This modelling study was intended to compare the Everolimus and Cyclosporine blood trough levels, measured during the B253 trial, with acute rejection rates and creatine levels. It concludes that there is no efficacy benefit, to the risk of acute rejection, of Everolimus trough concentration >8ng/mL. Although it found the risk of BPAR>3A was lower with Everolimus >3ng/mL, than Azathioprine.
-	Other	1001 patients	Everolimus 1.5 mg/day	Cost effectiveness	Incremental cost effectiveness ratio (ICER) over two scenarios, arising due to the necessarily to avoid double counting patients with acute rejections followed by death or graft loss. ICER is approximately the incremental cost over 6 months (difference in cost of MMF/everolimus and azathioprine) divided by efficacy gain (between MMF/everolimus and azathioprine) Scenario 1: Assumes Acute rejection <3A: 3.6% (MMF) vs 6.2% (Azathioprine) Death / Graft loss: 2.7% (MMF) vs 2.0% (Azathioprine) Scenario 2: Assumes Acute rejection <3A: 2.7% (MMF) vs 5.3% (Azathioprine) Death / Graft loss: 4.0% (MMF) vs 3.5% (Azathioprine)	Scenario 1: ICER (euros): 24,457 (for everolimus vs azathioprine) vs. 30,628 (for MMF vs azathioprine) Scenario 2: ICER (euros): 24,457 (for everolimus vs azathioprine) vs. 29,912 (for MMF vs azathioprine)	Efficacy gain. Incremental drug costs over 6 months.	Efficacy Gain: (Everolimus vs Azathioprine) 10.4% vs (MMF vs Azathioprine) 9.8%-10.1% Six month Incremental Cost gain (euros): (Everolimus 3008 vs Azathioprine 473) 2535 vs (MMF 3555 vs Azathioprine 548) 3007	Annemans, L.; Lemkuhl, H.; Tenderich, G.; Schulz, U.; Yang, X. L.; Ricci, J. F.; Hetzer, R.. Economic evaluation of everolimus and mycophenolate mofetil versus azathioprine in de novo heart transplantation. Transplant. Proc.. 2007.	The cost of adverse events not included.	-	This cost effectiveness study is based on two RCTs and subsequently makes two comparisons, one between Everolimus and Azathioprine and the other between MMF and Azathioprine. However, no direct comparison between MMF and Everolimus is made. Both MMF and Everolimus are more expensive and efficacious than Azathioprine. The study concludes that the ICER, the ratio of costs to efficacy, is lower for Everolimus by about 5000 euros. However, there are a number of limitations to this study, principally, that the included costs only include drug costs and not hospitalisations. It also not clear how sensitive the result is to variation in the efficacy, estimated by primary composite endpoint rates. This study was based on the German healthcare model.

2-	Crossover design	63 patients	Everolimus 1.0-1.5 mg/day	Clinical effectiveness of the intervention compared to existing interventions	Intravascular ultra sound measurements: Change in maximal intimal thickness (ΔMIT) Percentage Plaque volume index (%PVI) Vessel volume Index (VVI) Lumen volume index (LVI)	Mean MIT at study entry (mm): 1.31 everolimus vs 0.56 MMF Mean MIT after 1 year (mm): 1.18 everolimus vs 0.71 MMF Mean %PVI at study entry (mm^3/mm): 20.9 everolimus vs 9.2 MMF Mean %PVI after 1 year (mm^3/mm): 22.3 everolimus vs 9.8 MMF Mean VVI at study entry (mm^3/mm): 12.0 everolimus vs 12.6 MMF Mean VVI after 1 year (mm^3/mm): 11.8 everolimus vs 11.8 MMF Mean LVI at study entry (mm^3/mm): 8.2 everolimus vs 10.1 MMF Mean LVI after 1 year (mm^3/mm): 8.3 everolimus vs 9.0 MMF	-	-	Watanabe, Takuya; Seguchi, Osamu; Nishimura, Kunihiro; Fujita, Tomoyuki; Murata, Yoshihiro; Yanase, Masanobu; Sato, Takuma; Sunami, Haruki; Nakajima, Seiko; Hisamatsu, Eriko; Sato, Takamasa; Kuroda, Kensuke; Hieda, Michinari; Wada, Kyoichi; Hata, Hiroki; Ishibashi-Ueda, Hatsue; Miyamoto, Yoshihiro; Fukushima, Norihide; Kobayashi, Junjiro; Nakatani, Takeshi. Suppressive effects of conversion from mycophenolate mofetil to everolimus for the development of cardiac allograft vasculopathy in maintenance of heart transplant recipients. Int. J. Cardiol.. 2015.	-	-	This retrospective cross over study compares two cohorts of patients, initially treated with MMF, one cohort was switched to treatment with Everolimus (n=24) and the other continue to be treated with MMF (n=39). The study is primarily concerned with the change in a range of IVUS measurements. Since it is based after a year, the majority of the patients have established CAV (MIT >0.5mm). The study found that under MMF, there was an increase in MIT (from mean 0.56 mm to 0.71 mm) and percent plaque volume (from 9.2% to 9.8%), while the percent lumen volume index decreased (from 10.1mm^3/mm to 9.0mm^3/mm). These changes were not seen in the Everolimus cohort. In particular the MIT decreased (from 1.31mm to 1.18mm) and the lumen volume index remained the same. However, before concluding that converting from MMF to everolimus helps to attenuate CAV development, it should be noted that the baseline levels of the Everolimus cohort were significantly higher than those of the MMF. It is also not stated as to the motivations for transferring a patient to Everolimus, since this was not randomised and this was a retrospective study. The primary concern is that this difference in CAV level, at study entry, gives rise to a high risk of bias. There are also secondary concerns about the sample size.
2+	Cohort	143 patients	Everolimus target trough levels: 3-8 ng/mL plus standard dose of cyclosporine	Clinical effectiveness of the intervention compared to existing interventions	Change in coronary maximal intimal thickness (ΔMIT)	Early cohort: ΔMIT: 0.37±0.29mm (MMF n=71) vs 0.23±0.15mm (everolimus n=20) p=0.05 Late cohort: ΔMIT: 0.27±0.36mm (MMF n=33) vs 0.34±0.53mm (everolimus n=19) p=0.57	Levels of Triglycerides.	In early cohort, levels of triglycerides linearly correlated with change in MIT, R=0.24.	Masetti, M.; Potena, L.; Nardozza, M.; Prestinenzi, P.; Taglieri, N.; Saia, F.; Pece, V.; Magnani, G.; Fallani, F.; Coccolo, F.; Russo, A.; Rapezzi, C.; Grigioni, F.; Branzi, A.. Differential effect of everolimus on progression of early and late cardiac allograft vasculopathy in current clinical practice. Am. J. Transplant.. 2013.	-	-	This retrospective cohort study compared four cohorts of differing sizes. The two early cohorts (one treated with Everolimus and the other MMF) compare the change in patients IVUS results between week 3-6 and one year. While the two late cohorts (again one Everolimus and the other MMF) compared the IVUS 1 year after transplant, with 5 years after transplant. The study found the change in MIT in the Everolimus early cohort was lower than in the MMF cohort. However, the study also found no difference in the change in MIT, between the two late cohorts; so indicating that Everolimus does not influence development of CAV after 1 year after transplant. However, firstly the initial baseline levels of MIT are not stated in the paper and also the cohorts were of different sizes and small.

2+	Cohort	378 patients	Everolimus	Clinical effectiveness of the intervention	Distribution of patients across three groups: Group A: No evidence of CMV infection Group B: CMV infection not requiring pre-emptive treatment Group C: CMV infection or disease treated pre-emptively	Group A (n=104): Azathioprine 17.3% vs MMF 56.7% vs everolimus 26% Group B (n=93): Azathioprine 22.5% vs MMF 67.5% vs everolimus 9.8% Group C (n=104): Azathioprine 26% vs MMF 9.8% vs everolimus 4.3%	-	-	Durante-Mangoni, Emanuele; Andini, Roberto; Pinto, Daniela; Iossa, Domenico; Molaro, Rosa; Agrusta, Federica; Casillo, Roberta; Grimaldi, Maria; Utili, Riccardo. Effect of the immunosuppressive regimen on the incidence of cytomegalovirus infection in 378 heart transplant recipients: A single centre, prospective cohort study. J. Clin. Virol.. 2015.	-	-	This cohort study examines the treatment of 376 patients and compares the numbers of CMV infections with different drugs used. In particular, anti-thymocyte globulins or Thymoglobulin, Cyclosporine or Tacrolimus and Azathioprine, MMF or Everolimus. There was no difference in CMV infections between anti-thymocyte globulins or Thymoglobulin and Cyclosporine or Tacrolimus. However it was found that CMV infections were lower with Everolimus than Azathioprine and MMF.
2+	Cohort	121 patients	Everolimus - target trough levels 4-6 ng/mL	Safety of the intervention	The measure of Neutrophil gelatinase associated lipocalin (NGAL) as a 'better' measure of renal status than creatine levels.	Patients treated with everolimus had significantly lower NGAL concentrations in plasma (128 (97-176 95%CL) ng/mL vs 252 (224 -283 95%CL) ng/mL) and urine (6.4 (4.5-7.6 95%CL) ng/mL vs 15.7 (10.2 -25.9 95%CL) ng/mL), than patients treated with MMF.	-	-	Stypmann, Jörg; Fobker, Manfred; Rosing, Katharina; Engelen, Markus; Gunia, Stefan; Dell'Aquila, Angelo Maria; Nofer, Jerzy-Roch. Neutrophil gelatinase-associated lipocalin (NGAL) in heart transplant recipients after conversion to everolimus therapy. J Cardiol. 2015.	-	-	The motivation for this cohort study is that CNI (such as cyclosporine) induce nephroxicity which can lead to long term renal deterioration. This nephrotoxicity is typically measured using creatine clearance levels although, the paper argues that this is not always a reliable indication since marked deterioration can occur prior to release of serum creatine. This paper studies the NGAL levels in as an indication of renal status. It found significantly lower NGAL levels in patients being treated with Everolimus than those treated with MMF, favouring Everolimus.
2+	Cohort	154 patients	Everolimus and cyclosporine	Clinical effectiveness of the intervention compared to existing interventions	Death, graft loss or treatment failure.	Cyclosporine: 59.8% vs Tacrolimus 53.1% p=0.716.	Covariant adjusted glomerular filtration rate (eGFR) Freedom from CMV	No significant difference in eGFR Freedom from CMV: 93% (cyclosporine) vs 95.6% (tacrolimus)	Fuchs, Uwe; Zittermann, Armin; Ensminger, Stephan M.; Schulz, Uwe; Gummert, Jan F.. Clinical outcome in heart transplant recipients receiving everolimus in combination with dosage reduction of the calcineurin inhibitor cyclosporine A or tacrolimus. Transpl. Immunol.. 2014.	-	-	This retrospective cohort study compared the efficacy of Everolimus and Cyclosporine with Everolimus and Tacrolimus. It found no difference in clinical efficacy, CMV infection or glomerular filtration rate.

2+	Cohort	394 patients	Minimisation cohort: Everolimus or Sirolimus with a reduced CNI (cyclosporine) dose.	Clinical effectiveness of the intervention compared to existing interventions	Change in renal function measured with glomerular filtration rate (GFR) from base level (<60 ml/min/1.73 m^2)	Conversion: 0.45 ± 34.8 ml/min/1.73 m^2 vs Minimisation: --1.34 ± 38.1 ml/min/1.73 m^2 i.e. conversion marginally more effective, but not statistically significant (p=0.35) There are statistically significant improvements when considering sub groups of patients who received the mTOR-inhibitors for the full treatment and when considering the impact <1 year and 1-5 years after transplant. Overall change in GFR appears to reduce to close to zero > 5 years after transplant. Conversion group demonstrates greater improvement than minimisation group.	Mortality rate, acute rejection rate	Mortality rate: 67% in conversion group vs 33% in minimisation group. Acute rejection rate lower for minimisation arm than conversion (p=0.07).	Gonzalez-Vilchez, F.; Vazquez de Prada, J. A.; Paniagua, M. J.; Gomez-Bueno, M.; Arizon, J. M.; Almenar, L.; Roig, E.; Delgado, J.; Lambert, J. L.; Perez-Villa, F.; Sanz-Julve, M. L.; Crespo-Leiro, M.; Segovia, J.; Lopez-Granados, A.; Martinez-Dolz, L.; Mirabet, S.; Escribano, P.; Diaz-Molina, B.; Farrero, M.; Blasco, T.. Use of mTOR inhibitors in chronic heart transplant recipients with renal failure: calcineurin-inhibitors conversion or minimization?. Int. J. Cardiol.. 2014.	Cause of death by cohort: Conversion: Malignancy (25.4%), Infection (16.9%), CAV(15.2%), Sudden Death(15.3%), Cerebrovascular accident (6.8%), Renal failure (5.1%) Minimisation: Malignancy (13.8%), Infection (17.2%), CAV(41.4%), Sudden Death(6.9%), Cerebrovascular accident (3.4%), Renal failure (-)	-	This cohort study compared the use of Everolimus or Sirolimus with a reduced dose on Cyclosporine (minimisation), compared with no Cyclosporine (conversion). No significant differences in infection rates of mortality rates, but it was found that minimisation was found to have a significantly higher rejection rate (p=0.07). The benefits to renal function is greater in the conversion group, but is seen in both groups, but only in the 0-5 years period after transplant.
2-	Case series	381 patients	Initially cyclosporine and azathioprine. In 2001 azathioprine replaced by MMF. In 2006 cyclosporine is replaced by tacrolimus. From 2003 mTOR inhibitors also used (everolimus or sirolimus).	Safety of the intervention	Risk factors associated with increased risk of malignancy after heart transplant.	Old age, male recipients, dyslipidaemia, diabetes mellitus, renal insufficiency.	-	-	Rivinius, Rasmus; Helmschrott, Matthias; Ruhparwar, Arjang; Schmack, Bastian; Klein, Berthold; Erbel, Christian; Gleissner, Christian A.; Akhavanpoor, Mohammadreza; Frankenstein, Lutz; Darche, Fabrice F.; Thomas, Dierk; Ehlermann, Philipp; Bruckner, Tom; Katus, Hugo A.; Doesch, Andreas O.. Analysis of malignancies in patients after heart transplantation with subsequent immunosuppressive therapy. Drug Des Devel Ther. 2015.	-	-	This case study examines the risk factors associated with malignancy after heart transplant. Unfortunately it does not distinguish between sub-groups, determined by treatment, and so provides no evidence for the PICO.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	[None]
Updated search terms - Population	heart transplant* OR cardiac transplant*
Updated search terms - Intervention	Everolimus OR Certican OR Afinitor OR Zortress
Updated search terms - Comparator	Sirolimus OR immunosuppressant OR cyclosporine[MeSH] OR mycophenolate mofetil OR corticosteroids OR tacrolimus
Updated search terms - Outcome	patient survival OR graft survival OR kidney dysfunction OR renal dysfunction OR renal impairment OR quality of life OR cost effective

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	Randomised controlled trials or indirect comparisons only. Extend date range to 12 years for RTC to include key research since 2003.
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	[None]