DR. KASPAR BROCH (Orcid ID : 0000-0003-4316-805X)

PROF. LARS GULLESTAD (Orcid ID : 0000-0002-5932-6641)

Article type : Original Article

Cholesterol-lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in *De-novo* heart transplant recipients: Design of the randomized controlled EVOLVD trial

Kaspar Broch, MD, PhD[1]; Einar Gude, MD, PhD[1]; Kristjan Karason, MD, PhD[2]; Göran Dellgren, MD, PhD[2]; Göran Rådegran, MD, PhD[3,4]; Grunde Gjesdal, MD, PhD[3]; Finn Gustafsson, MD, PhD[5]; Hans Eiskjær, MD, PhD[6]; Jyri Lommi, MD, PhD[7]; Karl B Lemström, MD, PhD[7]; Arne K Andreassen, MD, PhD[1]; and Lars Gullestad, MD, PhD[1,8]

From the [1]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo; the [2]Transplant Institute, Sahlgrenska University Hospital, Gothenburg, Sweden; [3]The Clinic for Heart Failure and Valvular Disease; Skåne University Hospital and [4]Lund University, Lund, Sweden; the [5]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; the [6]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [7]Helsinki University Hospital Heart and Lung Center, Helsinki, Finland; and the [8]University of Oslo, Oslo, Norway

Short title: Design of the EVOLVD trial

Corresponding author

Kaspar Broch

Dept. of Cardiology

Oslo University Hospital

Postboks 4590 Nydalen

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CTR.13984

0424 Oslo, Norway

E-mail: kaspar.broch@ous-hf.no

K Broch; E Gude, K Karason; G Dellgren; G Rådegran; G Gjesdal; F Gustafsson; H Eiskjær; J Lommi; KB Lemström; AK Andreassen; L Gullestad. Cholesterol-Lowering with EVOLocumab to Prevent Cardiac Allograft Vasculopathy in De-novo Heart Transplant Recipients: Design of the Randomized Controlled EVOLVD Trial. J Clin Transplant

Abstract

Background: Cardiac allograft vasculopathy (CAV) is characterized by diffuse thickening of the arterial intima. Statins reduce the incidence of CAV, but despite the use of statins, CAV remains one of the leading causes of long-term death after heart transplant. Inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9) substantially reduce cholesterol levels but have not been tested in heart transplant recipients.

Methods: The Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients (EVOLVD) trial (ClinicalTrials.gov Identifier: NCT03734211) is a randomized, double-blind trial designed to test the effect of the PCSK9 inhibitor evolocumab on coronary intima thickness in heart transplant recipients. Adults who have received a cardiac transplant within the past 4 – 8 weeks are eligible. Exclusion criteria include an estimated glomerular filtration rate < 20 mL/min/1.73 m^2, renal replacement therapy, or contraindications to coronary angiography with intravascular ultrasound. 130 patients will be randomized (1:1) to 12-months' treatment with evolocumab or matching placebo. The primary endpoint is the coronary artery intima thickness as measured by intravascular ultrasound.

Conclusion: The EVOLVD trial is a randomized clinical trial designed to show whether treatment with the PCSK9 inhibitor evolocumab can ameliorate CAV over the first year after heart transplant.

Keywords: Heart transplant; Cardiac allograft vasculopathy; Cholesterol; Randomized controlled trial

Requests for offprints should be sent to Kaspar Broch, Dept of Cardiology, Oslo University Hospital, Rikshospitalet, Postboks 4950 Nydalen, 0424 Oslo, Norway

Introduction

The longevity of cardiac allografts is limited by cardiac allograft vasculopathy. This is a unique form of accelerated atherosclerosis that is characterised by a diffuse, progressive thickening of the arterial intima throughout the graft and loss of the microvasculature.[1] Cardiac allograft vasculopathy is present in 48 % of heart transplant recipients within 10 years after transplantation and accounts for 30% of deaths occurring beyond the first year.[2] The aetiology is likely to be multifactorial, but traditional risk factors for coronary artery disease are thought to contribute. Donor male gender, age, hypertension, and diabetes predispose to vasculopathy.[3] Animal models have shown that hyperlipidaemia accelerates the disease process.[4, 5] Finally, in human heart transplant recipients, elevated cholesterol levels are associated with an increased risk of developing allograft vasculopathy.[6-8]

The rate limiting enzyme in cholesterol synthesis is hydroxy-methyl-glutaryl Co-enzyme A reductase. Inhibitors of this enzyme, commonly known as statins, reduce cholesterol levels and mitigate cardiac allograft vasculopathy.[9] Statins are recommended in the routine treatment of heart transplant recipients,[10] but side effects and interactions with immunosuppressants limit the degree to which optimum lipid levels can be achieved with statin therapy alone in these patients.[11] The prevalence of hyperlipidaemia reaches 88 % five years after heart transplant.[2] On the other hand, there have been no randomized controlled trials to show whether second-line lipid lowering drugs improve outcomes in these patients.[11]

Evolocumab is an inhibitor of the enzyme pro-protein convertase subtilisin–kexin type 9 (PCSK9). PCSK9 binds to and degrades the low-density lipoprotein (LDL) receptor and prohibits the recycling of the LDL receptor to the cell surface. Evolocumab reduces circulating levels of LDL by inhibiting PCSK9, precipitating increased LDL clearance by receptor mediated endocytosis.[12] Evolocumab lowers LDL cholesterol on top of statin therapy, and the additional reduction in LDL cholesterol translates to a reduced incidence of myocardial infarction and stroke in patients with coronary artery disease.[13] The experience with PCSK9-inhibitors in heart transplant recipients is limited, [14-16] and the effect on cardiac allograft vasculopathy is unknown.

The strong association between cholesterol levels and coronary heart disease, the high cholesterol levels in heart transplant recipients, the high prevalence of vasculopathy in the cardiac allograft, and the association between elevated cholesterol levels and cardiac allograft vasculopathy provide a strong rationale for aggressive cholesterol lowering in heart transplant recipients.[17]

We hypothesise that evolocumab on top of statin therapy will significantly reduce LDL levels in *de novo* heart transplant recipients and that this reduction in cholesterol levels will manifest as a reduced burden of cardiac allograft vasculopathy as measured by intracoronary ultrasound. Ultimately, we assume that a reduced burden of vasculopathy will translate to reduced morbidity and long-term mortality in heart transplant recipients. The Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients (EVOLVD) trial is designed to test the hypothesis that a 12-month treatment with evolocumab can ameliorate cardiac allograft vasculopathy in heart transplant recipients. The rationale for the trial is summarised in Figure 1.

Methods

Trial overview

The EVOLVD trial (ClinicalTrials.gov Identifier: NCT03734211) is an investigator initiated, double blind, randomized, parallel group, placebo-controlled trial designed to assess the effect of evolocumab on the change in the coronary maximal intima thickness over the first year after heart transplant. The primary and secondary endpoints are listed in Table 1.

The participants are randomized in a 1:1 fashion to receive subcutaneous injections of 420 mg evolocumab or matching placebo every month for one year. The study is designed to show superiority regarding the primary endpoint in patients assigned to active treatment versus patients allocated to the placebo arm. An overview of the trial design is provided in Figure 2.

Trial conduct

The trial is performed at the six Scandinavian heart transplant centres; Oslo University Hospital, Rikshospitalet; Oslo, Sahlgrenska University Hospital, Gothenburg, Sweden, Skåne University Hospital, Lund Sweden, Rigshospitalet, Copenhagen, Denmark, Aarhus University Hospital, Aarhus, Denmark, and Helsinki University Hospital Heart and Lung Center, Helsinki, Finland. Together, these centres perform approximately 150 heart transplantations each year.

Patients

We recruit patients aged between 18 and 70 years who have received a cardiac allograft within the last 4 – 8 weeks, who are willing to participate, and who give written, informed consent. The key exclusion criteria are recent treatment with, an indication for treatment with, or intolerance of a PCSK9 inhibitor; estimated glomerular filtration rate < 20 mL/min/1.73 m^2; or contraindications to coronary angiography with intravascular ultrasound. A full list of exclusion criteria is provided in Table 2.

Randomization

A computer generated, balanced, permuted block randomization list governs treatment allocation in a 1:1: ratio for the two study arms. Randomization is stratified by centre. Treatment allocation is performed online on a password-protected platform designed for study purposes (Viedoc™) in a blinded manner once eligibility has been confirmed, the informed consent has been signed and baseline assessments have been performed.

Study drug

The investigational drug, evolocumab/placebo, is administered subcutaneously once monthly in abdomen, thigh, or upper arm for the duration of the intervention period (one year). Each month, 420 mg evolocumab/placebo will be administered by three consecutive injections à 140 mg within 30 minutes using a single-use prefilled autoinjector. The manufacturer (Amgen®) provides the active study drug and matching placebo. The first doses of the study drug or matching placebo are administered by trained hospital personnel. The patients administer the subsequent injections themselves.

Concomitant medication

The study participants receive standard-of-care treatment as recommended in prevailing guidelines. We routinely use induction therapy at the time of transplant. We introduce maintenance immunosuppressive therapy consisting of a combination of a calcineurin inhibitor, preferably tacrolimus; mofetil mycophenolate; and steroids on the first post-operative day with gradual tapering of the calcineurin inhibitor and steroid doses over the first year. In selected patients, we add everolimus and reduce the dose of the calcineurin inhibitor or altogether stop calcineurin inhibitor treatment. We treat our heart transplant recipients with trimethoprim-sulpha for the first 6 months according to current recommendations. We also give prophylactic treatment with valganciclovir to patients without protecting

antibodies to cytomegalovirus who receive grafts from cytomegalovirus antibody positive donors. A statin is routinely introduced during the first five postoperative days and continued indefinitely unless there are contraindications to statin use, or there is a need to escalate treatment. In the EVOLVD trial, Pravastatin 40 mg once daily is the drug of choice, but the investigators are free to select another statin or to switch to a more potent statin at their discretion. To keep investigators blinded to treatment allocation, we do not measure blood lipids for the duration of the treatment phase. In patients with blood pressure consistently above 140/90, we start anti-hypertensive treatment. Female participants who are not postmenopausal or sterilised, must agree to use highly effective methods of birth control for at least one month prior to screening, during treatment with the investigational drug and for an additional 15 weeks after the end of treatment.

Study outcomes

The primary and secondary outcomes are listed in Table 1. The primary endpoint of the trial is the baseline-adjusted maximal intima thickness as measured by coronary intravascular ultrasound. Intracoronary ultrasound is performed at baseline before randomization and at follow-up after one year's intervention. Echocardiograms are obtained at baseline and follow-up, and health-related quality of life is gauged with the SF-36, the Beck's depression inventory, and EQ 5D 3L questionnaires. We draw blood samples for the assessment of blood cholesterol and biomarkers at each visit. The samples are stored in a biobank for later analysis.

Study visits and follow-up

Study visits are scheduled every month for the first 3 months. During this period, a study nurse administers the investigational medicinal product. Thereafter, the patients return every third month for the duration of the treatment period. Between these visits, the patients must self-administer the study drug. Compliance is evaluated by the return of empty syringes and through regular measurement of cholesterol levels (performed *en bloc* after database lock).

Sample size and statistics

The sample size is based on calculations relating to the primary outcome. In the randomized controlled SCHEDULE trial, we observed an increase in the maximal intima thickness of 0.08 +/- 0.12 mm in the

placebo group, whereas the corresponding increase was 0.03 +/- 0.06 mm in the everolimus arm.[18] Intensive cholesterol reduction has been shown to stabilise or even reverse the coronary atherosclerotic volume in previous trials.[19] We therefore find it reasonable to aim for a 0.05 mm between-group difference in the change in the intima thickness in the EVOLVD trial. With an estimated 0.09 mm standard deviation, we will require 51 patients in each arm with a power of 80%, at a two-sided alpha level of 5%. To increase the chances of reaching the primary and secondary outcomes, and to compensate for uncertainties in this calculation, we will ensure that 120 patients complete the one-year follow-up. To allow for a dropout rate of 5 - 10%, we aim to include 130 patients.

All statistical tests will be performed using a two-sided 5 % level of significance. Continuous efficacy variables will be analysed using baseline adjusted ANCOVA for comparisons between the treatment arms. If necessary, values will be log-transformed to meet the assumptions of the tests. All analyses will be analysed according to the intention-to-treat principle. The number of major clinical events will be analysed using descriptive statistics. Between-group differences in ordinal categorical variables, such as NYHA class, will be analysed using ordinal logistic regression, whereas the count variables will be assessed by Poisson regression. Demographic, efficacy, and safety data will be summarised by treatment group. Secondary, per protocol analyses will be performed using the same methods as for the intention-to-treat analyses. We will perform *post hoc* analyses to adjust for the use of everolimus, and lipid lowering drugs other than the investigational medicinal product and pravastatin 40 mg o.d.

The secondary endpoints “Percent atheroma volume” and “Cardiac allograft vasculopathy” will be tested at a two-sided alpha level of 0.05 in a hierarchical fashion. Safety analyses will include tabulation of type and frequency of all adverse events. Serious adverse events will be reported with comprehensive narratives.

Missing data will be omitted from analyses, i.e. there will be no imputation or estimation of missing values. However, a comparison of the baseline characteristics of those with an intima thickness measurement at 12 months and the baseline characteristics of those without a value will be performed to assess any bias introduced due to missing data.

Ancillary studies

Assessment of coronary microcirculation, coronary optical coherence tomography, assessment of cognitive function, and analysis of the gut microbiome will be carried out in subsets of patients at baseline

and after one year's treatment. Baseline and follow-up blood samples are collected for future measurement of biomarkers of interest.

Trial governance

The EVOLVD trial is an investigator-initiated trial. The manufacturer of the investigational medicinal product, Amgen®, provide the investigational drug and matching placebo, and have provided a grant for the conduct of the trial. The investigators are responsible for the design, conduct, and interpretation of the trial, which is managed by an industry-independent steering committee. The sponsor, Oslo University Hospital, and the investigators take full responsibility for the integrity of the data. Amgen is not involved in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit results for publication.

Discussion

Several aspects of the EVOLVD trial design merit discussion. First, the rationale for the trial is the assumption that cardiac allograft vasculopathy is at least partly caused by the deposition of circulating cholesterol particles in the coronary arteries. However, the relative contribution of traditional atherosclerosis to the development of cardiac allograft vasculopathy is contested. Cardiac allograft vasculopathy seems in part to be caused by immunological mechanisms,[1] and antibody mediated rejection is associated with an increased risk of cardiac allograft vasculopathy. In the SCHEDULE trial, we showed that an early switch from a calcineurin-based immunosuppressive regimen to a drug combination based on everolimus ameliorated the increase in the allograft coronary artery intima thickness in *de novo* heart transplant recipients.[18] This fact suggests that drugs that primarily affect the immune system cells can affect the progression of the disease. However, the effects of statins in heart transplant recipients indicate that unchecked atherosclerosis is an important factor in the development of cardiac allograft vasculopathy.[20]

Second, vasculopathy rarely manifests as a clinical problem during the first year, but precipitates clinical events several years after transplant. It is therefore prudent to question whether one year's treatment soon after transplant can be expected to provide measurable results. On the other hand, data show that

there are substantial changes in the coronary arteries over the first year after transplant, suggesting that the adverse process starts shortly after transplant.[21] The changes observed over the first year are large enough to be quantified and are amenable to intervention.[9, 18] Moreover, there are data to suggest that, whereas early intervention can prevent long-term progression of cardiac allograft vasculopathy,[22] the same intervention is less effective when administered late after heart transplantation.[23] Thus, a window of opportunity for preventive measures against cardiac allograft vasculopathy in *de-novo* transplant recipients is likely to exist in the early phase after heart transplant.

Ideally, an intervention trial should be designed to assess meaningful clinical endpoints such as death, major cardiovascular events, or functional capacity. However, such trials often require thousands of participants to achieve adequate power and are not feasible among heart transplant recipients because the annual number of cardiac transplants is just 5000 worldwide. Therefore, we are forced to select surrogate endpoints that are likely to reflect clinically significant disease processes.

There is strong evidence to suggest that the coronary atherosclerotic volume reflects clinically significant coronary disease, and that drugs with the potential to ameliorate the coronary atheroma burden also reduce the rate of myocardial infarctions and cardiovascular death in patents with established cardiovascular disease or at risk of cardiovascular disease.[19] In heart transplant recipients, the coronary intima thickness is a strong predictor of outcomes.[24] The intima thickness and the atherosclerotic volume correlate closely. Taken together, these arguments provide a reason to assume that an intervention that reduces the coronary intima thickness would also manifest in less clinically significant cardiac allograft vasculopathy. The number of major clinical adverse events, defined as death, myocardial infarction, percutaneous coronary intervention/coronary bypass surgery, cerebral stroke, cancer, or end stage renal disease is an exploratory endpoint in the EVOLVD trial. The trial is not powered to demonstrate a between-group difference in clinical endpoints. However, we plan to perform follow-up after 3 and 5 years to assess the potential long-term legacy effect of early cholesterol reduction with evolocumab.

Solid organ transplant recipients are a distinct group of patients regarding safety. Commonly used immunosuppressive drugs have narrow therapeutic windows and are often subject to drug interactions. Evolocumab has a favourable safety profile when used in the non-transplant population. The only adverse effect that has reached statistical significance in large clinical trials has been injection site reactions. In the FOURIER trial, this minor adverse event occurred in 2.1% of patients allocated to evolocumab, and in 1.6% allocated to placebo.[13] Drug interactions have not been specifically assessed regarding the marketed PCSK9 inhibitors. However, there is little reason to assume that evolocumab would significantly interact with the immunosuppressants that we use after heart transplant. Evolocumab is a fully humanised,

monoclonal antibody. It is a large protein that is not metabolised by liver enzymes, but rather eliminated through target-mediated drug disposition. We routinely measure serum levels of immunosuppressants and adjust doses accordingly.

The main objective of the EVOLVD trial is to assess the effect of evolocumab on measures of cardiac allograft vasculopathy. Conventional coronary angiography is performed per current routine in our heart transplant recipient 8 - 12 weeks after heart transplantation and again one year after heart transplantation. In the EVOLVD trial, we plan to perform the first angiography 4 – 8 weeks after transplant if there is no contraindication to coronary angiography at this time. In conjunction with the conventional angiography, we will perform intravascular ultrasound and, in selected patients, optical coherence tomography and measurements of microvascular function. We have no reason to think that advancing the baseline angiography puts our patients at increased risk of complications. The addition of the ultrasound measurements will add approximately 15 minutes to the procedure. The added measurements are associated with a minimal increase in risk on top of the conventional angiography.[25]

Conclusion

The EVOLVD clinical trial is designed to test whether 12 months' cholesterol lowering with the PCSK9 inhibitor evolocumab can ameliorate the burden of cardiac allograft vasculopathy in heart transplant recipients. The trial is the first of its kind in these patients, and aims to resolve an important clinical question: Is cardiac allograft vasculopathy amenable to cholesterol-lowering treatment? Cardiac allograft vasculopathy is a major cause of morbidity and mortality after heart transplant, and the findings of the trial will have important consequences for the care of heart transplant recipients. Enrolment in the trial has begun, and results are expected in 2022.

Funding

The EVOLVD trial is an investigator-initiated trial. Amgen provides the medicinal investigational products and a grant for the conduct of the trial. The sponsor has no role in the design or conduct of the trial, or in the collection and interpretation of data, or in the decision to publish. The authors take full responsibility for the integrity of the data.

Disclosures

None of the authors have any conflict of interest regarding this study

References

1. Lee F, Nair V and Chih S. Cardiac allograft vasculopathy: Insights on pathogenesis and therapy. *Clin Transplant*. 2020;34(3):e13794.
2. Lund LH, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Heart Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant*. 2016;35(10):1158-1169.
3. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report--2010. *J Heart Lung Transplant*. 2010;29(10):1089-103.
4. Tilly-Kiesi M, Raisanen-Sokolowski A, Ustinov J, Myllarniemi M, Tikkanen MJ and Hayry P. Hyperlipidemia enhances chronic rejection in experimental rat model. *Transplant Proc*. 1995;27(1):582.
5. Tanaka H, Sukhova GK and Libby P. Interaction of the allogeneic state and hypercholesterolemia in arterial lesion formation in experimental cardiac allografts. *Arterioscler Thromb*. 1994;14(5):734-45.
6. Eich D, Thompson JA, Ko DJ, et al. Hypercholesterolemia in long-term survivors of heart transplantation: an early marker of accelerated coronary artery disease. *J Heart Lung Transplant*. 1991;10(1 Pt 1):45-9.
7. Park JW, Merz M, Braun P and Vermeltfoort M. Lipid disorder and transplant coronary artery disease in long-term survivors of heart transplantation. *J Heart Lung Transplant*. 1996;15(6):572-9.
8. Harris J, Teuteberg J and Shullo M. Optimal low-density lipoprotein concentration for cardiac allograft vasculopathy prevention. *Clin Transplant*. 2018;32(5):e13248.
9. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med*. 1995;333(10):621-7.
10. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *JHeart Lung Transplant*. 2010;29(8):914-956.
11. Shah MK, Critchley WR, Yonan N, Williams SG and Shaw SM. Second line options for hyperlipidemia management after cardiac transplantation. *Cardiovasc Ther*. 2013;31(3):138-46.
12. Dias CS, Shaywitz AJ, Wasserman SM, et al. Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. *J Am Coll Cardiol*. 2012;60(19):1888-98.

13. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017;376(18):1713-1722.

14. Moayedi Y, Kozuszko S, Knowles JW, et al. Safety and Efficacy of PCSK9 Inhibitors After Heart Transplantation. *Can J Cardiol*. 2019;35(1):104.e1-104.e3.

15. Kuhl M, Binner C, Jozwiak J, et al. Treatment of hypercholesterolaemia with PCSK9 inhibitors in patients after cardiac transplantation. *PLoS One*. 2019;14(1):e0210373.

16. Sandesara PB, Dhindsa D, Hirsh B, Jokhadar M, Cole RT and Sperling LS. PCSK9 inhibition in patients with heart transplantation: A case series. *J Clin Lipidol*. 2019;13(5):721-724.

17. Clemmensen TS, Holm NR, Eiskjaer H, et al. Layered Fibrotic Plaques Are the Predominant Component in Cardiac Allograft Vasculopathy: Systematic Findings and Risk Stratification by OCT. *JACC Cardiovasc Imaging*. 2017;10(7):773-784.

18. Arora S, Andreassen AK, Andersson B, et al. 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;15(7):1967-75.

19. Nicholls SJ, Puri R, Anderson T, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA*. 2016;316(22):2373-2384.

20. Vallakati A, Reddy S, Dunlap ME and Taylor DO. Impact of Statin Use After Heart Transplantation: A Meta-Analysis. *Circ Heart Fail*. 2016;9(10).

21. Azarbal B, Cheng R, Vanichsarn C, et al. Induction Therapy With Antithymocyte Globulin in Patients Undergoing Cardiac Transplantation Is Associated With Decreased Coronary Plaque Progression as Assessed by Intravascular Ultrasound. *Circ Heart Fail*. 2016;9(1):e002252.

22. Andreassen AK, Andersson B, Gustafsson F, et al. Everolimus Initiation With Early Calcineurin Inhibitor Withdrawal in De Novo Heart Transplant Recipients: Three-Year Results From the Randomized SCHEDULE Study. *Am J Transplant*. 2016;16(4):1238-47.

23. Arora S, Ueland T, Wennerblom B, et al. Effect of everolimus introduction on cardiac allograft vasculopathy--results of a randomized, multicenter trial. *Transplantation*. 2011;92(2):235-43.

24. Kobashigawa JA, Tobis JM, Starling RC, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. *J Am Coll Cardiol*. 2005;45(9):1532-7.

25. Batkoff BW and Linker DT. Safety of intracoronary ultrasound: data from a Multicenter European Registry. *Cathet Cardiovasc Diagn*. 1996;38(3):238-41.

Tables

Table 1 endpoints

Primary endpoint	• Baseline-adjusted maximal intimal thickness as measured by coronary intravascular ultrasound at end-of treatment, 12 months after randomization. The maximal intima thickness is defined as the largest distance (in mm) from the intimal leading edge to the external elastic membrane.
Secondary endpoints	• Percent atheroma volume as measured by IVUS • Cardiac allograft vasculopathy (defined as mean a maximal intimal thickness ≥0.5 mm over the entire matched segment) • LDL cholesterol • Estimated GFR • Quality of life as assessed by the SF-36 and 5D EuroQoL questionnaires, and the Beck's Depression Inventory • N-terminal pro-B-type natriuretic peptide • Cardiac troponin T • The number of allograft rejections • The number of adverse events • Time to major clinical adverse events, defined as death, myocardial infarction, percutaneous coronary intervention/ coronary bypass surgery, cerebral stroke, cancer, end-stage renal disease (exploratory endpoint)

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Heart transplant recipient within the last 4 – 8 weeks. Age between 18 and 70 years. Informed consent obtained and documented according to Good Clinical Practice (GCP), and national/regional regulations. No contraindications to coronary angiography with intravascular ultrasound Estimated glomerular filtration rate ≥ 20 ml/min/1.73 m^2 as assessed by the MDRD formula
Exclusion criteria	• Decompensated liver disease (Child-Pugh class C) • Severe renal failure, i.e. eGFR < 20 ml/min/1.73 m2 or on renal replacement therapy • Ongoing rejections or infections • Known sensitivity or intolerance to evolocumab or any of the excipients of Repatha® • Prior use of PCSK9 inhibition treatment • Indication for treatment with PCSK9 inhibitor • Alcohol or drug abuse within 3 months of informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake • Participation in another clinical trial involving an investigational drug and/or follow-up within 30 days prior to enrolment. • Pregnancy. • The subject is a nursing woman • Female subject who has either (1) not used at least one highly effective method of birth control for at least 1 month prior to screening or (2) is not willing to use such a method during treatment and for an additional 15 weeks after the end of treatment, unless the subject is sterilised or postmenopausal

Figure legends

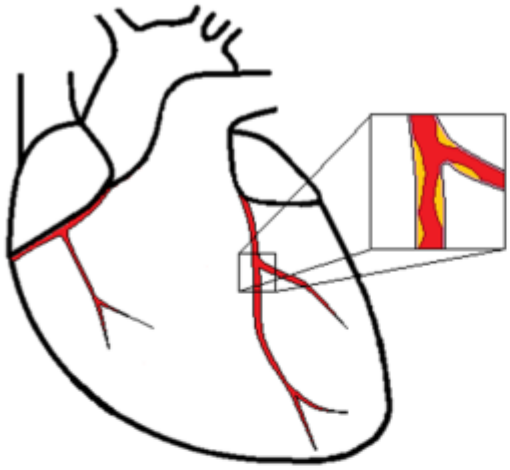
Figure 1

Cardiac allograft vasculopathy is a major cause of late morbidity and mortality in heart transplant recipients. The EVOLVD trial is devised to mitigate this clinical problem. The hypothesis is that evolocumab will reduce levels of circulating low density lipoprotein cholesterol and reduce the burden of cardiac allograft vasculopathy.

Figure 2

Trial overview. After verification of eligibility and receipt of written informed consent, we will randomly allocate patients to treatment with evolocumab or matching placebo for one year, after which efficacy will be assessed.

Cardiac allograft vasculopathy



Causes

30 %

of deaths beyond 1st year after HTx

Occurs in

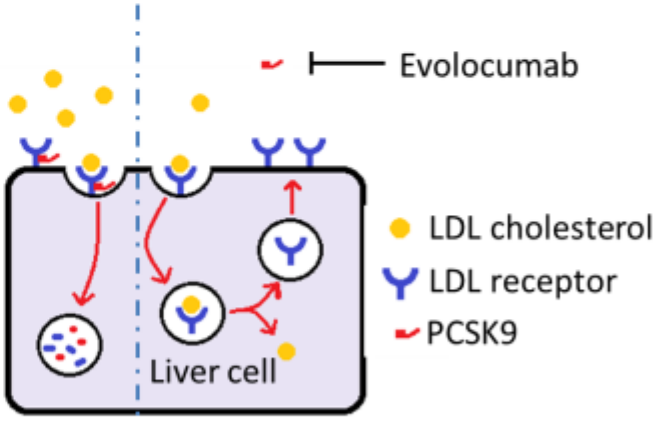
1/3

of recipients 5 years after HTx

EVOLVD trial

Hypothesis

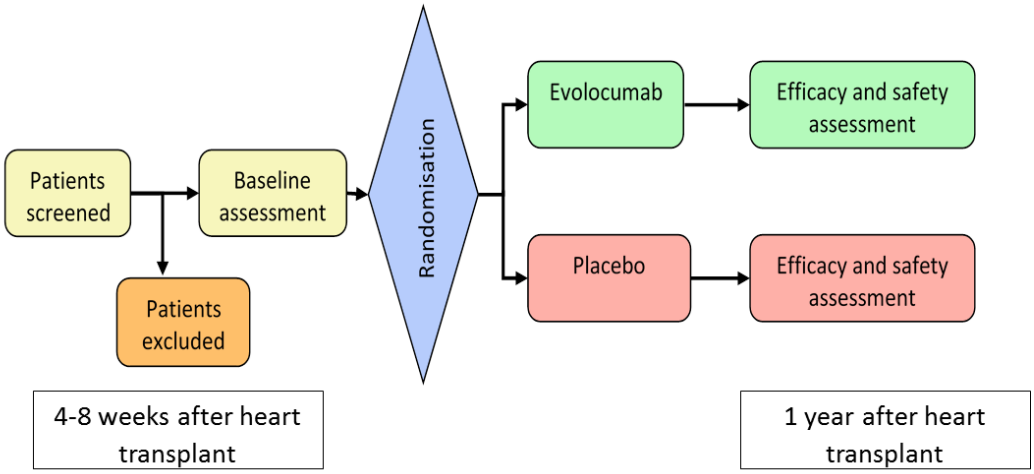
Evolocumab will lower LDL cholesterol levels, reduce the incidence of cardiac allograft vasculopathy and reduce morbidity and mortality in heart transplant recipients



Aim

To **reduce the burden of cardiac allograft vasculopathy** in heart transplant recipients

ctr_13984_f1.tif



ctr_13984_f2.tif