# Study Protocol

# Title: Lipid Management in Renal Transplant Recipients: a pilot study evaluating the use of the PCSK9 inhibitor, evolocumab

**Version: 5.5**

**Document Date: December 4, 2023**

**NCT: NCT04608474**

**Note: This is the current protocol version used for the study. The investigator list was updated administratively on October 15, 2025. No changes were made to the study design or statistical analysis.**

**STUDY PROTOCOL (Version 5.5 012/04/2023)**

**Title**: Lipid Management in Renal Transplant Recipients: a pilot study evaluating the use of the PCSK9 inhibitor, evolocumab

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## 1. INTRODUCTION

Cardiovascular disease is the leading cause of mortality after renal transplantation, accounting for more than 30% of deaths, followed by infection and malignancy (1). With the improvement in short-term allograft survival in the past decade, death with a functioning graft has become one of the major causes of graft loss (~40%) (2). Consequently, reducing cardiovascular mortality is a major goal in post-transplant medical care. In addition to the traditional cardiac risk factors, the pathogenesis of cardiovascular disease after transplantation involves transplant-specific factors, such as the duration of pre-transplant end-stage renal disease, new onset post-transplant diabetes and poor allograft function (3).

Dyslipidemia is a frequent finding following transplantation and the immunosuppressive medications play a central role in the development or worsening of hyperlipidemia. Historically, the prevalence of hyperlipidemia in renal transplant recipients (RTR) has been reported to be higher than 80% (4); however, more recent data, reflective of more modern immunosuppressive regimens, report that approximately 44% of RTR have a low-density lipoprotein (LDL) level above 100 mg/dL six months following transplantation (1, 5). This data also demonstrates that roughly 40% of RTR are being treated with a 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitor (i.e., statin) (1, 5).

In the general population, the correlation between elevated serum cholesterol and increased risk of atherosclerotic cardiovascular disease (ASCVD) is well established and the reduction in serum LDL cholesterol has proved to significantly reduce both morbidity and mortality of patients with or without ASCVD (6). Conversely, the role of dyslipidemia in post-transplant cardiovascular disease is not as clearly defined. There has only been a single prospective randomized trial in transplant recipients comparing statins (fluvastatin) with placebo (ALERT trial), which showed a 35% reduction in the incidence of myocardial infarction and cardiac deaths in statin-treated patients (p=0.005). Though this trial involved more than 2,000 RTR with a five-year follow up, fluvastatin only showed a non-

significant reduction in the primary composite endpoint of cardiac death, non-fatal myocardial infarction (MI) or coronary intervention compared to placebo (RR 0.83, 95% CI 0.64-1.06, p=0.139). An extension of the ALERT trial evaluated 1,652 patients from the original study reinforced the prior findings, demonstrating a 21% reduction of a major cardiac event (p=0.036) and a 29% reduction in cardiac death or definite non-fatal MI (p=0.014). However, there was no difference in graft survival between the groups (7). The safety profile of fluvastatin was comparable to placebo when co-administered with cyclosporine, with no difference in documented hepato- or myo-toxicities. In summary, statins improve lipid profiles and decrease cardiovascular events in transplant recipients; however, no trial has demonstrated a significant mortality benefit in this population. This is an important delineation, as there are currently no statin therapies that confer mortality benefit in RTR.

The tolerability of statins must always be considered when managing RTR. More than 20 years of experience with statins has proven that these agents have an excellent safety record and a favorable risk/benefit profile in the general population. Nonetheless, statins have been associated with hepatotoxicity and myotoxicity and are more common in kidney transplant patients and patients with CKD. This effect appears to be dose related and may be precipitated by administration with agents that inhibit cytochrome P-450 isoenzymes (8)

Although both tacrolimus and cyclosporine are known inhibitors of CYP3A4 enzyme in vitro, recent reports suggest that cyclosporine results in a stronger inhibitory effect of the enzyme in vivo when compared to tacrolimus (9,10), which could explain the higher association of cyclosporine with statin-related toxicities in clinical trials (11). Furthermore, cyclosporine also has inhibitory properties on several membrane transporters that mediate the uptake of statins into the liver (e.g. OATP1B1), possibly contributing to its effect on statin exposure (12). Simvastatin, atorvastatin and lovastatin are primarily metabolized by the CYP3A4 isoenzyme and are especially susceptible to drug-drug interactions with known inhibitors of these enzymes. Co-administration of these statins with known enzyme inhibitors carries a potential risk of elevation of serum statin levels and subsequent acute toxicities. Conversely, pravastatin, pitavastatin, fluvastatin and rosuvastatin have alternative metabolic pathways and do not carry a similar risk of drug-drug interactions (12).

Rosuvastatin has been associated with increased proteinuria and renal failure at higher doses in a post-marketing report from the FDA (13). This would be of special concern in RTR. The findings from the Prospective Evaluation of Proteinuria and Renal Function in Diabetic and Non-Diabetic Patients with Progressive Renal Disease trials, which have atorvastatin 80 mg/day with rosuvastatin 10 or 40 mg/day in dyslipidemic patients with moderate proteinuria, should help provide further insight into this potentially serious adverse event. Until these results are published, it is reasonable to limit rosuvastatin to the lowest recommended doses.

The 2014 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines mostly echo the recommendations of the ACC/AHA guidelines; which targeted overall ASCVD and abolished numeric LDL and non-HDL goals (14). These guidelines were based purely on randomized controlled studies, and no epidemiologic or observational studies were included. Therapy centered around the use of fixed-dose statin therapy:

- Moderate-intensity statin therapy (any daily dose of a statin that could reduce LDL from baseline by 30-50%)

- High-intensity statin therapy (any daily dose of a statin that could reduce LDL from baseline by more than 50%)

Overall, in these guidelines, there is a general lack of support for non-statin pharmacologic interventions, as well as no recommendations for management of patient with TG exceeding 500 mg/dl (14).

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK-9) have been approved by regulatory agencies for the treatment of individuals with inadequately treated levels of low density lipoprotein-cholesterol (LDL-C). These agents are capable of lowering LDL-C by as much as 60 percent in patients on statin therapy. In addition, they produce clinical benefits, such as reductions in the rates of stroke or myocardial infarction. These agents have been studied sparingly in patients with chronic kidney disease (CKD), but have not yet been analyzed in RTR.

The study has recruited 61 subjects from 3 sites, with 20% completing 3-, 6-, and 12-month follow-ups. Analysis of subjects at Brigham and Women's Hospital has shown that LDL levels have decreased significantly. In subjects that have completed the 3-month follow-up, 90% have shown a reduction in LDL levels with an average reduction of 52%. In subjects that have completed the 6-month follow-up, 95% have shown a reduction in LDL levels with an average reduction of 59%. In the 12 subjects that have completed the 12-month follow-ups, 100% have shown a reduction in LDL levels with an average reduction of 50%. Since the start of enrollment, there have not been any serious adverse effects, a few subjects have experienced rashes, and less than 6 patients have been withdrawn due to noncompliance.

**Study Amendment**

Given the very significant decrease in LDL, further enrollment will not add to this outcome's finding. Considering this information, we would like to amend the study to cap recruitment at 80 patients for the original study design and recruit a further 15 patients studying myocardial and coronary vascular changes with ECG, Echocardiogram and PET/CT at baseline, 6, and 12 months, and examine vascular changes within the kidney allograft with PET/CT from baseline, 6 and 12 months. This change would require no additional funding, but may provide useful preliminary data on disease progression and drug efficacy. The data generated may well provide provisional data that PCSK-9 inhibitor treatment reduces the progression of atherosclerosis within the coronary vasculature and the kidney allograft vasculature.

PCSK-9 inhibitor therapy has been shown to result in coronary epicardial plaque stabilization and regression (15- 16), which may be due to regulation of LDL levels as well as pleiotropic anti-inflammatory effects (17-20). PCSK-9 has been localized to vascular endothelial and vascular smooth muscle cells (21-22) and has been shown to increase endothelial cell apoptosis (23). Inhibition of PCSK-9 is associated with higher levels of circulating endothelial progenitor cells which are markers of endothelial and vascular health (24). Inhibition of PCSK-9 may influence endothelial cell function within the vasculature of the heart and transplanted kidney allograft in humans, which can be measured using surrogate imaging markers.

Dynamic myocardial perfusion PET has been viewed as a surrogate marker of arteriosclerosis and coronary vascular health and a predictor of IHD. Quantitative myocardial blood flow (MBF, ml/min/g) and myocardial flow reserve (MFR, the ratio of stress to rest MBF), as assessed by PET,

provide accurate measurements of myocardial ischemia and vascular health across the spectrum of CAD phenotypes in the general population. In the absence of significant epicardial stenosis, impairment in MFR represents the combined effect of diffuse epicardial atherosclerosis and coronary microvascular endothelial and smooth muscle dysfunction (25-27). Myocardial perfusion PET can provide a precise quantitative assessment of myocardial blood flow which is mechanistically linked with vascular endothelial function and is therefore well suited to study changes in coronary vascular health among patients after renal transplant and the impact of PCSK-9 inhibitor therapy.

In addition, we would also like to use PET-CT to examine progression of vascular disease in the transplanted kidney in the same patients. Dynamic perfusion imaging of the kidneys by PET has been used to measure renal blood flow in preclinical models (28), healthy volunteers (29-32), and patients with renal artery stenosis (33-34) or medical renal disease (34-35). PET RBF is correlated with the classical para-aminohippurate clearance method for quantification of renal plasma flow (34). PET-CT has not been used to measure renal blood flow of the transplanted kidney, however its use in this area is well justified based on these prior studies in native kidneys.

## 2. OBJECTIVES

The objectives of this study are multifold. We hope to:

1. Evaluate the safety and tolerability of evolocumab in RTR;
2. Evaluate the impact of evolocumab alone and combination statin-evolocumab on LDL-cholesterol levels in RTR.
3. Evaluate the change in cardiac myocardial perfusion after treatment of RTR with evolocumab, as measured by stress myocardial blood flow (MBF) and myocardial flow reserve (MFR) on dynamic perfusion PET/CT.
4. Evaluate the change in kidney myocardial perfusion after treatment of RTR with evolocumab, as measured by resting renal blood flow (RBF) on dynamic perfusion PET/CT.

## 3. ORIGINAL STUDY DESIGN and DURATION

This is a multi-center, prospective analysis that will evaluate the need for lipid-lowering therapies in RTR. Patients are eligible for enrollment if they require lipid-lowering therapy, whether it is primary therapy or therapy in patients already on statin therapy, but needing further reductions in LDL cholesterol yet they cannot receive statin dose increases due to being on the maximum recommended dose, a drug-drug interaction, or are on their maximally tolerated dose. The goal is to recruit 120 kidney transplant recipients. The duration of patient follow-up will be from the time of first screening and initiation of new therapy for hyperlipidemia, until a 12-month follow-up visit. Enrollment into the study will be tracked at 3 and 6 months after the initiation of the study to make sure that enrollment is on target and allow the consideration of additional sites. If 30 percent of the total study population has not been enrolled by 6 months, a correction plan will be formulated and submitted to the sponsor. A 6-month interim analysis will be carried out in order to check for efficacy of evolocumab at lowering LDL levels in this population and may be useful in designing a larger study that would be appropriately powered to show a statistical difference between groups. It is expected that enrollment will be completed within 1 year of receiving IRB approval.

Amended design

Cap recruitment at 80 in original design with a plan to recruit 15 patients who will undergo a ECG, Echocardiogram and PET SCAN at baseline, 6 and 12 months of treatment of the transplanted kidney and heart. Serum beta HCG test will be done prior to PET scan procedure to rule out pregnancy (if applies). Additionally, labs will be drawn for metabolic and gene profile studies at 0, 6, and 12 months. The 15 additional patients will be recruited at Brigham and Women's Hospital only and a number of patients have already been identified for inclusion based on the original screening criteria. We are confident that these patients can be recruited within 8 weeks following IRB approval.

**Institutional Review Board (IRB)**
Prior to study initiation and when amended, the protocol and any applicable advertisement for patient recruitment will be submitted for review and approval to the BWH IRB. Site personnel will provide reports of the progress, or completion, termination or discontinuation of the study to the IRB at appropriate intervals. The investigator will verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

## 4. STUDY POPULATION

All individuals having already undergone a renal transplant and who are at least 1-year post-transplant will be identified for inclusion in this study. All identified subjects should meet the entering criteria listed below. The study will be conducted at three Harvard Medical School affiliated transplant centers:

Brigham and Women's Hospital (main site)
PIs: Anil Chandraker, MD and Steven Gabardi, PharmD

Beth Israel Deaconess Hospital
PI: Amtul Aala, MD

Massachusetts General Hospital
PI: Kassam Safa, MD

### 4.1 Inclusion Criteria

1. Adult renal transplant recipients greater than 1-year post-transplantation, men and women between 18 and 85 years of age, inclusive.
2. Any patient with documented ASCVD or diabetes and 1 or more risk factors for ASCVD, including, but not limited to obesity, inactive lifestyle, hypertension, smoking, and family history. and a LDL >70 mg/dl (Highest-Risk Patients)
3. Any patient not classified as one of our highest-risk patients, that has a LDL >100 mg/dl

### 4.2 Exclusion Criteria

Patients who meet the following criteria will be excluded:

1. Patients currently enrolled in another interventional clinic trial.
2. Patients being actively treated for cellular or antibody-mediated rejection.
3. Serious hypersensitivity to evolocumab or any component of the formulation.
4. Patients who are pregnant or intend to get pregnant with in the next 1 year

## 5. STUDY PROCEDURES

### 5.1 Patient Evaluation

All renal transplant recipients that are eligible for evaluation will have their inpatient and clinic medical charts and computerized longitudinal medical records reviewed for demographic data, use of induction and maintenance immunosuppressive therapies, and LDL-cholesterol. See Section 5.3 for Schedule of Assessments.

### 5.2 Study Medication and Dosing Regimen

Patients will receive:
Evolocumab: 140 mg SC every 2 weeks or 420 mg SC once monthly, depending on the patient's preference.

### 5.3 Schedule of Assessments

| | SCREENING | BASELINE | MONTH 3 | MONTH 6 | MONTH 9 | MONTH 12 |
|---|---|---|---|---|---|---|
| **Study Procedures** | | | | | | |
| Informed Consent | ● | | | | | |
| Evaluation of Inclusion/Exclusion | ● | | | | | |
| **Medical Record Review** | | | | | | |
| Demographics | ● | | | | | |
| Medical History | ● | | | | | |
| Induction Therapy | ● | | | | | |
| Maintenance Immunosuppression | ● | ● | ● | ● | ● | ● |
| Concomitant Medications | ● | ● | ● | ● | ● | ● |
| Adverse Event Assessment | ● | ● | ● | ● | ● | ● |
| **Study Treatment** | | | | | | |
| Evolocumab | | ● | ● | ● | ● | ● |
| **Laboratory Assessments** | | | | | | |
| Apolipoprotein B, Apolipoprotein A-1 | | ● | ● | ● | | |
| Lipoprotein A | | ● | ● | ● | | |
| Lipid Panel[1] | | ● | ● | ● | ● | ● |
| CPK | | ● | ● | ● | ● | ● |
| ALT, AST | | ● | ● | ● | ● | ● |

| | | | | | | |
|---|---|---|---|---|---|---|
| Tacrolimus/CNI Level | | ● | ● | ● | ● | ● |
| Serum beta HCG test | ● | ● | | ● | | ● |
| Metabolomic Study*[2] | | ● | | ● | | ● |
| **Other Assessments** | | | | | | |
| Memory Impairment Screen | | ● | ● | ● | ● | ● |
| PET SCAN*[3] | | ● | | ● | | ● |
| ECG* | | ● | | ● | | ● |
| Echocardiogram* | | ● | | ● | | ● |

[1]Cholesterol, LDL, HDL, Triglycerides
[2]2 6 ml K2EDTA (ethylenediaminetetraacetic acid) tubes for whole blood (PBMC) and 1 7ml SST (with or without clot activator or gel) tube for serum at baseline visit, 6 and 12 months visit, (Approximately 1 ½ tablespoon total each visit).
*Only for subjects enrolled at Brigham and Women's Hospital.
[3]2 PET (Positron Emission Tomography) scans to be performed at the baseline visit, 6 and 12 months visit. The effective dose from a PET scan is modest and depends on the activity of the injected contrast and is typically the same dose whether a part of the body or the whole body is imaged.

***Positron Emission Tomography (PET)***
PET scans will be performed using a whole-body PET/CT scanner. Study participants will be asked to refrain from drinking caffeine-containing beverages and taking theophylline-containing medications for 12 hours before the PET study. Studies will be performed after 4 hours of fasting. Myocardial blood flow (MBF) will be measured at rest and during vasodilator-stress with regadenoson or adenosine using N-13 ammonia or Rubidium-82 as the flow tracer. N-13 ammonia and Rubidium-82 are used in clinical and research studies and have been validated for the quantification of myocardial blood flow and CFR. After transmission imaging and beginning with the intravenous bolus administration of N-13 ammonia (~5 mCi) or Rubidium-82 (~15-20 mCi), list mode images will be acquired for 6-10 minutes. The patient will then undergo a standard regadenoson bolus injection (0.4 mg) or infusion of adenosine (140 mcg/kg/min) for 4 mins. One minute after the regadenoson bolus or two mins into the adenosine infusion, a second dose of N-13 ammonia (~20 mCi) or Rubidium-82 (~15-20 mCi) will be administered, and PET images collected in the same manner. Heart rate, blood pressure, and 12-lead electrocardiogram will be recorded at baseline, every minute during the infusion, and during 5 minutes after completion of regadenoson injection or the adenosine infusion.

An additional scan of the transplanted kidney will be performed beginning with the intravenous bolus administration of N-13 ammonia (~5 mCi). List mode images of the abdomen and pelvis centered on the transplanted kidney allograft will be acquired for 6-10 minutes.

*Assessment of PET myocardial blood flow and MFR*
Absolute MBF (in ml/g/min) will be computed from the dynamic rest and stress images using commercially available software (Corridor4DM; Ann Arbor, Michigan) and previously validated methods (26). Automated regions of interest will be used to generate blood pool (arterial input function) and tissue time-activity curves. Regional and global rest and vasodilator stress MBF will

be calculated by fitting the N-13 ammonia or Rubidium-82 time-activity curves to a two-compartment tracer kinetic model as described previously (26). Per-patient global MFR will be calculated as the ratio of MBF at peak vasodilator-stress over that at rest for the entire left ventricle. This method for quantitation of MBF is highly reproducible. In the PET core laboratory at BWH, the intra-class correlation coefficient for MFR among four readers is 0.94 (95%CI 0.88-0.98), indicating excellent reproducibility (27).

*Assessment of PET renal blood flow*

Resting renal blood flow (RBF) will be computed using commercially available software (Hermes HybridViewer; Stockholm, Sweden and PMOD Technologies LLC; Zurich, Switzerland). Image registration between the CT and PET will be confirmed visually and manually adjusted when needed. Rectangular regions of interest in the descending aorta above the iliac bifurcation will be used for the blood pool (arterial input function), approximately 8x25 mm in size. Volumes of interest in the renal parenchyma will be generated by manual tracing, avoiding the collecting system and ureter, on summed axial 2-dimensional slices of the transplanted kidney. Resting renal blood flow will be calculated by fitting the tissue time activity curves to a 2-compartment kinetic model for N-13 ammonia with an incorporated metabolite correction.

## 6. EFFICACY EVALUATION

Primary efficacy measure will be the percent change from baseline in the LDL cholesterol level at 12 months as compared to baseline. Secondary outcome measures will include the absolute change from baseline in the LDL cholesterol level, the number of patients who achieved LDL-cholesterol of < 70 mg/dl, LDL/HDL ratio and evaluation of transplant-related outcomes, such as renal function, tacrolimus concentrations and rejection episodes. Tertiary outcome measures will be the difference in stress myocardial blood flow (MBF) and myocardial flow reserve (MFR) in the heart and the difference in the resting renal blood flow (RBF) in the transplanted kidney vessels from baseline, 6 months, and 12 months and will be evaluated with N-13 Ammonia or Rubidium-82 PET.

| **Endpoint** | |
|---|---|
| Primary | Percent change in LDL cholesterol at 12 months from baseline |
| Secondary | Absolute change in LDL cholesterol at 12 months from baseline |
| | Percentage of patients with LDL cholesterol <70 mg/dl) at 12 months compared to baseline |
| | Change in LDL/HDL ratio at 12 months compared to baseline |
| | Absolute change from baseline in eGFR at 12 months |
| | Change in tacrolimus trough concentration (ng/ml) at 12 months compared to baseline |
| | Incidence of cellular rejection within study period |
| | Incidence of antibody-mediated rejection within study period |
| Tertiary | Difference in stress myocardial blood flow (MBF) and myocardial flow reserve (MFR) in the heart and the |

| | |
|---|---|
| | difference in the resting renal blood flow (RBF) in the transplanted kidney vessels from baseline, 6 months, and 12 months evaluated with N-13 Ammonia or Rubidium-82 PET |

Categorical variables will be analyzed using the Fisher's exact test and means of continuous variables will be evaluated using the Student's t-test. Differences will be considered significant at p-values of $< 0.01$. GraphPad Prism 5.0 (GraphPad Software, San Diego, CA) will be used to perform all statistical analyses.

**Power Analysis:**
To detect a 20% effect size, the study will need to recruit approximately 8 patients. This assumes an estimated mean MFR of $2.04 \pm 0.40$, based on 13 patients that we retrospectively identified in the PET registry at Brigham and Women's Hospital without coronary artery disease while on the renal transplant waitlist. Mean MFR among patients after renal transplant is not known. It also assumes a moderate correlation between baseline and follow-up measurements of 0.7 and a 15% attrition rate. The 20% effect size is based on the minimum change that would be considered clinically relevant and is similar to the reported change in CFR with pharmacologic therapies such as statins (28).

*Table. Sample size calculations for change in cardiac MFR (paired means t test, SAS 9.4)*

| **Effect Size** | **Mean MFR difference (12 months post PCSK-9 inhibitor** | **SD** | **Total Sample Size (80% power)** | **Total Sample Size (85% power)** | **Total Sample Size (90% power)** |
|---|---|---|---|---|---|
| 20% | 0.40 | 0.40 | 8 | 9 | 10 |

Because renal blood flow has not been measured in the transplanted kidney, power analysis for the change in renal blood flow was not performed.

## 7. SAFETY EVALUATION

All patients will have baseline measurements for hepatic transaminase levels and creatinine phosphokinase at the initial study visit. These measurements will be followed at each study visit. Patients will be monitored for new-onset diabetes and memory impairment during the analysis.

## 8. SAFETY REPORTING

| **Safety Data** | **Timeframe for Submission to Amgen** |
|---|---|
| Suspected Unexpected Serious Adverse Reaction (SUSARs) | Sent to Amgen at time of regulatory submission |
| Serious Adverse Events (SAEs) | Not required, unless contractually specified per study |
| Adverse Events not meeting serious criteria | Not required, unless contractually specified per study |
| Events of Interest | Not required, unless contractually specified per |

| | |
|---|---|
| | study |
| Pregnancy/Lactation | Within 10 calendar days of Sponsor awareness |
| Event listing for reconciliation | As specified per contract |
| **Annual Safety Report**<br>(eg, EU Clinical Trial Directive [CTD] **DSUR**, and US IND Annual Report) | **Annually** |
| **Other Aggregate Analyses**<br>(any report containing safety data generated during the course of a study) | **At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc) |
| **Final (End of Study Report, including):**<br>• Unblinding data for blinded studies<br>• Reports of unauthorized use of a marketed product | **At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc) but not later than 1 calendar year of study completion |

## 9. RISKS AND DISCOMFORTS

### 9.1. Vasodilator stress

Vasodilator-stress with regadenoson and adenosine, as will be performed in this study, has been used routinely for many years for evaluation of known or suspected coronary artery disease in conjunction with myocardial perfusion imaging. During the infusion of the vasodilator stress agent, the patient may experience flushing, chest pain/pressure, nausea, or lightheadedness. If significant symptoms are present, patients will be given aminophylline (reversal agent) IV to relieve these symptoms. There will be continuous monitoring of heart rate, blood pressure, and 12-lead ECG throughout the infusion and recovery. These procedures are routinely performed in patients with coronary artery disease and are considered safe.

Regadenoson stress as performed in this study has been used routinely for many years for evaluating patients with known or suspected CAD. The most common side effects associated with the regadenoson bolus include: flushing, chest pain/pressure, shortness of breath, palpitations, headache, mild hypotension and heart block. These side effects are usually mild and self-limiting. If they are severe in intensity, aminophylline IV (1 mg/kg) will be given as per standard protocol.

Subjects with a history of seizures may receive adenosine instead of Regadenoson. The side effects associated with this product include: facial flushing, headache, sweating, palpitations, chest pain, hypotension, shortness of breath/dyspnea, chest pressure, hyperventilation, head pressure, lightheadedness, dizziness, tingling in arms, numbness, apprehension, blurred vision, burning sensation, heaviness in arms, neck and back pain, nausea, metallic taste, tightness in throat, and pressure in groin. Adenosine is administered as a continuous infusion over 4 minutes and administered in a dose of 0.14 mg/kg/min. The half-life of adenosine is less than 10 seconds. If the patient is having symptoms the infusion can be stopped, no further medication is administered, and the symptoms would stop within seconds because the medication would already be cleared from the heart. Therefore, no reversal medication is needed.

Rarely, an aminophylline IV injection may be used to reverse side effects of regadenoson infusion. Aminophylline is generally well tolerated; possible side effects of aminophylline may include nausea, headache, restlessness, convulsions, rapid breathing, a rapid heart rate, and allergic reactions such as rash.

9.2. Radiation risk

The estimated whole-body effective radiation dose from each N-13 ammonia or Rubidium-82 PET scan is approximately 4.8 mSv. This includes the N-13 ammonia or Rubidium-82 tracer doses at rest/stress of the heart and the attenuation correction CT as well as the N-13 ammonia tracer dose at rest of the transplanted kidney. Each subject will undergo up to three PET studies during the trial for a total dose of 14.4 mSv. This total dose is approximately equivalent to 4-5 years of radiation exposure from natural background sources of radiation (53).

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