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I, Vibha CA Desai , hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences/Biopharmaceutics.

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Comparative Effectiveness of Tacrolimus-Based Steroid Sparing versus Steroid Withdrawal Regimens in Patients with Kidney Transplantation: Results from Discrete Event Simulation Modeling

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Comparative Effectiveness of Tacrolimus-Based Steroid Sparing versus Steroid Withdrawal Regimens in Patients with Kidney Transplantation: Results from Discrete Event Simulation Modeling

A dissertation submitted to the

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by

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Abstract

Background: Acute rejection (AR) and graft loss (GL) that occur as a complication following kidney transplantation (KT) are a major cause of concern in patients with KT. Corticosteroids used as potent immunosuppressants in preventing AR and GL are associated with potentially serious side effects such as development or progression of cardiovascular diseases (CVD), new onset diabetes (NODM), infections and malignancies. Deaths with a functioning graft account for 40% of deaths following KT and CVD are a major cause of these deaths. Trials on tacrolimus-based regimen have found no significant difference in the AR or GL rates and a significant reduction in total cholesterol with steroid withdrawal regimens compared to steroid maintenance regimens. However, majority of these trials were short-term of a duration of <=5 years and included low immunologic risk patients. Long-term effects of these regimens on GL and cardiovascular events such as stroke, myocardial infarction (MI) and deaths due to CVD (D-Cardio) are not known.

Objectives: The objectives of the study were to determine the optimal steroid withdrawal strategy that minimizes the incidence of both graft loss as well as cardiovascular events, amongst the five strategies: 1) steroid avoidance 2) 7-day steroid withdrawal 3) 6-month steroid withdrawal 4) 12-month steroid withdrawal and 5) steroid maintenance, using a discrete event simulation model.

Methods: A discrete event simulation model was developed that included the following events: AR, GL, MI, stroke, other CVD, NODM, cancer, bacterial infection (BI), cytomegalovirus infection, fracture, D-Cardio, death due to GL and death due to other reasons. The United States Renal Data System registry that follows patients with transplantation was used to derive risk estimates of patients for the above events using parametric regressions adjusting for patients' demographic characteristics, immunologic risks and comorbidities. The estimates were then used to obtain Weibull distributions to transition a cohort of 10,000 patients in the model, using minimum of sampled time approach. The model was run for 20 years for base patient with mediocre risk frequently seen in practice and for African-American patients and patients with a history of CVD.

Results: At the end of 20 years, base patients in the 6-month and 12-month steroid withdrawal group were significantly less likely to experience MI (9.6-9.8% vs 12.2%), NODM (37.2%-42.4% vs 46.4%), BI (51.7%-57.6% vs 67.4%), fractures (51.1%-54.8%% vs 59.1%) and D-Cardio (24.5%-25.7% vs 28.8%), compared to steroid maintenance. The incidence of AR and GL were significantly higher in the steroid avoidance and 12-month steroid withdrawal group compared to the steroid maintenance group (42.6%-51.4% and 57.9%-76.4% vs 30.5% and 40.9%). Compared to base patient, patients with a history of CVD and African-American patients were more likely to have a GL (46.6%-58.0% vs 40.7%-42.2%) and NODM (44.4%-44.9% vs 37.2%-42.4%).

Conclusion: At 20 years, the steroid withdrawal between 7-days to 12-months post kidney transplantation has benefits of significantly reduced rates of cardiovascular event with no significantly worse effects on AR and GL rates compared to steroid maintenance in mediocre risk patients. Future simulation studies on a heterogenous patient population are needed.

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1. INTRODUCTION

1.1 Background

Kidney transplantation is the treatment of choice in patients with End Stage Renal Disease (ESRD), a condition in which the kidneys become dysfunctional in filtering the wastes from the blood, thus endangering a patient's life due to buildup of toxins and disturbance in hemodynamics. Patients with kidney transplantation live longer and have a significantly improved quality of life as compared to those on dialysis. According to the United Network of Organ Sharing (UNOS), 93,000 patients with ESRD are on the waiting list for kidney transplantation in the United States.[1]

Graft loss resulting from rejection of the transplanted kidney is a major concern in transplant recipients. Corticosteroids have long been used in the immunosuppressive regimen of kidney transplant patients and are effective in preventing acute rejection and hence graft loss. However, long-term steroid use is associated with potential side effects such as development or progression of cardiovascular diseases, new onset diabetes and malignancies, the complications from which, incur high cost of treatment and can result in death with a functioning graft. In fact, a study following patients for 9 years found that 40% of deaths post kidney transplantation were with a functioning graft rather than deaths due to graft loss itself and cardiovascular disease was a leading cause of these deaths.[2] While withdrawing steroids from the immunosuppressive regimen carries a risk of acute rejection and graft loss, maintaining patients on steroids has a risk of development of or progression of cardiovascular diseases.

Trials have been conducted to determine the efficacy and safety of steroid withdrawal (steroid-sparing strategies) from the immunosuppressive-regimen at 7-days 3-months, 6-months and 1-year post-transplantation or of complete steroid avoidance, compared to steroid maintenance. A meta-analysis by Morris et al.[3] in 2010, on steroid avoidance/withdrawal versus steroid maintenance trials showed no significant difference in patient or graft survival between the two groups while significant reduction in rates of new-onset diabetes mellitus, hypercholesterolemia and hypertension with steroid avoidance/withdrawal regimen ($p<0.0001$). The authors categorized the steroid avoidance/withdrawal regimens in the trials as steroid avoidance, steroid withdrawal within 7 days and steroid withdrawal between 8 days to 12 years. The trials included in this study were either cyclosporine-based or tacrolimus-based; both of which vary in the immunosuppressive potency and cardiovascular risk. Majority of these were short-term trials of a patient follow-up time of ≤ 5 years and were conducted on low-immunologic risk patients. Though the authors concluded steroid withdrawal to have beneficial effects on cardiovascular risk profile, they could not determine an optimal time of steroid withdrawal due to absence of significant differences in the proportion of patients with cardiovascular events among the different regimen groups as a result of small sample size of some of the trials included. To date, the long-term effects of steroid withdrawal on graft survival and that of steroid maintenance on cardiovascular diseases and events such as stroke, myocardial infarction and deaths due to cardiovascular diseases on a patient population with a heterogenous immunologic as well as cardiovascular risk as well as an optimal time of steroid withdrawal are not known.

1.2 Discrete event simulation

A discrete event simulation (DES) is a computer-based modeling approach that can represent complex systems involving interactions between individuals and environments as well as between individual states, such as those occurring in disease epidemics or those related to utilization of healthcare resources by patients or those occurring in patient disease progression. It has been used for opertations research in the field of industrial engineering since 1960s and more recently in health care, examples of it being clinical trial design, health policy evaluation and survival modeling.[4-9] The latter involves comparing treatment strategies using patient level simulation which reflects a natural disease progression and treatment course of a patient. It takes into account several parameters affecting the treatment outcomes downstream and can provide results for heterogenous patient population, as opposed to a single clinical trial with a specific patient population and a limited follow-up period.

1.3 Significance

Though randomized controlled trials are a standard way for determining effectiveness and cost-effectiveness of clinical interventions, in medical decision making, it is important to take into account the factors influencing the natural history of disease, patient compliance, dose adjustments and clinical benefits and a single clinical trial does not take these into account. Mathematical models such as discrete event simulation model provide with a complete picture of the course of treatment, natural history of the disease and downstream consequences of the treatment alternatives for heterogenous group of patients and hence help in making intelligent decisions on treatment alternatives. Additionally, mathematical models can simulate disease history of a large patient cohort within a matter of few minutes as opposed to clinical trials and

can extrapolate the results to determine long-term outcomes which otherwise is rarely feasible with clinical trials. Moreover, mathematical models deal with uncertainty in model parameters such as event probabilities and costs, by means of sensitivity analysis and can provide decisions for an individual patient based on his risk level for a particular event.

This study would provide a risk benefit analysis for different steroid withdrawal regimens and hence provide an insight on an optimal time to withdraw steroids from an immunosuppressive regimen. By using discrete event simulation to determine the effectiveness of different steroid regimen, the results of the study would help in providing an optimal decision in choosing between the steroid sparing regimen and steroid maintenance regimens for individual kidney transplant patients with different risk levels, by taking into account his risk for graft loss and that for cardiovascular diseases associated with steroids. By having an insight for the long-term outcomes of patients with different risk levels, clinical decision makers will be able to provide a patient tailored immunosuppressive therapy that would have a comparatively reduced risk of long-term acute rejection, graft loss, and hence of dialysis or re-transplantation, of cardiovascular diseases and cardiovascular events such as stroke and myocardial infarction as well as of death. The decision makers will hence be able to have a better prognosis for an individual patient with a particular risk. The model, in future, would also have capabilities of analyzing a cohort of heterogenous patient with kidney transplantation for long-term effectiveness as well as cost-effectiveness of the steroid sparing versus steroid maintenance regimens, necessary for clinical decision making as well as for long-term resource planning.

1.4 Innovation

The trials that exist in the literature on steroid sparing versus steroid maintenance regimen in patients with kidney transplantation have a short follow-up period of less than 5 years. Trials on cyclosporine containing regimen have shown a significant difference in acute rejection and in total cholesterol levels with steroid-maintenance regimen having a protective effect on graft function and a negative effect on serum cholesterol; while trials on tacrolimus containing regimen have shown no significant differences in acute rejection and a significant difference in total cholesterol levels with steroid sparing versus steroid maintenance regimens.[10,11] The trials, as discussed in section 1.1, are of steroid sparing regimens that withdrawal steroids at either 1-day, within 7-days, within 3-6 months, within 1 year post kidney transplantation or any time after 1 year post kidney transplantation. Again, as discussed in section 1.1, the trials are of small sample sizes and do not have significant differences in outcomes and hence the optimal time of steroid withdrawal remains inconclusive.[3] Since the trials are of a short term duration, the effect of steroid withdrawal and of acute rejection on long-term graft function remains unknown. Also, are not known, the long-term cardiovascular outcomes such as stroke and myocardial infarction that occur with or without progression of cardiovascular diseases such as hypertension and hypercholesterolemia as well as of diabetes, due to the negative effect of steroids on glucose metabolism and cardiovascular risk profile. Patients with kidney transplantation with a cardiovascular disease or diabetes are at a higher risk of stroke and myocardial infarction compared to patients with a cardiovascular disease and without chronic kidney disease or without a kidney transplantation. A 10 year follow-up study by Oliveras et al. found that 10% of patients with diabetes nephropathy experienced a stroke in 10 years.

Lentine et al. found patients with new-onset diabetes mellitus post kidney transplantation were 1.6 times more likely to experience myocardial infarction at 3 years.[12]

Majority of the trials on steroid sparing and steroid maintenance regimen included low immunologic risk patients with mean HLA mismatches of approximately 2.5 and panel reactive antibody levels of between 20-50% and had a low sample size. Majority of the patients in most of these trials were Caucasian and very few were African-Americans and Hispanics, who are at a higher risk for both graft loss and cardiovascular diseases.[3,13] The trials also excluded patients with HIV disease and other severe conditions. In the real world, patients with kidney transplantation are heterogenous with respect to their immunologic and cardiovascular risk. Moreover, in clinical trials patients are treated in a controlled environment and hence have better outcomes compared to patients in the real world where they are non-adherent to the treatment and where practice patterns vary across different centers.

Mathematical models that synthesize information from various sources can take into account a heterogenous patient population with varying risks that exist in real world and can predict long term outcomes of a large cohort of patients in no time. Few mathematical models exist in literature that predict long-term outcomes post-kidney transplantation. These models are either cohort simulation models[14,15] that can analyze only a homogenous patient population with typical characteristics and cannot update the changing risks or individual simulation models[16] that are not detailed, do not take into account various immunologic and cardiovascular risks and do not predict cardiovascular outcomes.

The present study, using discrete event simulation modeling, predicts long-term outcomes post-kidney transplantation, including acute rejection (AR), graft loss (GL), malignancy, bacterial infection (BI), cytomegalovirus infection (CMV), new-onset diabetes mellitus (NODM), stroke, and myocardial infarction (MI), fracture (FX), death due graft loss (D-GL), death due to cardiovascular diseases (D-Cardio) and death due to other reasons (D-Other). The study employs United States Renal Data System (USRDS) to determine risk estimates for various events in order to derive equations that predict long-term outcomes post kidney transplantation. The study takes into account a patient population with a variety of immunologic and cardiovascular risk factors, patient demographics and comorbidities that predict the outcomes. Since it uses a national disease registry, USRDS, to predict outcomes, it accounts for a large cohort of heterogenous patient population, patient non-adherence and variations in treatment protocols that exist in the real-world as compared to the clinical trials with limited patient population and strict treatment protocols. Being an individual simulation model, it takes into account the heterogenous baseline risks, complex pathways and the changing risks that a patient with kidney transplantation undergoes, thus providing a more natural disease progression scenario compared to the existing models which are either cohort simulation models[14,15] or individual simulation models[16] that do not take into account the varying risks and outcomes post kidney transplantation. Employing an individual simulation model, as much as it can predict the outcomes of a heterogenous patient population, the current study uses the model to predict the outcomes for patients with typical immunologic and cardiovascular risks, in order to be able to derive patient-tailored treatment decisions.

1.5 Objectives

The objective of the study was to determine the optimal steroid withdrawal strategy that minimizes the incidence of both graft loss as well as cardiovascular events, amongst the five tacrolimus-based regimens: 1) steroid avoidance, 2) 7-day steroid withdrawal, 3) 6 month steroid withdrawal, 4) 1 year steroid withdrawal, and 5) steroid maintenance using discrete event simulation model. Since approximately 90% of patients are now being treated with tacrolimus versus cyclosporine, we decided to conduct the analysis with patients who received tacrolimus at discharge.

Specific objectives of the study were to 1) develop and estimate time to event models for various events post kidney transplantation, 2) develop discrete event simulation model that simulates natural disease progression post kidney transplantation, 3)determine the optimal time of steroid withdrawal for patients commonly seen in practice, that is, for: White, 50-year-old male, with hyperlipidemia and hypertension, exposure to CMV pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor, HLA mismatch = 2, cold ischemic time between 12 and 24 hours, on a polyclonal antibody induction regimen, 4) to compare the results with an African-American patient and a patient with a history of cardiovascular disease.

2. LITERATURE REVIEW

In order to better understand the gaps in the existing literature on the post-kidney transplantation outcomes with steroid sparing and steroid maintenance regimens and the importance of this study, this section first briefly explains some key clinical features in patients with kidney transplantation, followed by a description of the existing clinical trials and their key clinical findings. This section then explains the need for a decision model apart from clinical trials and describes and compares the advantages and disadvantages of various decision modeling techniques and the limitations and points to consider in order to help choose an appropriate decision modeling technique that would suit a decision-makers need. It briefly describes why the modeling technique may not be an appropriate choice for kidney transplantation. It then describes the post-kidney transplantation models in literature and explains the need for a decision model apart from clinical trials. It further explains why we chose to develop a discrete event simulation model versus a Markov model to predict outcomes in kidney transplantation patients and then describes the uniqueness and significance of our model as compared to the existing models.

2.1 Chronic kidney disease and end-stage renal disease

Chronic kidney disease (CKD) is a condition in which kidneys fail to filter wastes and water from the body, leading to accumulation of fluids in the body. The build-up of wastes in the body leads to several complications such as cardiovascular disease, anemia, and bone disease.[17]

Approximately 10% of people aged 20 years or older, in the United States have CKD.[1] Diabetes is one of the most common causes of CKD, followed by high blood pressure.[1] Other risk factors for CKD include obesity, smoking and an older age.[18] Often CKD progresses slowly over years and leads to *end-stage renal disease* (ESRD), complete kidney failure, requiring *dialysis or kidney transplantation* for patient survival. According to USRDS, the incidence of ESRD was 113,636 in 2009, suggesting a rise of 3.3% since 2000, while the incidence rate of ESRD per million population has remained relatively stable at 1.1% since 2000. Number of new ESRD cases has risen in the age group of 45-64 years while it has declined in the age group of 65 years and older.[4]

2.2 Kidney transplantation:

Kidney transplantation is the transplantation of a donor kidney into a patient with ESRD. It is the treatment of choice for patients with ESRD. Clinical focus has shifted to kidney transplantation from dialysis. Patients with kidney transplantation live longer and have a significantly improved quality of life as compared to those on dialysis.[19] The 5-year survival rate of transplant patients has been found to be twice that of patients on dialysis.[20] (NIH). Moreover, the costs of kidney transplantation and medical care post-transplantation are also substantially lower compared to dialysis. The annual costs associated with hemodialysis are thrice that for kidney transplantation (NIH). [20]

According to the United Network of Organ Sharing (UNOS), 93,000 patients with ESRD are on the waiting list for kidney transplantation in the United States.[21] According to USRDS, in 2009, 17,736 patients underwent kidney transplantation.

2.2.1 Graft Rejection:

The kidney transplant recipient patient's immune system recognizes the donor kidney as a foreign body and tries to reject the transplanted kidney, termed as rejection. Rejection can be acute or a more chronic process, both potentially resulting in damage to the kidney and decrease in the kidney function or even graft loss, even if treated. The degree and frequency of rejection depends on many factors including living versus deceased donor kidney and the degree of Human Lymphocyte Antigen (HLA) match between the donor and the recipient. In order to prevent transplant rejection, patients are maintained on immunosuppressive drugs.

2.3 Immunosuppressive Regimen:

The course of immunosuppressive therapy is divided in three phases: induction therapy, initial therapy and maintenance therapy. *Induction therapy* is a course of intensive immunosuppressive regimen for the first few days of kidney transplantation. The risk of graft rejection is the highest in the first seven days and induction therapy suppresses the recipient's immune system considerably in this period so as to prevent graft rejection. Induction therapy consists of medications such as a non-depleting IL-2 receptor antagonist such as basiliximab or a depleting antibody such as thymoglobulin. At the time of transplant, patients are also started on their *initial therapy* consisting of a calcineurin inhibitor such as cyclosporine or tacrolimus, an antiproliferative agent such as azathioprine or mycophenolate mofetil (MMF) and potentially a corticosteroid such as prednisone. A combination of these agents is also used for *maintenance therapy*. Another option for maintenance immunosuppression is sirolimus, a medication that targets the mammalian Target of Rapamycin. This medication often replaces the calcineurin

inhibitor in the regimen but cannot be started until at least three months after transplant secondary to its contributions to complications in wound healing.

Induction therapy is followed by initial therapy, which is a course of three to six months of rather high dose immunosuppression consisting of one or more types of the immunosuppressive agents except the induction agents. The degree of immunosuppression given to patients is still considerable for this period, since the risk of acute rejection remains high within the first three to six months post kidney transplantation.[22] The dose of the immunosuppressive regimen is tapered thereafter and this course of therapy is termed as maintenance regimen. The choice and dose of drugs in an immunosuppressive regimen are tailored according to a patient's immunologic risk of graft failure based upon many factors including the recipient-donor match and according to the patient's risk for side effects of immunosuppressive therapy. The goal of the therapy is to improve patient survival and graft survival.

2.4 Steroid withdrawal strategies and outcomes

Corticosteroids have long been used as potent immunosuppressants. However, chronic use of corticosteroids in the immunosuppressive regimen of kidney transplant recipients has been associated with a serious side effects profile due to their effects on lipid and glucose metabolism and blood pressure regulation.[23] Due to these effects, use of steroids leads to development or progression of cardiovascular risk factors such as hypertension and hyperlipidemia and to the development of new onset diabetes. These risk factors result in cardiovascular complications such as myocardial infarction and stroke, as well as allograft nephropathy, a major cause of graft

loss.[24] According to a registry analysis, death with a functioning graft accounted for more than 40% of graft losses and cardiovascular diseases were the leading cause of such deaths.[25] Steroids are also associated with other side effects such as infections, lymphoproliferative diseases, cataracts, osteoporosis and fractures. Morbidity and mortality as a result of steroids is a major cause of concern in kidney transplant patients. With the advent of new potent immunosuppressive drugs, attempts have been made to completely avoid or withdraw steroids from the immunosuppressive regimen to avoid the steroid-related side effects resulting from its long term use and to improve outcomes and patient safety. However, these attempts pose a risk for acute rejection due to decreased immunosuppression and hence result in graft loss or pose a risk for cardiovascular diseases due to replacement of the steroids with potent immunosuppressants in the regimen.

With the advent of cyclosporine, it became possible to reduce the dose of steroids for immunosuppression in order to prevent the side effects of steroids. Trials on cyclosporine based steroid withdrawal showed a reduction in the steroid-related side effects. However, this benefit was subdued due to the increased risk of acute rejection and graft failure due to withdrawal of steroids. In a 12 month follow-up study by Vanrenthengham and colleagues, patients in the cyclosporine based six month steroid withdrawal arm had significantly reduced serum cholesterol, triglycerides and systolic blood pressure ($p<0.001$). However, this benefit was offset by a significantly increased rate (23% vs 14%; $p=0.008$) of acute rejection compared to the steroid maintenance arm.[26] Another 12 month follow-up study by Hricik et al on a 3 month steroid withdrawal regimen also found significant difference in the cumulative incidence of acute rejection 1 year post transplant in the cyclosporine based 3 month steroid maintenance versus

withdrawal arm (9.8% vs 30.8%; p=0.0007).[27] Patients in the steroid withdrawal arm had a benefit of lower cholesterol levels (P = 0.0005), and a lower need for antihypertensives (P = 0.001). Again, a meta-analysis of 6 randomized controlled trials showed a significantly increased risk of acute rejection in patients in whom steroids were withdrawn at 3 months compared to those on maintenance (p<0.0001).[28]

The use of cyclosporine in the immunosuppressive regimen of kidney transplant patients has now been replaced significantly by tacrolimus, a more potent immunosuppressant. Several trials have studied the outcomes, such as acute rejection, graft loss, new onset diabetes mellitus, and hypertension and cholesterol levels, in tacrolimus-based steroid sparing regimens. Henceforth, the following several paragraphs are a discussion of tacrolimus-based steroid sparing trials.

Three studies with a follow-up period of 1 year, studied the outcomes of steroid withdrawal at 3 months, of which one was an open label trial and the other two compared the outcomes with the steroid maintenance arm.[29,30] These studies did not find a significant difference in the acute rejection or graft failure rates between the two groups, nor did they find any significant difference in cardiovascular outcomes, NODM and patient survival.

Again, studies[31,32] comparing early steroid withdrawal (7 day) with steroid maintenance and following patients for 1 year, also did not find significant differences in acute rejection and graft failure rates; even when the study population consisted of high immunologic risk patients, albeit, more African Americans and more patients with a higher degree of HLA mismatching. Additionally, these studies also did not find any statistically significant differences in the

cardiovascular risk profile, except in total cholesterol. Interestingly, Woodle et al, found a significantly lower mean total cholesterol in the steroid withdrawal arm, which the authors attributed to high tacrolimus trough levels. Laftavi et al, did not find any significant differences in the same owing to liberal use of statins and intensive medical management of the study patients. Of interest, these authors performed protocol biopsies and studied allograft fibrosis, an indicator of long term graft function. Patients in the steroid withdrawal group, over time, had a higher incidence of allograft fibrosis ($p<0.001$); a finding that favors steroid maintenance regimen, for its protective effect towards graft function.

Corticosteroids are known to have pharmacokinetic and pharmacodynamic drug interaction with tacrolimus, raising the tacrolimus trough levels after steroid withdrawal. This effect is likely to affect the graft function, as shown, in a 5 year large multicenter prospective trial, by a comparatively higher serum creatinine level and a lower creatinine clearance rate at 5 years, in the 7 day steroid withdrawal group compared to steroid maintenance group, again favoring the steroid maintenance regimen for its protective effect on graft function.[33]

While 3 month or 7 day steroid withdrawal trials did not show any significant differences in the AR rates, steroid avoidance trials have shown conflicting results. Helden et al[34], Rostaing et al[35] , Mysore et al[36] and Cantorvich et al[37] did not find any significant differences in the acute rejection rates at 1 year. Vitko et al[38] and Kramer et al[13], showed a statistically significant difference in the rates of acute rejection at 6 month or 1 year.

The trials that exist to date on tacrolimus-based steroid sparing versus steroid maintenance regimen are short term of a follow-up period of no more than 5 years. The trials have not found a significant difference in graft loss for steroid sparing and steroid maintenance regimen. The results on acute rejection and cardiovascular outcomes are conflicting, with majority of trials showing no statistically significant difference between the two types of regimen, except for steroid avoidance. The optimal time of steroid withdrawal also remains unknown. Since the trials are not long-term, the effects of the regimen on long-term outcomes such as stroke, myocardial infarction, deaths due to cardiovascular disease and graft loss are not known. A steroid withdrawal regimen which appears beneficial during the first few years may become detrimental later, in terms of cardiovascular as well as kidney function outcomes. Moreover, the sample size in these trials was low and the patient population in majority of the trials had low immunologic risk. It is important to determine the effects of the regimen on different patient populations in order to obtain some insights on patient tailored therapy.

2.5 Decision Modeling

Decision modeling is a technique that allows one to compare several options by taking into account several details which are displayed graphically and incorporated into calculations, thus facilitating complex decision making.[39]

2.5.1 Why decision modeling:

Randomized controlled trials are a standard way of determining which of the available strategies is the most effective, safer and less costly. Being experimental studies, the trials possess strong

internal validity. However, randomized controlled trials are performed in a controlled environment, ensuring patient compliance and safety and with predefined treatment protocols and in a limited small size sample of patients. Because of ethical reasons and exclusion criteria, the trials omit certain groups of patients.[40] These are costly to perform and require patients to be followed for a long period of time. In the real world, practice patterns and treatment decisions vary, patients are non-compliant, and the disease population consists of highly heterogenous groups of patients. Also, many trials are performed against placebo, hence not knowing the efficacy and safety of one drug compared to the other.[41] Hence, for knowing the effectiveness of drugs in the real world and for decisions to be made in the real world, clinical trials are not sufficient.

Models such as discrete event simulation models or Markov models synthesize information and the best available evidence from multiple sources and provide with a real-world picture of the course of treatment, natural history of the disease and downstream consequences of the treatment alternatives and hence help in making informed decisions on treatment alternatives. The stronger the data and modeling inputs, the stronger are the modeling results. They can be used to answer questions about sub-populations who cannot be enrolled in the trials due to ethical reasons –such as patients with severe health conditions and patients at high risk of adverse events.[40,42] Additionally, such models can simulate disease history of a large patient cohort within a matter of a few minutes as opposed to clinical trials.

2.5.2 Comparison of decision modeling techniques in health care and recommendations for choosing an appropriate technique

Patients experience a variety of events post-kidney transplantation based on their immunologic and cardiovascular risks as well as on their demographic characteristics. These risks change as patients experiences the events and as time progresses. A decision model that can predict the long-term outcomes in patient with kidney transplantation patients, while taking into account the baseline risks as well as the risks that change over time is needed to determine the optimal steroid withdrawal strategy.

Several types of decision models are used in medical decision making. The choice of a model depends on the research question, the purpose of the research question and tradeoff between level of model accuracy and model complexity and run time. This section briefly describes and compares the commonly used decision modeling techniques in health care and literature-based recommendations for choosing an appropriate model. The section is then followed by the post kidney transplantation models that exist in literature and an explanation on choosing discrete event simulation to model post kidney transplantation outcomes.

2.5.2.1 Simple Decision Modeling:

A simple decision model in general consists of a decision tree composed of branches and nodes. Branches in the decision tree lead to the options that need to be compared and to the outcomes following those options. The nodes in a decision model are either choice nodes, chance nodes or terminal nodes. Choice nodes branch out to options that need to be compared. Chance nodes branch out to probable events that occur with the options. Terminal nodes represent the final outcome of interest or a censoring event like death or an absorbing state following which a

patient/entity is no longer evaluated. The choice nodes are assigned a probability and costs of an event and/or a quality adjusted life years (QALY) value for an event. A simple decision tree cannot be used to model chronic conditions or conditions where time sequence of time of events is important, since it does not incorporate time at which the events occur. In kidney transplantation, risks of events change with time, such as the risk of acute rejection is the highest in the first three months and the risk of graft loss increases as time progresses. Dialysis cannot occur without a graft loss and acute rejection cannot occur following a graft loss. Hence, a simple decision tree is not a good choice to model outcomes post kidney transplantation.

2.5.2.2 Markov Modeling:

Unlike simple decision models that do not factor in the time at which an event occurs or the sequence of the events, in Markov models, it is possible to follow patients over a long period of time. In Markov models, a cohort of patients is followed at fixed intervals of time, called a cycle and different proportions of patients in a cohort are transitioned to different states within a cycle, for several cycles, based on transition probabilities. For example, some patients transition from being well to sick, some patients transition from being sick to dead and some patients remain well at one month of follow-up.

In the next month, again, some of the patients in the sick state transition to the well state some die while some remain sick. Those in the well state either become sick, die, or remain well. At each month, each of the health states is assigned a utility value and/or associated costs and the proportion of patients in the health states in a month is multiplied by the respective utility values. The summation of the resulting values is called a cycle sum. The cycle sums for all the cycles are added to give a cumulative utility over time. The model is run for several months until all

patients die or until a certain percentage of patients die, as relevant to the clinical question. A Markov model with fixed transition probabilities at each cycle is called a Markov chain while a Markov model that has different transition probabilities at different cycles is called a Markov process. The cycle length in a Markov model is determined based on the disease in question and the likelihood of an event within a time interval.

Markov models are useful when there is a continuous risk over time, when events can be repetitive as well as when the risk of events is time-dependent or when the time at which an event occurs is uncertain.[43]

Markov models, due to their being cohort simulation models instead of individual simulation models, are limited by the assumptions with respect to state, time and memory. Within each cycle that consists of fixed time intervals, patients can transition to only one of the several possible states, irrespective of their characteristics. Future states are not dependent on past history, since the past states are 'forgotten'. Hence, patients would be modeled as having the same likelihood of experiencing a state, irrespective of the past states or the time duration of the past states. To overcome this, tunnel states are structured in the model. With the tunnel states method, each of the health states that the patient experiences are modeled separately based on a set of patient characteristics, such as elderly patients are modeled to experience an increased risk of heart failure, while a younger age group is modeled to experience a comparatively lower risk for heart failure, or different time durations of past states are structured separately and modeled explicitly to predict future events, such as elderly patients are modeled to experience heart failure earlier and risk of death resulting from it higher and earlier, compared to younger patients who are

modeled to experience heart failure later and risk of death resulting from it lower and later. However, this leads to large number of permutations of different health states and transitions and makes the model enormously complex.[44] To avoid this, model is simplified and only specific health states and transitions of interest are modeled. As a result, disease progression cannot be accurately represented due to such simplifying assumptions.

Since the transitions in a Markov model, from one state to another, occur only at the end of the cycle, the time at which a patient transitions to a state would be over-estimated. (In studies where a cost-utility analysis need so be performed, it would overestimate the utility (QALY) values. Half-cycle correction is applied to the calculation of utilities in order to avoid this. Though this method tries to encounter the limitation of over-estimated utility values, it does not give an accurate representation of utilities over time).

Patient population in a Markov model is assumed to be homogenous and hence all patients in the cohort are modeled as having similar risks. The aggregate outcomes with this cohort approach are biased, since in reality patients in a disease population are not homogenous and their characteristics are not normally distributed to be able to produce accurate mean outcomes.

Markov models do not take into account the changes in the distribution of patient characteristics over time that result from high risk patients moving to a state earlier than the lower risk patients, termed in epidemiology as 'depletion of susceptibles'[45,46]- again due to the assumption of homogenous population transitioning to different states. This results in inaccurate calculation of utilities that accumulate over time.

Again, since patients can only be in one of the several possible states at a time, patients who die first do not experience certain states, hence underrepresenting the proportion of patients experiencing those states.[40,45,47]

Patients with kidney transplantation represent a heterogenous population with a varying immunologic and cardiovascular risks and events that occur during the course of a patient's life depend on these risks as well as on events that occur in the past. Such as a patient with a higher number of HLA mismatches or an African-American patient is at a high risk for acute rejection compared to patients with lower number of HLA mismatches or Caucasian patients. A patient who experiences an acute rejection is at a high risk for a graft loss, a patient who develops new-onset diabetes mellitus is at a high risk for myocardial infarction and a patient with new-onset diabetes mellitus and Hispanic descent is at a lower risk for myocardial infarction.[12] Building a Markov model would require explosively large number of tunnel states in order to account for all individual risks at baseline and all the risks that change with the occurrence of events. A detailed explanation of why Marko modeling is not an appropriate decision modeling technique to model outcomes following kidney transplantation is given in section 2.6.2.1

Markov models can evaluate a cohort of large number of patients or simulate individual patients in a cohort several times; the latter called as a Monte Carlo simulation.

2.5.2.3 Monte Carlo Simulation:

While a Markov model is a cohort simulation model, Monte Carlo is an individual sampling model. An individual in a Monte Carlo simulation model, takes pathways in the model based on random draws at each chance nodes. One patient is sent at a time through the model. At each cycle, the patient may undergo a state transition. Based on various risk factors, a vector of transition probabilities is produced. A random number between 0 and 1 is then generated to determine the state to which the patient will transition to next. The model is run for a large number of patients in order to decrease variance around outcomes.[40,48] However, Monte Carlo simulation does not model time at which the events occur and hence is not suitable when risks change with time, such as that in kidney transplantation.

2.5.2.4 Discrete Event Simulation:

Like Monte Carlo simulation model, discrete event simulation is also an individual sampling model, however, in DES, time progresses on its own via a simulation clock and patients experience events at discrete points in time based on a random draw. It is the most flexible among the existing modeling techniques, in that, it takes into account patient characteristics and past history of the patients. All the limitations of a Markov model previously mentioned are avoided in a DES model. Patients undergo events based on their characteristics, which can be updated over time as they change or upon occurrence of an event. With the change in the characteristics, the risk for the events is again calculated accordingly. Patients can have multiple risks at a time and the events associated with these risks occur in ascending order of time. Hence competing risks can be accounted for correctly rather than avoiding certain risks for certain patients as in a Markov model. Risks that change over time or with the duration of a particular health state can also be taken into account in a DES, with simple programming steps. Also, due to random

sampling of patients for different events, it takes into account the heterogeneity of patients, disease progression and treatment decisions that exist in real world, which is not possible with deterministic models, such as Markov model and simple decision tree.[45] Hence, a discrete event simulation model can closely represent naturally disease progression in kidney transplant patients who possess a variety of risks and whose risks change with time and with occurrence of events. A detailed explanation on the decision to choose a discrete event simulation to model post kidney transplantation outcomes is given in section 2.6.2

A detailed description of the DES methodology is described in section 2.7.

2.5.2.5 Agent based modeling:

Agent-based modeling permits interaction of the patients with each other or with the environment based on decision rules. It has been used to examine to epidemiological questions such as the spread of HIV in certain populations. By such modeling, one is able to understand the role of environment in the interactions of patients and the emergence of complex behaviors from simple behaviors. In agent based modeling, agents have the autonomy to behave in a certain way whereas in DES, patient's behavior is based on their characteristics.[40] An agent based modeling is not suitable to model kidney transplantation outcomes, since in kidney transplantation, patients undergo events based on their characteristics.

2.5.3 When to choose a particular decision modeling technique

Simple decision trees and cohort models have several assumptions which need to be taken into consideration when interpreting the results from these for policy making. These models are simpler to develop and understand compared to individual sampling models and have been the mainstay for decision modeling. Individual sampling models are emerging in the field of health of healthcare due to flexibility of model structuring without any limiting assumptions. However, these models require a lot of effort and are complex to perform and understand and hence have been stunted from gaining popularity.

Choosing an appropriate model is very important in order to be able to make accurate decisions and avoid wasting of resources and compromising patients' wellbeing from incorrect decisions.[49] Few papers have given recommendations in choosing an appropriate model. This section provides a summary of those guidelines.

One must consider the assumptions that each of the models have in order to choose an appropriate model for a given question. The decision must be based on the assessment of whether the outcomes are time-dependent, whether interactions are required, whether there is uncertainty around variables, whether cohort level answers or individual patient level answers are required and how many subgroups need to be assessed.

Some authors have suggested using a simpler easy to understand models that describe the disease adequately.[50,51] However, when inaccuracies or limitations in the models or limited ability to mimic real world scenario are likely to affect the decisions, choice should be made for a complex model. [49]

When the outcome of interest occurs in a short period of time, a simple decision tree maybe a good fit. However, when it is important to include repetitive events or when the disease of interest involves a chronic condition, when the duration of event is important in calculating costs/disease severity or when time sequence of events is important, a simple decision tree is not useful, since the cost of repetitive events or the events that follow or complications that occur or risks that change as time passes will not be included, resulting in under-representation of the disease and its severity and the total costs and/or disease free survival time of a strategy. Simple decision trees can only branch out events that can occur without considering the timing at which the events occur. In patients with kidney transplantation, risks of complications such as acute rejection and graft loss as well as side effects of medications such as infections, cardiovascular diseases and malignancies remain throughout the patients' lifetime. Events such as acute rejection, stroke, infections and fractures can occur more than once. The risk of rejection is highest initially and decreases as time progresses. Patients who experience acute rejection are at a higher risk for graft loss to occur earlier compared to those who do not. Hence, a simple decision tree is not suitable to model kidney transplantation patients.

When a model requires interaction of patients with each other or with the environment, such as a model involving a spread of infectious disease or waiting in emergency department, a discrete event simulation or agent-based modeling are appropriate models. Such interactions are not possible to be modeled with cohort simulation models.[49] A disease progression model in kidney transplantation does not require patient interaction with the environment. If we were to model

the waiting time for a retransplant and its impact on cardiovascular outcomes, a discrete event simulation model that incorporates resource constraints would be an appropriate fit.

Cohort simulation models are deterministic models that do not use randomness and so are not appropriate when there is variability or uncertainty in variables, since the mean outcome measure may not be accurate due to higher standard deviations. Again in such cases, individual sampling models such as discrete event simulation or agent based models should be used. Markov cohort models give aggregate/mean outcomes of the entire population, instead of mean outcomes resulting from mean measures obtained from several individual patients runs for all patients in a heterogenous patient population (as in case of DES) and hence should be avoided when the patient population has varying risks of events, as in patients with,[49] as in patients with kidney transplantation.

In cases where patient characteristics affect the outcomes of interest linearly, a semi-Markov model maybe used – such as when age linearly affects the outcome of interest. When patient characteristics are non-linearly related to the outcomes of interest, an individual sampling model should be used. [40] The outcomes in kidney transplantation are dependent on characteristics that are either linearly related such as risk of myocardial infarction increases linearly with age and duration of diabetes or on characteristics that are non-linearly related such as patients with Hispanic ethnicity are at an increased risk of diabetes compared to patients with non-Hispanic ethnicity[12] and patients experiencing an acute rejection earlier are at an increased risk of graft failure compared to patients experiencing an acute rejection later.[52]

In situations where decisions need to be made regarding resource constraints and considerable variability is expected in time to events, such as arrival of patients at variable times and formation of queues in emergency departments, individual sampling models need to be considered. When it is important to study the optimal allocation resources, such as planning the placement of controlled drug dispensing units, patient bedside units, intensive care unit rooms and emergency operating rooms in a hospital, a discrete event simulation model or agent based simulation model come as useful tools. [49]

When a model needs to be used for long term so as to adapt it to newer strategies or when a model needs to be adapted for similar disease but for different population, a discrete event simulation model gives flexibility to do so and should be used for such projects. If the model is only for one time use, then a simpler less complex and transparent model is recommended. According to Karnon et al (1998)[44], one must ensure that the conclusions are not affected by any bias that is caused by avoiding the details and complexity of the problem by using a simpler model. When the research question involves cost-effectiveness comparison between two alternatives and when the interest is more on the cost of introducing an alternative, an error of 20% in the calculation of costs would not make any impact in decision making, as long as the cost remains less than $50,000 per QALY, the threshold for an alternative to be considered cost-effective.[47] On the other hand, when the research question involves cost accumulated over time and when the time and costs spent in a health state varies between high and low risk patients, an error in the calculation of costs can change the decision with respect to the costlier alternative.

Individual sampling models need several replications of patients in order to get estimates of mean measures with low variability. This takes a large amount of time when the population to be modeled is large and even a longer time when performing probabilistic sensitivity analysis. This is because the model samples time for each individual's transitions and maintains a list of future events in ascending order. With variance reduction techniques, as described in section 2.7.4, the run time can be decreased to some extent. A Markov cohort model is a possibility in cases where the population is large and when the past events and patient characteristics do not affect future events or when these are linearly related as well as when no interactions are involved in the model.

Cooper et al[47], in 2005, compared the development and run time for different types of models. They found that when the number of states was small, a simple decision tree was quickest to build. The time to develop a Markov model and discrete event simulation model with small number of states was similar and no differences in the output were found between the two models; however discrete event simulation model took longer time to run compared to Markov model. When the number of states was large, it was easier to incorporate the complexity of using a discrete event simulation model compared to a Markov model. Upon reviewing models for coronary heart disease interventions, the authors concluded that when the number of states are more than 35 and number of transitions of interest are more than 140, a discrete event simulation model should be used.

An explanation of using discrete event simulation model versus a Markov model for modeling outcomes post kidney transplantation is given in section 2.6.2.1

2.6 Discrete Event Simulation to Evaluate Post Kidney Transplant Outcomes

2.6.1 Post Kidney Transplantation models in literature

To date, three pharmacoeconomic models comparing treatment alternatives post kidney transplantation exist in literature.

McEvan et al[15] (2005), compared the cost-effectiveness of cyclosporine and sirolimus post kidney transplantation in the United Kingdom. The authors conducted a discrete event simulation with acute rejection, graft failure and dialysis as the health states/events. Using registry data of 937 patients, monthly transition probabilities were obtained from a Cox proportional hazard regression. Data about patient characteristics and the hazard ratios for these were also obtained using the registry data. The authors conducted a similar study to compare the cost-effectiveness of tacrolimus and sirolimus.

Morton et al[14] (2009) developed a Markov model to compare the cost-effectiveness of antibody induction versus interleukin 2 receptor antagonist. Acute rejection, graft failure, malignancy, recurrence of primary disease and death were the health states of the model. In order to account for the time dependent rates of acute rejection, graft failure and malignancy, the authors embedded in the model, three categories of these health states – health states at 1 year, at 2 year and after 2 years. The time horizon for the model to run was 20 years. Transition probabilities were obtained from a meta-analysis of 38 randomized control trials on induction agents.

Earnshaw et al[16] (2008) compared the cost-effectiveness of sirolimus based calcineurin inhibitor (CNI) withdrawal regimen versus calcineurin inhibitor containing maintenance regimen. The cost-effectiveness model consisted of two parts: 1) A decision tree reflecting the treatment management of patients during the first year, including the treatment management for acute rejection. 2) A Markov model with health states of acute rejection, 1 year serum creatinine level, graft failure, dialysis, transplant, diabetes, statin use and death, with a time horizon of 5 years. Serum creatinine level was used to predict graft survival. Data were obtained from clinical trials.

The models by Morton et al. and Mc Ewan et al. do not take into account the varying immunologic and cardiovascular risks among patients with kidney transplantation. These models, being Markov models, do not update risks when a patient experiences an event. Patients in the model experience events like acute rejection and graft loss, independent of their characteristics and independent of the past events and hence do not adequately represent natural disease progression in kidney transplantation. The models also do not represent several other events that occur following kidney transplantation as a result of patient's inherent characteristics, due to the inherent risk of rejection as well as due to side effects of the immunosuppressive regimens. Due to fixed cycle lengths employed in the models, the duration and time to events is over-estimated and so the disease free survival is under-estimated.

The discrete event simulation model for kidney transplantation developed by Earnshaw et al. to compare the CNI withdrawal versus maintenance regimen, does not model post-transplantation events such as stroke, myocardial infarction and deaths due to cardiovascular diseases. Kidney

transplantation patients are at an increased risk of these life-threatening events compared to the general population. It is important to model these events post kidney transplantation to obtain an appropriate tradeoff between immunosuppressive regimens. Also, the model by Earnshaw et al. uses non-parametric regressions to obtain risk estimates and hence does not incorporate randomness and uncertainty due to heterogenous patient population.

2.6.2 Why Discrete Event Simulation for Post Kidney Transplant Outcomes/Innovation

Clinical trials assessing the safety and efficacy of post kidney transplant regimen are either performed on low immunologic population, have short duration of follow-up, follow a strict treatment regimen which is variable in real-world practice (treatment patterns vary in real-world from region to region while the treatment regimen in clinical trials is followed strictly according to protocol and patient adherence rates are high) and/or have a small sample size. In the real world, patients with kidney transplantation have heterogenous characteristics with variable risks and treatment and disease management patterns are different. An immunosuppressive regimen that seems effective for the first few years' post-kidney transplantation can be less effective or detrimental due to continued risk for graft loss and worsening of cardiovascular diseases. Hence, a model that can 1) answer questions for a patient population with heterogenous risks, 2) incorporate disease management decisions and 3) estimate long-term outcomes in an accurate manner so as to avoid unforeseen consequences in the future is needed.

2.6.2.1 Decision to use Discrete Event Simulation Model versus Markov Model for Post Kidney Transplantation Outcomes

Patients with kidney transplantation are a heterogeneous group of patients that has variable risks for acute rejection, graft loss, infection, cardiovascular outcomes and death. Patient characteristics such as HLA mismatch, living/deceased donor, race, sex and age affect the graft function while a history of cardiovascular disease can lead to cardiovascular events such as stroke and myocardial infarction. Also, patients on different maintenance immunosuppressive regimen, develop variable degrees of risk for worsening of an existing cardiovascular disease, developing new onset diabetes, acute rejection and infections. These events can further increase the risk for cardiovascular events such as stroke and MI and infections, graft loss and patient death. Also, the risk of cardiovascular events and patient death increases with the duration of time the patient has had a cardiovascular disease. Moreover, certain events such as stroke, myocardial infarction and acute rejection can occur repeatedly and increase the risk each time they occur. Treatment and management of these events/diseases can further change the risks.

Markov models for kidney transplantation that exist in literature are not an appropriate choice to model post kidney transplantation patients because of the following reasons 1) Post kidney transplant patient population is extremely heterogenous with respect to charcteristics that have variable risks. 2) Future events depend on patient characteristics, events and disease/event management that occur downstream and duration of time a patient is in a particular health state. 3) Because of fixed cycle lengths, the duration of time for which a patient has cardiovascular disease and the time at which a patient had acute rejection, will be erroreneous, both of which are important risk factors for transplant outcomes. 4) A level of detailing is important to incorporate the variable risks and disease/event management downstream because of the huge impact they have on the outcomes. Avoiding such details will lead to inaccurate mean measures

and hence wrong decisions with respect to treatment alternatives. 5) A Markov model that incorporates such details with tunnel states will be explosive and nearly impossible to build.

Immunologic and cardiovascular characteristics of patients largely determine the health outcomes of patients with kidney transplantation. Also, the time at which acute rejection occurs is important in predicting graft loss and hence the length of dialysis free survival. Cardiovascular diseases can accumulate a large amount of costs and diminished quality of life over time and affect the length of patient survival. Hence, it is important to not avoid all these details and level of accuracy, as doing this can lead to largely inaccurate measures of costs, quality of life and patient survival. With discrete event simulation model, it is easier to build and represent an accurate and detailed disease course over time that a simple decision tree or a Markov model cannot. It is possible to simulate the kidney transplant patients individually and hence keep track of the events that the patients undergo and the time at which these occur, update the risks and transition patients to future events based on these risks. Since events occur at discrete points in time, it can capture the time at which the events occur accurately. The analysis required to capture all the details can be done with time to event regressions using registry database that follows patients over time and contains information on patient attributes, outcomes as well as time at which outcomes occur. Hence, a true picture of the disease course of kidney transplant patients can be represented easily and accurately. Also, the variability and uncertainty around treatment management and disease course that exists in real world for kidney transplant patients is accounted by discrete event simulation modeling, due to its stochastic nature.

For the above same reasons, a Monte-Carlo simulation model and an Agent-based model are not an appropriate choice to model post kidney transplantation outcomes.

With a discrete event simulation model, this study models and predicts several outcomes that occur at different points in time, in 20 years post-kidney transplantation, such as acute rejection, graft loss, stroke, myocardial infarction, death due to cardiovascular diseases, death due to graft loss, death due to other reasons, bacterial infections, cytomegalovirus infection, fractures and cancer and incorporates a variety of risk factors including immunologic risk, comorbidities and patient demographics, thus allowing the patient to follow complex pathways and updating risks upon occurrence of events, as in real-world situation. It uses parametric regressions to model these events using data from USRDS and obtains predictive equations of time to event, based on probability distributions, thus accounting for randomness and hence patient uncertainty that exists in the real world. Due to the above mentioned reasons, the model thus, as opposed to the existing models, mimics real world natural disease progression of patients with kidney transplantation, which is necessary to make important real-world treatment decisions to obtain the best outcomes 20 years post kidney transplantation.

2.7 DES Methodology

Discrete event simulation has long been used for operations research to analyze, design and improve systems and processes such as delivery of prompt services to patients in hospital, minimizing queues at airport and process flow in a manufacturing industry. Later, it started being used in the health care to design patient flow in clinics, hospitals/emergency departments, to design clinical trials and to study epidemics.[4,8,53] More recently, it is being used to simulate

disease progression to compare treatment alternatives. The DES methodology here describes that used for healthcare models that simulate disease progression.

2.7.1 Model Structure

A DES model structure represents the pathways that a patient goes through. The pathways consist of events, activities that patients experience and/or resources that patients consume or occupy. Often the model structure is developed based on expert opinions either through surveys[41] or through personal interviews about health states that patients experience in a particular disease with a particular treatment alternative, treatment algorithms and/or referrals or resources used by patients. Treatment algorithms may also be derived from patient records.

Basically, a discrete event simulation model consists of entities, attributes, variables, events, activities, resource and time, each of which is described below[40,54,55].

2.7.1.1 Entities:

Entities represent units that are to be simulated. These are mobile units that move in the model, interact with each other, interact with the environment and have individual characteristics that can change over time. In a healthcare model, these generally represent patients and sometimes physician's or caregiver's of patients. In a disease progression model, a cohort of patients is created in the beginning of simulation model while in healthcare model that studies epidemics or hospital organization, patients enter the model at any time when triggered. In our model, entities are patients with kidney transplantation that have individual characteristics, some of which, change over time.

2.7.1.2 Attributes:

Each entity has a set of attributes. Examples include demographic characteristics such as age, race and sex, comorbidities, etc. The attributes possess values that are assigned to the entities to create a unique entity. Such as a 51 year old, African American male with diabetes creates a unique patient. Attributes can change anytime whenever triggered. For instance, age changes as time advances in the model. The attributes determine the fate of entities in the model. Presence of atrial fibrillation and the duration of atrial fibrillation determine a patient's risk and time for heart failure. Time at which an event occurs can also be recorded as an attributed for an individual, in order to calculate costs and quality of life or to determine risk for future events.

2.7.1.3 Global variables:

Global variables in discrete event simulation model are characteristics of the environment (such as disease in a disease progression simulation model). Examples of global variable in a disease progression model include, a simulation clock or the time to various events. The variables are not characteristics that individualize the entities uniquely, but are common for all the entities and can be changed by individual entities depending upon their attributes.

Resources and queues are not used for disease progression model but are explained here solely for the purpose of explaining the features that help in modelling other types of healthcare models.

2.7.1.4 Resources:

Resources represent services to entities, such as a physician's office or a group hospital beds in a hospital. Entities compete with each for the resources. A physician's office is available to the

next patient only when a prior patient who arrived earlier leaves the office. When all the hospital beds are occupied, the waiting patient gets a bed when one of the beds is left vacant upon recovery of a patient. This makes it possible for the model to determine average waiting time. It is also possible to determine the average service times, such as time taken to transition patient from an outpatient clinic to an operating theater and the time taken for anesthesiologists to arrive at the operating theater from another ward, in emergencies.

2.7.1.5 Queues:

Queues in a discrete event simulation healthcare model represent patients waiting for a service. With a discrete event simulation analysis, efforts are made to minimize such queues by designing the hospital organization and flow of services in a manner so as to provide prompt services to the patients.

2.7.1.6 Events:

Events are things that happen to the entities or environment at a point in time. In a disease progression model, this could be occurrence of heart failure to a patient, hospital admission of a patient with diabetes or change in drug treatment for a patient experiencing side effect. In a model that studies hospital organization, this could be entry/exit of patient to/from an emergency room or transfer of patient from hospital to emergency department. Events that have some duration of time associated with them, such as hospital admission or transfer of a patient, are also referred to as activities. With the occurrence of events, attributes or variables may change. A list

of future events is maintained with information about the entity involved and the time of the event. This, in Arena is called event calendar.

2.7.1.7 Statistical Accumulators:

Statistical accumulators accumulate statistics, such as average service times, average time to events, number of events, etc. These are updated whenever something happens during the model run.

2.7.1.8 Simulation Clock:

The simulation clock is an in-built clock in the model and holds current time. It doesn't run continuously but the time jumps as and when the events occur. Hence, the name 'discrete'. The time in the clock moves forward at the scheduled event time, attributes and variables are updated and the time in the clock then moves forward to the next event time.

Information such as events or points in time when a treatment decision needs to be made, when patient attributes need to be updated and when certain future events should be blocked or resumed, should be coded in the model structure. This also applies to continuous disease parameters such as serum creatinine levels post kidney transplantation or HbA1c levels in diabetes patients that change through a patient's disease course.

2.7.2 Input Data

For the DES model, one requires data about patient population, transition probabilities of events, time to events, duration of health states, costs and quality of life associated with the

health states and factors influencing these. These are obtained either from literature or from patient registries. When certain information cannot be obtained from these two sources, expert advice is solicited or certain sections of the model are omitted if these are not likely to affect the conclusions or are not very important in making decisions.

A Delphi Panel method should be used to elicit data from expert opinion. To ensure validity of data obtained through expert solicitation, one must derive answers for other relevant data and cross check the answers with empirical data.

2.7.3 Transitioning patients in the model:

Patients are transitioned in the model depending upon the time-dependent risks derived from predictive equations of their attributes. Whenever a patient experiences an event or undergoes a treatment, his attributes are updated and hence the risk of future events. Certain attributes may also be updated as time advances, if these change with time – such as HbA1c levels or total cholesterol levels.

2.7.3.1 Accelerated failure time model and interpretation of parameter estimates:

A stochastic discrete event simulation model that transitions patients randomly to events employs accelerated failure time model to develop predictive equations. Accelerated failure time models are used for survival data to predict time to event. These are parametric models, using which one can obtain precise estimates about future values based on a distribution of observations. Unlike the commonly used proportional hazards model, accelerated failure time models can quantify the improvement in time, in addition to determining the hazard ratios.

Meaning, according to the accelerated failure time model, $S_1(t)=S_2(ct)$[56] ; where S_1 is survival function with the first alternative and S_2 is the survival function with the second alternative and c is a constant. One survives c times longer with the first alternative compared to the second alternative.

Again, if μ_i is the population mean then,

$\mu_2= \int S_2(t)dt$

$= c\int S_2(c\mu)d\mu$ (c times mean time = total time, $t=c\mu$)

$= c\int S1(\mu)\, d\mu$

$= c\mu_1$

Hence the expected mean survival time with the second alternative is c times that of first alternative.

An accelerated failure time model for a subject 'i' is denoted by:

$\log(T_i) = \beta_0 + \beta_1 x_{i1} + \ldots\ldots + \beta_n x_{in} + \sigma\varepsilon_i$

where T_i is the survival time, β_0--β_n represent parameter estimates, x_{i1}-- x_{in} represent the covariates, σ is the shape parameter and ε_i is the random error term with distribution N(0,1)

2.7.3.2 Interpretation of accelerated failure time model estimates

Assuming that, a covariate x_k increases by one unit denoted by x_{k+1}, let the parameter estimates be represented by β_k and β_k+1 respectively. Then the corresponding survival times for the subject is given by[56]:

$T_1 = e^{\beta_0 + \beta_1 x_{i1} + \ldots + \beta_k x_k + \ldots\ldots + \beta_n x_{in} + \sigma\varepsilon_1}$

$T_2 = e^{\beta_0 + \beta_1 x_{i1} + \ldots + \beta_{k+1} x_{k+1} + \ldots\ldots + \beta_n x_{in} + \sigma\varepsilon_2}$

For the interpretation of β_k and β_k+1, assume that other covariates are fixed. Then this gives:

$T_1 = e^{\beta_k x_k} * e^{\sigma\varepsilon_1} = c_1 e^{\sigma\varepsilon_1}$

$T_2 = e^{\beta_{k+1} x_{k+1}} * e^{\sigma\varepsilon_1} = c_2 e^{\sigma\varepsilon_2}$; $e^{\beta_k x_k}$ and $e^{\beta_{k+1} x_{k+1}}$ are constants denoted by c_1 and c_2

Now,

$e^{\beta_{k+1} x_{k+1}} / e^{\beta_k x_k} = e^{\beta_k}$

Hence, $c_2/c_1 = e^{\beta_k}$ and $c_2 = c_1 e^{\beta_k}$

The survival distributions for the populations with the two covariates values x_k and x_{k+1} for variable β_k are given by:

$S_1(t) = P(T1 \geq t) = P(c_1 e^{\sigma\varepsilon_1} \geq t) = P(e^{\sigma\varepsilon_1} \geq c_1^{-1} t)$

$S2(t) = P(T2 \geq t) = P(c_2 e^{\sigma\varepsilon_2} \geq t) = P(e^{\sigma\varepsilon_2} \geq c_1^{-2} t)$

Multiplying t in the LHS and RHS with e^{β_k} in the survival function of the population with value of x_{k+1} for variable β_k gives:

$S_2(t) = P(e^{\sigma\varepsilon_2} \geq c_2^{-1} t)$

$S_2(e^{\beta_k} t) = P(e^{\sigma\varepsilon_2} \geq c_2^{-1} e^{\beta_k} t)$

$= P(e^{\sigma\varepsilon_2} \geq c_1^{-1} e^{\beta_k{}^{-1}} e^{\beta_k} t)$

$= P(e^{\sigma\varepsilon_2} \geq c_1^{-1} t) = (e^{\sigma\varepsilon} \geq c_1^{-1} t) = S_1(t)$

Hence, if μ_1 and μ_2 are average survival times for populations with covariate values of x_k and x_{k+1} respectively, then we have

$\mu_2 = e^{\beta_k} \mu_1$

μ_2-1 = e^{β_k} $\mu_1 - 1$

$\mu_2 - \mu_1 / \mu_1 = e^{\beta_k} - 1$ (divide both sides by μ_1)

If $\beta_k \rightarrow 0$ (i.e. β_k is very small) then $\mu_2 - \mu_1 / \mu_1 = \beta_k$ (exponential of a small number is equal to the number itself)

Hence the interpretation of βk is such that the relative increase in survival time for population with covariate value of x_{k+1} equals β_k compared to the survival time for population with covariate value of x_k. (Proc Lifereg function in SAS is used for accelerated failure time model. It models the survival time in logarithm form and hence the interpretation of estimates differs from that described above, depending upon whether βk<0 or β_k>0). In that, if β_k<0 then the relative decrease in survival time for population with covariate value of x_{k+1} equals β_k and vice versa for βk>0.

There exist several accelerated failure time models that have different parameters describing the shape of the distribution of survival time and random error terms. These are exponential, Weibull, gamma, log-normal and log-logistic. For the purpose of this dissertation, this section will give explanation for the Weibull distribution.

2.7.3.3 Weibull distribution

For $t > 0$, the probability density function is expressed as:

$$f(t) = \alpha \beta^{-\alpha} t^{\alpha-1} \exp(-(t/\beta)^{\alpha})$$

α is the shape parameter, which is the reciprocal of the scale parameter, obtained from proc lifereg function in SAS.

β is the scale parameter, given by $\beta=\exp(\beta_0 + \beta_1 x_{i1} + \ldots\ldots + \beta_n x_{in})$

Hazard function is given by:

$h(t) = \alpha\ \beta^{-\alpha}\ t^{\alpha-1}$

Survival function is given by:

$s(t) = \exp(-(t/\beta)^{\alpha}$

Cumulative density function is given by:

$c(t) = 1 - \exp(-(t/\beta)^{\alpha}$

2.7.3.4 Truncated Weibull distribution

After a patient has an event, the distribution of time to future events changes (and so do the α and β change), since time advances further and the risk changes due to the current event. To deal with this, a truncated Weibull distribution needs to be used. It is obtained through the following steps:

1) The probability p(a) of the current event 'a' at the current time 't', is calculated using the cumulative density function: $c(t) = 1 - \exp(-(t/\beta)^{\alpha}$.
2) A random number, x, is obtained from a uniform distribution between p(a) and 1.
3) A trunctated Weibull distribution is then obtained using the formula: $\beta*(\ln(1-x))^{1/\alpha}$. A new time is sampled for the next event from this distribution.

The time that is obtained from truncated Weibull represents the time passed after the patient enters the model. Hence the advancing of time to determine time from one event to the

next, needs to be adjusted according to the time at which event 'a' occurs. Subtracting the time that is sampled at current time from the current time would give the time to event from the current time.

2.7.3.5 Approaches for patient transition

A discrete event simulation model that studies disease progression employs either of the following four methods to transition patients from one event to the other, as described by Barton et al[41]:

a)Time-Slice Approach: The time the patient is on a treatment is divided into short intervals and during these intervals, the probability of occurrence of each of the events is calculated. Then a random number between 0 and 1 is drawn. The patient transitions to an event based on this random draw. Due to short intervals, the time to events obtained with this approach is shorter than actual time to event. This approach requires long running times, since random number needs to be drawn for each of the intervals for each patient.

b)Event-based transition approach: An overall probability of occurrence of an event is determined first. A random number between 0 and 1 is drawn and patient is transitioned to an event based on the drawn random number. Patient transitions at a time, sampled from the survival distribution of the chosen event. Since this approach takes into account overall probability of occurrence of events, it is not suitable when events depend on patient characteristics and past events.

c) Time-based transition approach: An overall survival curve is determined for each of the events. Then based on a random draw, a time is selected and a probability conditional on this time is determined for each of the events. Again, a random number is drawn between 0 and 1. Patient transitions to an event, based on this random number. Since this approach considers overall survival time for the events, it is not suitable when the survival times depend upon patient characteristics and patient history.

d) Minimum of the sampled times approach: A survival curve is estimated for each of the events. Times are sampled from the survival curves of these events and the minimum of these times is selected. Patient transitions to the event that corresponds the minimum time. With this method, individual survival curves for each patient are generated, hence taking into account patient characteristics and patient history. We used this approach to transition patients in our model.

We used the minimum of sampled times approach to transition individual patients to events.

2.7.4 Producing robust estimates/Variance reduction techniques

Since patients are transitioned randomly to the events, the estimates produced by the model are not robust, that is there is variance around the probability of event transitions. In order to produce estimates with low variance, the following methods may be used:

1) **Using optimal number of patients and replications of patients derived by using ANOVA based formula**

Suppose the population mean and standard deviation are μ and σ respectively. We desire a standard deviation of 'd'. Let $c_1 = d/\sigma$. Then coefficient of variation $c_2 = 2c_1$.[57] Let τ be variance obtained by running a single patient through the model. Let $k = 1/\tau^2$ σ^2. Let $M = 8k/c_2^2$.

Then number of patients required to obtain a desired standard deviation d is k+1 and number of replications is M/n.

2) **Creating identical sets of cohorts and separate streams of random numbers**

Identical patients having similar attributes are created for each alternatives to be compared. In order to minimize the variances created by random experience of different pathways by these patients, separate streams of common random numbers are created for different events.[55]

3) **Signaling to resynchronize the experience of pathways**

Even when patients among the cohorts to be compared are matched across their attributes and the effect of alternatives to be compared is constant, the patients are likely experience different events due to randomization. This leads to variance in the outcomes. To avoid this, when one patient in one cohort experiences an event, an

identical patient in the comparative cohort is signaled to experience the event but adjusted for the effect of the alternatives.[58]

If the time to event sampled for a patient i on strategy 1 is T_1 and if $\beta_1 x_{i1}$ is the treatment effect for strategy 1 and $\beta_1 x_{j1}$ is the treatment effect of for a patient j on strategy 2, then the adjusted time to event T_2 for patient j, given that the attributes of the patients i and j are the same, equals:

$T_2 = T_1 - \beta_1 x_{i1} + \beta_1 x_j$.

2.7.5 Sensitivity and Uncertainty Analysis

More often there exists uncertainty around model inputs. In order to quantify the impact of this uncertainty on model outcomes, The Panel on Cost-Effectiveness in Health and Medicine recommends performing sensitivity analysis.[59] By studying the impact of varying model inputs, one can determine the level of stability of an outcome and hence be cautious in deriving conclusion. Also, with sensitivity analysis, one can instigate research on reducing the variability of model inputs. For example, if an alternative becomes less cost-effective when the risk is above a certain value then research on reducing the risk below this value would provide an insight for making the alternative cost-effective.[60]

Four types of uncertainties exist around model inputs:

1) **Stochastic uncertainty:**

   Stochastic uncertainty is the uncertainty around the outcomes of an individual patient. It is also termed as first order uncertainty. It arises due to the probability assigned to an

outcome and an individual patient experiencing that outcome based merely on this probability. It is dealt with individual level models such as first order Monte Carlo simulation or discrete event simulation modeling. In such models, an individual patient with specific characteristics takes the pathway in the model and such patient goes through the model several times, but each time experiences a different pathway because of a random chance of experiencing an event based on the probability of an event and on the past history of the patient. The higher the number of times a patient goes through the model, the higher is the precision on the probability of the outcomes.

2) **Parameter uncertainty:**

Parameter uncertainty is the uncertainty around the probability of an outcome or the utility measure of an outcome. It is dealt with deterministic sensitivity analysis and probabilistic sensitivity analysis.

In deterministic sensitivity analysis, the analysis is performed over a range of values for one or more parameters. In probabilistic sensitivity analysis, the analysis is performed over a range of values for all parameters together, to determine the joint effect of uncertainty of all parameters. Probabilistic sensitivity analysis is also termed as second order Monte-Carlo simulation.

3) **Patient Heterogeneity:**

An analysis of the entire cohort gives decisions with regards to the entire cohort. However, results may vary within subgroups of patients and hence decisions may

change for those subgroups. To identify such subgroups, a sensitivity analysis is performed with such subgroups, in order to make patient-tailored decisions. Similarly analysis is required when decisions differ according to various settings. This cannot be performed with a cohort simulation model and requires individual simulation modeling such as a Monte Carlo simulation or a discrete event simulation.

4) **Structural Uncertainty:**

Structural uncertainty is the uncertainty around the model. It occurs when information around certain events or treatment decisions is not available or uncertain or when there is uncertainty around events that occur following a disease management or when there is uncertainty around the interventions chosen for comparison. A structural sensitivity analysis would take into account this uncertainty by adding into the model structure or model flow such events or information.

3. METHODS

A discrete event simulation model to reflect the natural disease progression of patients with kidney transplantation was generated based on literature review, expert opinion and KDIGO guidelines as well as on the availability of data.

3.1 Clinical features of patients with kidney transplantation:

Patients with kidney transplantation undergo complex pathways due to their inherent characteristics as well as due to their treatment management.

Patients who are recipients of a live donor kidney are less likely to experience acute rejection compared to the recipients of a deceased donor kidney. These patients have improved long-term outcomes due to a shorter cold ischemia time, lesser likelihood of a graft loss and a lesser susceptibility to adverse events related to immunosuppressants such as cardiovascular diseases, infections and cancer, due to a need for a less rigorous immunosuppression compared to those with a deceased donor kidney. While live donor kidney comes from those who know the transplant recipient, deceased donor kidney comes from patients who are brain dead with a beating heart or from patients with a cardiac death, the former being more common.[61] According to the UNOS transplant registry year 2000 report, the 5-year graft survival rate between 1995-1999 was 66% for patients with deceased donor kidney and 78% for patients with live donor kidney. [62]

Patients with a higher HLA mismatches with the donor kidney are at an increased risk for acute rejection. These patients are also at an increased risk for death with a functioning graft, due to infections or cardiovascular diseases, again due to an increased need for a higher dose of immunosuppressive therapy.[63] Held PJ et al[64] (Impact of HLA mismatches) found a graft survival rate of 84.3% and 77.4%, for patients with a deceased donor kidney with HLA mismatches 0 and 4 respectively.

Race has been found to have an impact on transplant outcomes. According to the UNOS transplant registry[62], year 2000 report, the 5-year graft survival rates were 80%, 64% and 84% for live donor transplant and 70%, 55% and 76% for deceased donor transplant, for Whites, African Americans and Asians respectively. The rate of early acute rejection was 34% among African Americans while 28% among Whites. One year post-transplantation, Whites were more likely to die with a functioning graft due to cardiovascular diseases and malignancy whereas African Americans were more likely to die from immunological graft loss.

BMI less than 18 and greater than 36 is an independent risk factor for both patient and graft survival.[65] While a lower BMI is an indicator of poor nutrition and more susceptible for overimmunosuppresion due to increased dose per kilogram, patients with higher BMI are more prone to cardiovascular diseases such as hyperlipidemia and hypertension as well as to proteinuria and glomerular disease.[66,67]

Hispanic ethnicity and African-American race have associated with lower risk for post-transplant myocardial infarction and cancer and with higher risk for new-onset diabetes mellitus.[12,68,69] While African-American patients are more likely to lose their graft compared to Whites, the results for Hispanics are ambiguous with respect to graft loss.[70]

While cardiovascular diseases such as hypertension, hyperlipidemia, cardiac arrhythmia and angina as well as diabetes (whether pre-transplant or post-transplant) are risk factors for cardiovascular events such as myocardial infarction and stroke as well as for death, these diseases and events are also a significant risk factors for graft loss.[71,72]

Patients who experience infections such as cytomegalovirus infection, Epstein-Barr virus and BK virus are at an increased risk for malignancies as well as for graft loss.[73-75]

Above all, acute rejection is solely the greatest risk factor for graft loss, with the risk increases as the number of acute rejection episodes increase. A very early acute rejection – termed as delayed graft function increases the risk for graft loss considerably. Whether patients experiencing early acute rejection are at a greater risk for graft loss compared to patients experiencing late acute rejection is still not definite.[52]

3.2 Model Description:

The health states of interest in our model included acute rejection (AR), graft loss (GL), new onset diabetes mellitus (NODM), stroke, myocardial infarction, other cardiovascular diseases (other CVD) (cardiac arrhythmia, angina, ischemic heart disease, peripheral vascular disease), bacterial infections (BI), fractures cytomegalo-virus infection (CMV), cancer, death from graft loss, death from cardiovascular disease and death due to other reasons.

The model consisted of a cohort of post kidney transplant patients with attributes for age, sex, race, BMI, presence of pre-transplant conditions such as diabetes mellitus, hypertension, hyperlipidemia, other cardiovascular diseases and cytomegalo virus infection as well as their steroid regimen, viz., steroid avoidance, early steroid withdrawal, steroid withdrawal at 6 months, steroid withdrawal at 1 year and steroid maintenance. The cohort was divided into five arms based on their steroid regimen. Individual patients in each arm were sent through the

model where they could initially experience either of acute rejection, graft loss, new onset diabetes mellitus, stroke, myocardial infarction, other cardiovascular diseases, bacterial infection, cytomegalo virus infection, cancer, death from cardiovascular disease or death due to other reasons, depending upon their attributes and time to the events. Patients experienced an event that was earliest to happen based on a random sampling of their Weibull distribution, derived using their attributes.

Upon experience of an event, patients' attribute related to the event as well patients' age, depending upon the time at which the event occurred, was updated. However, if a patient experienced new-onset diabetes mellitus, his attribute for diabetes was updated after 3 years for his Weibull distribution for myocardial infarction, stroke, other cardiovascular disease, cancer, bacterial infection, fracture, death from cardiovascular disease and death due to other reasons. Similarly, if a patient experienced other cardiovascular disease, his attribute for other cardiovascular disease was updated after 1 year for his Weibull distributions for acute rejection, graft loss, myocardial infarction, stroke, new-onset diabetes mellitus, bacterial infection, cytomegalo virus infection, fracture, death due to cardiovascular disease and death due to other reasons. This was done to reflect the higher risk with already existing pre-transplant diabetes and other cardiovascular diseases present pre-transplant, respectively, compared to newly diagnosed new-onset diabetes mellitus and other cardiovascular diseases. Also, once a patient had a graft loss his attribute for medium dialysis time updated after 1 year and long dialysis time updated after 3 years, for his Weibull distributions for graft loss, stroke, other cardiovascular disease, new-onset diabetes mellitus, bacterial infection, cytomegalo virus infection, fracture, death from cardiovascular diseases and death due to other reasons. The

decisions were based on expert opinion. The attributes were updated for those events for which they were statistically significant. Because of updating of attributes, time to future events were also updated.

The pathway of events that the patients experienced was determined by the attributes that they had after the occurrence of an event and by their truncated Weibull distributions. We validated the data fit for Weibull distribution by using expert opinion on charts of Weibull curves for various events for patients with and without certain risk factors (Appendix I). Following the experience of an event, the parameters for a patient's Weibull distributions for various events were updated based on the current attributes (attributes after the occurrence of the event). To account for the change in risk at the current time, time to the next events were sampled from the patient's truncated Weibull distributions derived from the updated Weibull parameters. Patient then encountered an event that had the shortest time of occurrence, at a time that was equal to the difference between the time sampled from the patient's truncated Weibull distribution and the current time. Though the patients went through different pathways individually, multiple patients were sent through the model and the simulation clock moved in advancements of time whenever a patient had an event.

The events to which a patient could transition following the occurrence of an event is displayed in Table 2. Patients who died were not allowed to have any events following death. Patients who had a graft loss were not allowed to have an acute rejection or a second graft loss. Patients who developed new-onset diabetes mellitus and patients with pre-existing diabetes mellitus

were not allowed to develop new-onset diabetes mellitus again. Patients with cancer were not allowed to have cancer again.

Variance reduction technique of separate streams of common random numbers for different events was applied in order to have robust outcomes.

3.3 Data source:

The United States Renal Transplant Data System (USRDS) was used to derive parameter estimates for Weibull distribution for various events. The USRDS is a nationwide database of patients with End Stage Renal Disease (ESRD). The data for USRDS comes from CMS (Center for Medicaid and Medicare Services), ESRDS network, United Network for Organ Sharing (UNOS) and USRDS special study reports. Although, the data come from different sources, they have unique patient IDs which can be linked across to provide comprehensive patient information. For the purpose of this study, we used the transplant data that originated from UNOS (after 1994), the inpatient and outpatient Medicare claims data, physician supplier Medicare claims and the Medical Evidence report given by the renal provider of each new patient with ESRD and collected by CMS.

The transplant data contains information about donor and recipient characteristics and events that occur at the time of and following transplantation as well as immunosuppressive treatment at the time of and following transplantation. The data are collected at the time of transplant, six months post-transplant, each year then after and at the time of graft failure.

The medical evidence report is collected only once for each ESRD patient and contains information about the primary cause of ESRD, comorbidities, begin date of chronic kidney dialysis, lab values at the first diagnosis of ESRD and ethnicity. The institutional and physician supplier Medicare claims database include inpatient, outpatient, skilled nursing facility, home health agency and hospice claims and physician visit claims respectively. These include information such as service dates, diagnosis and procedure codes and total charges.

3.4 Data analysis:

3.4.1 Patient selection

Patients with kidney transplantation were identified using the transplant data by UNOS. Patients with a previous kidney transplantation and patients with other organ transplantation such as pancreas, instestine, lung, bone marrow, heart, liver and pituitary gland were excluded. We selected only those patients who were on tacrolimus at the time of transplant, to avoid any bias resulting from other immunosuppressants such as cyclosporine or sirolimus. Tacrolimus is the most commonly prescribed calcineurin inhibitor for kidney transplant patients. In 2011, 91% of patients with kidney transplantation received tacrolimus as their initial calcineurin inhibitor (USRDS 2013 annual report). Patients with tacrolimus were identified using the drug code ‘5’ given by USRDS.

3.4.2 Patient attributes

Patient attributes such as age, race, sex, body mass index, cold ischemic time, duration of dialysis (derived from dialysis start date and transplant date), donor type (living or deceased)

and HLA mismatch, acute rejection and presence of Epstein-Barr virus infection, Hepatitis C virus infection, BK virus infection or Cytomegalo virus infection were obtained from the transplant data, whereas as comorbidity information such as hypertension and malignancy was obtained from the transplant data and medical evidence report. The attribute, 'other cardiovascular disease' was defined as presence of cardiac arrhythmia, congestive heart failure, angina, myocardial infarction, peripheral vascular disease, ischemic heart disease, cardiac failure, cerebrovascular disease and atherosclerotic heart disease and identified from the medical evidence report data.

3.4.3 Definition of regimens

Steroid Avoidance:

No mention of steroid at the time of transplantation or within 6 months post transplantation.

Early steroid withdrawal:

Mention of steroid at the time of transplantation but no mention of it in the 6 months following transplantation.

6 month steroid withdrawal:

Mention of steroid at the time of transplantation, in the 6 months following transplantation but no mention of it in 7 to 12 months following transplantation.

1 year steroid withdrawal:

Mention of steroid at the time of transplantation, in the 6 months following transplantation, in 7 to 12 months following transplantation but no mention of it between 1 to 2 years following transplantation.

Steroid maintenance:

Mention of steroid at the time of transplantation, in 6 months following transplantation, in 7 to 12 months following transplantation and between 1 to 2 years following transplantation.

Mention of steroids were identified using the drug codes '1', '2' and '49' given by USRDS. Follow-up codes were used to determine follow-up periods.

3.4.4 Event analysis

First graft loss after the first kidney transplantation was identified using the graft failure date and first kidney transplantation date in the transplant follow-up data.

Patients having an acute rejection episode were identified using the following variables: 'Did the patient have any acute rejection episode between transplant and discharge?', 'Was acute rejection the contributory cause of graft failure?' and 'Was the patient treated for acute rejection?, in the transplant follow-up data.

Deaths due to graft loss, cardiovascular disease and other reasons were identified using the cause of death codes '3200', '3400-3599' and '3300-3399', '3600-3914' , respectively, from the transplant follow-up data.

Events such as stroke, myocardial infarction, other cardiovascular diseases, new-onset diabetes mellitus, bacterial infections, cytomegalovirus infection, cancer and fracture were identified using ICD-9/HCPCS codes, listed in Appendix I, from the Medicare inpatient and physician

supplier claims. These were considered as events, if the occurred after the first transplant. Separate cohorts of patients were created for these events and patients with a diagnosis of the respective events, any time prior to the first date of transplant were excluded. Since the claims data were available from January 2004 (whilst the transplantation data were used from January 1994 – the year of approval of tacrolimus), only those patients who had a transplantation later than 30th June, 2004 were included, in order to be able to identify any previous diagnosis of an event, as well as to avoid any gap in the follow-up between transplantation and occurrence of an event.

3.5 Statistical analysis:

3.5.1 Parametric survival analysis

Parametric regressions with a Weibull distribution were performed with the log of time to event as dependent variable and the patient attributes as independent variables. Proc Lifereg available in SAS was used to conduct the regressions. Only those attributes that were statistically significant ($p<0.05$) were included as parameters in the Weibull distributions for various events.

Age, race, sex, BMI, HLA mismatch, cold ischemic time, dialysis duration prior to kidney transplantation, donor type (live or cadaveric), hypertension, hyperlipidemia, cardiovascular diseases, Epstein barr virus infection, HIV/HCV infection, serum creatinine level 6 months post kidney transplantation, acute rejection were the independent variables. The dependent variable was time to event as determined from the length of follow-up period explained in section

3.6.1.1. Separate regressions were performed on separate cohort of patients for each of the events. The patient cohorts were different since the exclusion criteria were different for each of the events. Patients with a history of the event to be analyzed were excluded.

3.5.1.1 Follow-up period

Date of first transplantation was the start date of follow-up for all the events in the model. For each of the events, patients were followed till the occurrence of the respective events or till the occurrence of any of the censoring events, whichever occurred first. For graft loss and acute rejection, the censoring endpoints were death or last follow-up date. For death due to graft loss, death due to cardiovascular disease and death due to other reasons, the censoring endpoint was last follow-up date. For other events, viz., stroke, myocardial infarction, new-onset diabetes mellitus, fracture, cancer, bacterial infection and other cardiovascular diseases, the censoring endpoints were death or date of last claim, after the date of first transplantation. Patient attributes such as cytomegalo virus infection, malignancy and acute rejection were assessed for their presence prior to the occurrence of an event or a censoring endpoint. If these occurred post the follow-up period, they were considered as absent.

3.5.2 Propensity analysis:

The analysis being retrospective in nature, a selection bias is likely to exist. Steroid avoidance and withdrawal regimen are preferred for patients with low immunologic risk, while maintenance regimen is preferred for patients with a higher immunologic risk. Hence, due to this bias, a definite conclusion cannot be derived, since the patient characteristics on which the choice of regimen is based on are likely to affect the outcome, than the chosen regimen itself.

Several propensity score analysis methods exist to adjust for selection bias, such as propensity score matching, propensity score regression adjustment, stratification with propensity scores and inverse propensity weighting. We used the inverse propensity weighting to adjust for selection bias. Using other methods would have required inclusion of propensity scores in the parametric regression leading to the prediction of effect on the outcome majorly by the propensity scores than by the patient variables. In DES, the effect of patient variables is required to be incorporated since these determine the pathways through which a patient goes through in disease progression.

Propensity to receive maintenance regimen was determined using patient variables. Then an inverse of propensity score was used to create a sample in which the distribution of patient characteristics was similar in the treatment arms. The weights were then applied to determine the effect of regimens and patient characteristics on various events.

3.6 Analysis of discrete event simulation results

The outcomes of interest in our model included total number of events, average time to events as well as average number of events per patients for patients in each of the steroid regimen arms.

The model was run for base patient defined as a white, 50 year old male with hyperlipidemia and hypertension, exposure to cytomegalo virus pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor, HLA mismatch = 2, cold ischemic time between 12 and 24 hours and on a polyclonal antibody induction regimen. The results were compared with a patient with

cardiovascular disease and with an African-American patient, other characteristics being the same as the base patient.

Statistical significance was determined based on half-widths determined by ARENA for each of the events. Confidence intervals were generated based on half-widths and compared with the results of steroid maintenance regimen to determine whether the effect of the regimen was significantly better or worse compared to steroid maintenance. The number of events was multiplied by the half-width times 10,000 patients and this number was subtracted from the number of events to give lower limit and added to the number of events to give upper limit. If the number of events in the lower limit for a regimen was higher than the number of events in the upper limit of steroid maintenance regimen, then the regimen was considered to be significantly worse compared to steroid maintenance. If the number of events in the upper limit for a regimen was lower than the number of events in the lower limit of steroid maintenance regimen, then the regimen was considered to be significantly better compared to steroid maintenance.

4. RESULTS:

4.1 Results from USRDS Database Analysis

4.1.1 Graft loss, acute rejection, death due to graft loss, death due to cardiovascular diseases and death due to other reasons

A cohort of 55,028 patients with kidney transplantation was obtained after excluding patients with previous organ transplantation, patients with incomplete records and patients without tacrolimus as their initial immunosuppressive agent. Of these, 87.4 % of patients received

steroid maintenance, 4.2% of patients were withdrawn from steroids after one year of kidney transplantation, 4.4% of patients were withdrawn from steroids after six months of kidney transplantation, 3.3% of patients were withdrawn from steroids 7 days post kidney transplantation and 0.6% of patients were never received steroids (steroid avoidance), even at the time of transplantation. In the steroid continuation cohorts, 50-52% of patients were older than 60 years while only 45-48% of patients in the steroid sparing cohorts were older than 60 years ($p<0.0001$). 28% of patients were African-Americans in the steroid maintenance regimen compared to approximately 16% in the steroid-sparing regimens ($p<0.0001$). However, in the steroid avoidance cohort, 24% of patients were African-Americans. More Hispanics received steroid-sparing regimen compared to non-Hispanics. From a total of 8,256 Hispanics in the cohort, 90.8% received steroid avoidance, 3.1% were withdrawn from steroids at 7 days while only 0.3% were maintained on steroids. Among patients within the steroid-sparing regimen, 19-14% of patients had HCV/HIV infection compared to 9% in the steroid maintenance cohort. 11.1%-16.4% of patients in the steroid-sparing regimens received alemtuzumab induction versus only 1.4% - 6.1% in the steroid continuation cohort ($p<0.0001$). The distribution of patients with respect to the immunologic risk was not relevant to the steroid regimen. More patients in the 6-month and 1-year steroid withdrawal group had 0-1 HLA mismatches compared to those in the steroid avoidance or steroid maintenance group. (17% vs 12-14%, $p<0.0001$). More patients in the 6-month steroid withdrawal group were recipients of live donor kidney compared to the steroid avoidance or steroid maintenance group (46% vs 42%, $p<0.05$). (Table 3)

20.4%-20.9% of patients in the steroid avoidance and 7-day steroid withdrawal group had a graft loss compared to only 9% in the 6-month steroid withdrawal group and 14.5%-14.8% in the 1-year steroid withdrawal and steroid maintenance group. The median time to graft loss for patients in the steroid avoidance and 7-day steroid withdrawal group was only 26-30 months compared to 42 months in the steroid continuous group (Table 4).

More patients on steroid avoidance and 7-day steroid withdrawal regimen had acute rejection compared to steroid maintenance (27-30% vs 15-16%) (Table 5). Only 0.1% of patients died due to graft loss (Table 6). The rate of death due to graft loss across the 5 regimen was similar. However, considerable difference between rate of death due to cardiovascular diseases existed. Only 0.9% of patients in the steroid avoidance group died due to cardiovascular diseases compared to 2.5% of patients in the steroid maintenance group. (Table 7). 7-day steroid withdrawal as well as 1-year steroid withdrawal group also had a rate of 2.5-2.7% for death due cardiovascular diseases.

4.1.2 Myocardial infarction:

6 month steroid withdrawal group had the lowest percentage of patients experiencing cardiovascular diseases (31.8%). Higher percentage of patients received alemtuzumab induction in the steroid avoidance and 7-day steroid withdrawal group and higher percentage of patients switched from tacrolimus to cyclosporine in this groups. Compared to steroid maintenance, the percentage of patients with hyperlipidemia was higher in other groups (9.2% vs 7.2%, $p<0.05$). (Table 9). 1-year steroid withdrawal group had the lowest percentage of

patients with myocardial infarction 3.9%, while steroid avoidance had the highest, 6.7%. (Table 10).

4.1.3 Stroke:

The distribution of patients across the 5 regimen was similar with respect to patient demographics (age, race, sex and ethnicity). More patients in the steroid maintenance group compared to 6 month and 1 year steroid withdrawal group were recipients of cadaveric donor (63.90 % versus 55.7%-57.9% versus , $p<0.0001$). (Table 11). Steroid maintenance group had the highest percentage of patients who experienced a stroke (15.6%) whereas steroid avoidance and 6 month steroid withdrawal group had the lowest percentage of patients who experienced a stroke (10.4-10.6%). (Table 12).

4.1.4 Other cardiovascular diseases:

Percentage of elderly patients of age >60 years in the 6-month steroid withdrawal group was highest, 30.4%, compared to 16.7 to 18.2% in other groups. Percentage of patients with Hispanic ethnicity trended up moving from steroid avoidance to steroid maintenance strategy from 7.8% to 13.7%. The percentage of patients with HLA mismatch 0-1 was highest in the six month steroid withdrawal group 19.2% while the lowest in the 7-day steroid withdrawal group (9.1%). More patients in the steroid avoidance and 7-day steroid withdrawal group received alemtuzumab induction (19.5% and 24.9%) versus 2.5% to 10.3% in other groups ($p<0.0001$)

(Table 13). The percentage of patients experiencing acute rejection was highest in the 6-month steroid withdrawal group (8.2%). (Table 14).

4.1.5 New-Onset Diabetes Mellitus

The percentage of patients with hyperlipidemia decreased from 11.3% to 7.2% on going from steroid avoidance to steroid maintenance. The percentage of patients with hypertension was highest in the steroid avoidance group (6.2%). Percentage of patients with acute rejection was highest in the 6-month steroid withdrawal group (8.6% vs 4.1-5.3%, $p<0.0001$). (Table 15). The percentage of patients who developed new-onset diabetes mellitus was 42.9% overall, with steroid maintenance group having the highest percentage of patients developing new-onset diabetes mellitus,17.8% while steroid avoidance group having only 1.1% of patients with new-onset diabetes mellitus. (Table 16)

4.1.6 Cancer:

The percentage of patients with Hispanic ethnicity increased from 8.7% to 16.2% on moving from steroid avoidance group to steroid maintenance group. There were more males in the steroid avoidance group. 6-month steroid withdrawal, 1-year steroid withdrawal and steroid maintenance groups had more patients with 0-1 HLA mismatches compared to steroid avoidance and 7-day steroid withdrawal group (12.6-15.8 vs 9.2-9.4, $p<0.0001$). Patients in the steroid avoidance group and 7-day steroid withdrawal group were more likely to receive Alemtuzumab induction (15.2%-28.3% vs 2.5% to 9.9%, $p<0.0001$). 10.1% of patients in the 6-month steroid withdrawal group experienced acute rejection, the highest across the five

regimen. (Table 17). 12.6% of patients in the steroid maintenance group developed cancer versus only 1.3% of patients in the steroid avoidance group. (Table 18).

4.1.7 Bacterial infection:

No trend was observed in the distribution of patients across the three regimens other than Hispanic ethnicity, where 8.7% in the steroid avoidance group were Hispanics versus 15.2 in the steroid maintenance group ($p<0.0001$) (Table 19). 28.6% of patients experienced a bacterial infection. Steroid avoidance group had the highest percentage of patients who experienced bacterial infection 35.3% versus 23.0% in the 1-year steroid withdrawal group (Table 20).

4.1.8 CMV infection:

African-Americans were more likely to receive 6-month and 1-year steroid withdrawal immunosuppression compared to steroid maintenance immunosuppression (22% vs 29%, $p<0.0001$). Similarly, Hispanics were more likely to receive steroid sparing immunosuppression compared to steroid maintenance ($p<0.05$, $p<0.0001$) (Table 21). Patients in the steroid sparing immunosuppression group were more likely to receive induction with alemtuzumab compared to patients in the steroid maintenance group (7.2%-27.5% vs 2.6%, $p<0.0001$). 17.1% of patients in the steroid maintenance group had a CMV infection while only 1.2%-6.1% of patients in the steroid sparing group had a CMV infection (Table 22).

4.1.9 Fracture:

The percentage of patients with Hispanic ethnicity increased from 8.3% to 15.6% on moving from steroid avoidance group to steroid maintenance group. 6-month steroid withdrawal group had 10.8% of patients who experienced acute rejection, the highest among all regimen. (Table 23). The percentage of patients who experienced fractures ranged from 11.2-14.5% across the regimens. (Table 24)

4.1.10 Parametric survival analysis results (Proc 'Lifereg' results)

Patients on 7-day steroid withdrawal regimen were 1.3 (exp(0.27)) times ($p<0.0001$) and patients on steroid avoidance regimen were 1.8 times ($p<0.0001$) more likely to experience graft loss whereas patients on 6 month steroid withdrawal regimen were 1.1 times less likely to experience graft loss ($p<0.02$). Similarly, patients on steroid avoidance were 5.6 times more likely to experience acute rejection; patients on 7-day withdrawal were 2.8 times more likely to experience acute rejection whilst patients on 6 month steroid withdrawal regimen and 12 month steroid withdrawal regimen were 1.05 times and 1.2 times less likely to experience acute rejection, compared to steroid maintenance. Similar results were observed for death due to graft loss, however the coefficient estimates were very low. Compared to steroid maintenance, patients on the other four regimen, in order of steroid avoidance, 7-day steroid withdrawal, 6-month steroid withdrawal and 1- year steroid withdrawal were 1.04, 1.27, 1.95 and 1.4 times less likely to experience new-onset diabetes mellitus. The results for 6-month steroid withdrawal and 1-year steroid withdrawal were statistically significant. Patients on steroid avoidance were 1.22 and 1.23 times, 6-month steroid withdrawal were 1.59 and 1.1 times, 12 month steroid withdrawal were 1.69 and 1.10 less likely to experience myocardial infarction

and stroke, respectively, whereas patients on 7-day steroid withdrawal were 1.17 and 1.27 times more likely to experience myocardial infarction and stroke respectively. The results were not statistically significant except for stroke for 7-day steroid withdrawal regimen ($p<0.01$). Again, patients on 7-day steroid withdrawal were 1.19 times less likely to develop cancer compared to steroid maintenance ($p<0.01$). Results for steroid regimen for cardiovascular diseases and death due to cardiovascular diseases were not statistically significant. Patients on 6-month steroid withdrawal regimen were 2.12 times less likely to experience CMV infection compared to steroid maintenance ($p<0.0001$). Patients on 6-month and 1-year steroid withdrawal regimen were 1.32 and 1.57 times respectively, less likley to experience bacterial infection ($p=0.001$ and $p=0.004$ respectively) compared to steroid maintenance. Patients on 6-month and 1-year steroid withdrawal regimen were 1.19 and 1.19 times respectively, less likely to die due to other reasons ($p=0.0124$ and $p=0.0104$ respectively). Patients on 6-month and 1-year steroid withdrawal regimen were 1.18 and 1.32 times less likely to have a fracture respectively ($p=0.0239$ and 0.0101) while patients on steroid avoidance regimen were 0.52 times more likely to have a fracture ($p=0.0003$) (Tables 25-37).

Patients with HLA mismatch =>2, females and elderly patients were more likely to experience acute rejection ($p<0.0001$). Patients with BMI≥35 were 0.32 times more likely to experience acute rejection. Patients with creatinine level >1.4 mg/dl were 1.4 times more likely to experience acute rejection and 0.37 times more likely to experience graft loss. These patients were also more likely to experience death due to cardiovascular diseases, death due to graft loss and death due to other reasons, compared to patients with creatinine level <1.4 mg/dl. Young patients (18-40 years), African-American patients, Hispanics, HLA mismatches =>2 and

patients with cadaveric donors were more likely to have a graft loss ($p<0.0001$). Not surprisingly, elderly patients, patients with a history of diabetes and other cardiovascular diseases were more likely to experience stroke and myocardial infarction ($p<0.0001$). African-American patients, patients with Hispanic ethnicity and patients with dialysis duration of greater than 3 years pre-transplantation were more likely to develop new-onset diabetes mellitus ($p<0.0001$). Patients with alemtuzumab induction were more likely to experience stroke, myocardial infarction and death due to cardiovascular diseases ($p<0.0001$) (Tables 25=37).

4.2 Discrete event simulation results

Results from discrete event simulation modeling of a cohort of 10,000 patients with characteristics of 50-year old male, white with hyperlipidemia and hypertension with exposure to CMV pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor kidney recipient, with HLA mismatch 2, cold-ischemic time 12-24 hours and with polyclonal antibody induction (base patient) showed that the maximum number of acute rejection episodes (67.8%) and graft loss (76.4%) occurred in the steroid avoidance group followed by 7-day steroid withdrawal (53.2% and 57.9%). The least number of acute rejection episodes and graft loss occurred in the steroid maintenance group (35.5% and 40.9%). Compared to steroid maintenance group, patients in the 6 month steroid withdrawal group and the 12 month steroid withdrawal group had significantly lower number of myocardial infarctions (9.6-9.8% vs 12.2%), new-onset diabetes mellitus (37.2%-42.4% vs 46.4%), bacterial infections (51.7%-57.6% vs 67.4%), cytomegalo virus infections (41.8%-52.3% vs 57.2%), fractures (51.1%-54.8%% vs 59.1%) and deaths due to cardiovascular diseases (24.5%-25.7% vs 28.8%). The rate of cancer and

fractures was the highest in the steroid avoidance group, 94.2% and 79.8% respectively. Death due to cardiovascular diseases was lowest in the steroid avoidance group, 11.4% compared to 28.8% in the steroid maintenance group. Steroid maintenance group had the highest rate of bacterial infections and cytomegalovirus infections (67.4% and 57.2% respectively). Bacterial infections occurred the least in steroid avoidance, 55.5%. The average time to event for acute rejection was only 36 months for acute rejection and 98 months for graft loss with steroid avoidance. The rate of any of the events, viz., acute rejection, graft loss, cardiovascular diseases/events, infections, deaths fracture and cancer was never significantly higher for the 6-month and 12-month steroid withdrawal groups compared to the steroid maintenance group. Instead, the groups had significantly decreased rates of acute rejection, myocardial infarction, new-onset diabetes mellitus, bacterial infection, cytomegalovirus, fractures, death due to other reasons and death due to cardiovascular diseases. (Table 39, 40)

Results at 20 years post transplantation of patients with characteristics similar to the base patient but with a history of cardiovascular disease were similar to those of the base patient, except that the 12-month steroid withdrawal group had a significantly higher incidence of cancer compared to steroid maintenance (89.2% vs 86.8%). Similar results as for the patient with cardiovascular disease were seen for patients with characteristics similar to the base patient but with African-American descent. (Tables 41, 42, 43, 44)

Compared to base patient, patients with a history of other cardiovascular diseases and African-American patients were more likely to have a graft loss (46.6%-58.0% vs 40.7%-42.2%), more likely to have new-onset diabetes mellitus (44.4%-44.9% vs 37.2%-42.4%), whereas less likely

to develop cancer (82.9%-89.3% vs 90.7%-91.9%), with 6-month and 12-month steroid withdrawal regimen. These patients were also significantly more likely to experience acute rejection with 12-month steroid withdrawal regimen compared to base patient (29.6%-31.2% vs 29.1%) (Tables 45, 46).

5. DISCUSSION

Our study estimated the health outcomes of kidney transplant patients 20 years post-transplantation. The results showed that 20 years post kidney transplantation patients in the 6-month and 12-month steroid withdrawal group were significantly less likely experience NODM, myocardial infarction, fracture, bacterial infection and cytomegalovirus infection, death due to cardiovascular diseases and death due to other reasons and never more likely to experience acute rejection, graft loss, other cardiovascular diseases, cancer and death due to graft loss, as compared to maintenance, at 20 years post transplantation. This was not the case with steroid avoidance and 7-day steroid withdrawal regimen, where patients were significantly more likely to experience graft loss at 20 years. Hence the 6-month and 12-month steroid withdrawal regimen showed benefits in terms of the tradeoff between graft loss and steroid-related cardiovascular side effects, as compared to all other regimens.

The beneficial effects of late steroid withdrawal are consistent with the findings of Pascual et al.[11] The authors, with the help of meta-analysis of 9 trials, found significant reductions in the total serum cholesterol levels with late steroid withdrawal compared to steroid maintenance. Elevated serum cholesterol levels are a significant cause for cardiovascular events such as myocardial infarction and deaths due to cardiovascular diseases. The findings by the authors

thus explain the comparatively decreased incidence of the cardiovascular events with late steroid withdrawal found in our study, compared to steroid maintenance.

Short-term clinical trials have found no difference in graft loss or acute rejection at 5 years between steroid sparing and steroid maintenance regimens. Hence the findings of our study are contradictory with the short term clinical trials. However, studies have shown patients with late acute rejections to be more likely to have graft loss compared to those with early acute rejection.[76] In our study, the average time to acute rejection ranged from the 3 years to 4 years within the steroid regimen groups, thus explaining the increased incidence of graft loss with the steroid-sparing regimen at 20 years. Also, as mentioned in the literature review section, a study found a significant difference in the allograft fibrosis between steroid withdrawal and steroid maintenance regimen. Fibrosis has been found to be the most common reason for graft loss.[77] A study found acute rejection to be the most common cause of graft loss within 5 years post kidney transplantation and fibrosis to be the most common cause after 5 years of transplantation.[78] The significant differences in the rates of allograft fibrosis explain the significant differences in long-term rates of graft loss. BK virus infection, multiple episodes of acute cellular rejection, antibody mediated rejection, recurrent pyelonephritis, poor allograft quality and calcineurin inhibitor toxicity are the factors that have been found to be associated with allograft fibrosis.[78] Hence, it is important to consider including graft biopsies to detect fibrosis or any of the above mentioned factors and take appropriate measures in order to minimize the risk of graft loss.

Trials have shown significantly reduced incidence of NODM in the steroid avoidance and 7-day steroid withdrawal groups compared to steroid maintenance group (Table 1). Steroids regulate glucose metabolism and hence long-term use of steroids has been associated with the development of new-onset diabetes in patients with kidney transplantation.[79] Our findings are consistent with those of the trials, at 20 years post kidney transplantation, with 7-day steroid withdrawal, 6-month steroid withdrawal and 12-months steroid withdrawal showing significantly reduced incidence of new-onset diabetes mellitus compared to maintenance (37.2%-42.4% vs 46.4%). However though, in our study, the results were reverse at 5 years post kidney transplantation, the incidence of NODM across the steroid sparing arms ranged from 37-46% versus only 17% in the steroid maintenance arm. This could probably be due to the use of potent induction agents in the steroid sparing arms that may have resulted in higher rates of NODM in arcoss these arms initially and the long-term steroid use which could probably have increased the cumulative incidence of NODM in the steroid maintenance arm at 20 years post transplantation. NODM is a serious complication post transplantation. The complications of NODM in patients with kidney transplantation, viz., cardiovascular diseases, nephropathy and hyperglycemia-induced injuries of extremities and eyes, are similar to those in general population with diabetes but occur at an increased rate.[80] Additionally, these patients experience severe complications such as cardiovascular events, graft failure and death, which occur very soon after the onset of diabetes. Immunosuppressive agents are a major risk factor for NODM. Calcineurin inhibitors exert diabetogenic effect by interfering with the pathways that regulate insulin secretion, with tacrolimus being more diabetogenic compared to cyclosporine.[81-83] A study found that 42% of patients with NODM experienced remission from NODM when switched from tacrolimus to cyclosporine.[84] Hence in patients with NODM with

a high risk for cardiovascular diseases and graft loss, steps should be taken to reduce immunosuppression in order to cause a remission or a decrease in severity of diabetes.

Kasike BL et al[69] found a three year cumulative cancer rate in patients with kidney transplantation to be 15% using Medicare claims. Similar to the study by Kasike et al, our study found the incidence of cancer to be higher in older, White, non-Hispanics patients and lower in patients with diabetes compared to those with diabetes. Patients with transplantation are 3-fold more likely to experience cancer than general population.[69] The incidence of non-skin cancers has been found to increase over time post transplantation according to a study by Bustami et al.[85] Consistent with the above two findings, simulation results of our study showed a 20-year cumulative cancer rate to be as high as 85-94%.

Our database and Medicare claims based study with a median follow-up of 3 years and found a cumulative rate of cancer to be 66.7%. Unlike the study by Kasiske BL et al.[69], our study looked for benign neoplasms in addition to malignant neoplasms. Benign neoplasms can become malignant and it is important to consider such a high incidence of neoplasms, whether benign or malignant, in order to implement precautionary measures. Because the risk of cancer is associated with oncogenic viral infections such as Epstein bar, herpes, papilloma and hepatitis viral infections, screening patients for this infections as well as prophylaxis with antimicrobial therapy should be considered. Overimmunosuppresion is a major factor in the risk for cancer and an appropriate tradeoff should be considered weighing the risks of both over and under immunosuppression.[86] Our study found that patients with steroid avoidance were significantly more likely to experience cancer compared to steroid maintenance. A probable

explanation for this could be the use of potent induction agents with the steroid avoidance regimen or the use of steroids following an acute rejection event. Knight et al in their meta-analysis of 11 studies did not find a significant difference in the incidence of cancer between steroid avoidance/steroid withdrawal versus maintenance regimen, except for leukemia (RR:1.66; $p<0.0001$), suggesting increased risk of leukemia with steroid avoidance/withdrawal strategy.[3]

According to the results of discrete event simulation, at 20 years the incidence of fractures was more among patients on steroid avoidance compared to patients on other regimen. This could be the result of use of steroids upon an acute rejection episode or the use of potent immunosuppressants in the steroids avoidance arm. Patients on steroid avoidance had at higher cumulative incidence of acute rejection compared to those on maintenance and other steroid continuation regimen and this could have probably resulted in a higher incidence of fractures among this group as a result of acute rejection therapy compared to patients within other regimen groups. It is true that patients on 7-day withdrawal regimen also had a higher incidence of acute rejection at 20 years compared to patients on steroid continuation regimen and yet a comparable but not an increased incidence of fractures as compared to the steroid continuation regimen groups. Patients on steroid avoidance had a shorter median time to graft loss compared to patients on 7-day withdrawal (97 months versus 108 months). Time on dialysis has been associated with an increased risk of fracture and this could probably explain an increased incidence of fractures among patients on steroid avoidance who had an earlier graft loss compared to patients on 7-day withdrawal.[87]

As with other studies, our study found female gender, diabetes and medium and long dialysis time as risk factors for fractures, in addition to steroid maintenance regimen. Also the rate of fractures (14.1%) with a median follow-up of 35 months was similar to other short-term studies.[88-90]

The number of fractures in the steroid avoidance group in our study was double that of the number of patients experiencing fractures, suggesting that many of these patients had a fracture more than once by the end of 20 years post transplantation. We did not allow in our study a second transplantation after a graft loss and hence patients on steroid avoidance regimen with a fracture transitioning to a longer dialysis time would have had an increased risk for a second fracture.

Similar to the study by Lentine et al. who used the USRDS database to identify the incidence and risk factors of myocardial infarction, myocardial infarction in our study was more likely to occur in patients with diabetes and other cardiovascular diseases. The incidence of myocardial infarction in our study was almost half of that found in the Lentine et al., probably because we excluded patients with pretransplant myocardial infarction who are at a four-fold risk of myocardial infarction post transplantation. The death rate among patients with myocardial infarction post-transplantation has been found to be as high as 36.1%. Myocardial infarction is also associated with an increased incidence of graft loss - 12.9% at 2 years, as found in the study by Lentine et al. Hence precautions should be taken in these patients to prevent the development or progression of cardiovascular risk factors in the patients by using an appropriate dose of immunosuppression and by withdrawing steroids at an appropriate time, in

order to avail the protective effects of the immunosuppressants on graft function as well as to prevent the cardiovascular side effects of the immunosuppressants.

Short term studies in literature comparing 3 month steroid withdrawal with maintenance have found significant improvement in cardiovascular outcomes with 3 month steroid withdrawal regimen, and those comparing early steroid withdrawal (steroid avoidance/7-day steroid withdrawal) with steroid maintenance have found significant improvement in cardiovascular outcomes with early steroid withdrawal and no difference in acute rejection and graft loss rates, with early steroid withdrawal regimen. At 20 years, post-transplantation late steroid withdrawal (withdrawal between 7 days to 6 months post-transplantation and withdrawal between 6 months to 1 year post-transplantation) is beneficial in terms of both cardiovascular outcomes as well as graft-related outcomes and hence late withdrawal should be considered, at least in patients with a history of cardiovascular diseases such as hyperlipidemia and hypertension and with a low immunologic risk.

Significant difference existed (18-27% vs 2-4%) in the proportion of patients receiving alemtuzumab between steroid avoidance/7-day steroid withdrawal regimen versus other steroid continuation regimen. This probably could explain the lack of significant difference in the incidence of stroke, myocardial infarction and other cardiovascular diseases among the two groups when the median follow-up time was three years. However, this warrants further research on the effect of alemtuzumab on the development or progression of cardiovascular diseases. Nevertheless, the considerable lower incidence of death due to cardiovascular diseases in the steroid avoidance group, when the median follow-up was 5 years, explains the

importance of steroid sparing strategies to reduce the long-term incidence of cardiovascular events and deaths due to cardiovascular diseases. The 6-month and 12-month steroid withdrawal regimen seems to be a perfect balance to minimize the use of steroids to prevent cardiovascular diseases and to minimize the incidence of acute rejection and graft loss, resulting from early withdrawal of steroids.

5.1 Limitations

One of the prime utilities of discrete event simulation modeling is its ability to model and analyze results for heterogenous patient population. Since we wanted to identify steroid-withdrawal regimen that best suits a subgroup of individuals frequently seen in practice and the risk factors associated with the outcomes with this steroid withdrawal regimen, we used our model to determine the optimal steroid withdrawal strategy for the base patient and compared the results with African-American patients and patients with a history of other cardiovascular diseases such as cardiac arrhythmia, heart failure and angina. In future, using this model, one can also determine an effective steroid withdrawal regimen in a heterogenous kidney transplantation population with varying immunologic and cardiovascular risk. Analysis of a cohort of heterogenous population to determine a cost-effective regimen would be more appropriate to determine the costs saved and for appropriate resource allocation than to analyze individual patients separately.

Our DES model did not incorporate two important cardiovascular outcomes post-transplantation: hypertension and hyperlipidemia and/or severity levels of hypertension and hyperlipidemia. Most patients (approx. 80%) in the database had a prior history of these

hypertension and had no information regarding the treatment regimen (diet, exercise and/or medications) to determine the progression of these diseases. However, these are surrogate outcomes and cardiovascular events such as stroke and myocardial infarction are better indicators of cardiovascular outcomes post transplantation. Nevertheless, it would have been useful if the severity of their pre-existing conditions – a better predictor for cardiovascular events was known. Had we included these events and their severity levels, we would have better been able to simulate a more natural disease progression in these patients and the results on cardiovascular events at 20 years post-transplantation would have differed. The results of the study are applicable with an assumption that patients in the different steroid regimen arms were not significantly different with respect to the severity levels of hypertension and hyperlipidemia. Caution must be taken in applying the results of this study to patients with high severity levels of these diseases. Having said this, with today's treatment protocols, these diseases are well managed and hence are likely to affect the results on the incidence of cardiovascular events only when they become uncontrollable with regular treatment protocols. Also, the severity of hypertension and hyperlipidemia and the duration of these would be more useful if we were to determine cost-effectiveness of the steroid regimen. Similarly, our model also did not incorporate BK virus infection, a rare event but a significant predictor of graft loss. We also did not stratify the types of bacterial infections or the types of cancer, again, necessary to determine the costs of these based on the duration.

Patients in the USRDS database were asked about their regimen at 6 months post transplantation and every year after that. Hence, we could not determine the exact time of withdrawal of steroids due to the nature of the database. Hence results from this study must be interpreted keeping in mind the way the regimens were defined in the study. Accordingly, the

interpretation for the results on 6-month and 12-month steroid withdrawal is such that steroid withdrawal anytime between 7 days to 1 year post transplantation has benefits of significantly reduced rates of cardiovascular events and infections whilst no significantly worse effects on graft function. Were the patients asked about their regimen at more closer time intervals, we would have been able to determine the effects, specifically of steroid withdrawal at 3 months, a more commonly used regimen compared to 6-month and 12-month steroid withdrawal. We would have then be able to determine the exact time of steroid withdrawal. We could not use the Medicare claims data to determine the exact time of withdrawal of steroids, since the Medicare part D was available to patients from 2006 and we would have had only three years' worth of data since then.

As in randomized controlled trials, we determined the steroid regimen beforehand. This resulted in some patients having an event even before the steroids were withdrawn. This would have led to a misclassification bias in our study. In our future study, we plan to conduct a sensitivity analysis by excluding these patients to see if the results remain robust. We also aim to include downstream treatment decisions for acute rejection, infections and cardiovascular diseases in order to mimic the disease progression more closely. In our database study, the median follow-up time for various events was 3-5 years. Based on parameter estimates derived with this follow-up time, we derived the Weibull equations to obtain the outcomes at 20-years post-transplantation. Risks change over time and hence do the parameter estimates. The outcomes would have been more accurate had there been a longer follow-up time.

Twenty years is a long time to forecast the health outcomes, since advances in treatment are likely to emerge within this time frame and the decisions may change based on these advancements. Nevertheless, the current model can always be adapted to any treatment advances that may evolve over time.

Assumptions were made based on expert opinion to elicit the effect of duration of hypertension, hyperlipidemia and diabetes on the health outcomes. In future, we plan to conduct a sensitivity analysis over these assumptions to determine the robustness of the results.

5.2 Conclusion:

Based on the results of our study, immunosuppressive regimens with steroid withdrawal between 7-days to 12-month post transplantation show a benefit in terms of significantly reduced rates of myocardial infarction, new-onset diabetes mellitus, fractures, infections, deaths due to cardiovascular diseases and deaths due to other reasons, at 20 years post transplantation, with no detrimental effect on graft function, compared to steroid avoidance, 7-day steroid withdrawal and steroid maintenance

Despite the limitations mentioned above, our study has value in it, being able to mimic the real-world disease progression post kidney transplantation, by incorporating a variety of events in its model and by including in its analysis a variety of patients (including both high and low risk) and patient characteristics that no other clinical trial or existing post kidney transplant model have been able to. Our study was able to determine the long-term effects of steroid

withdrawal and the optimal steroid withdrawal strategy, a long-standing question that hasn't been answered to date.

Finally, our model can be used to compare other treatment options post kidney transplantation, such as induction agents or other options as they emerge in the long run, to compare treatment options for pediatric population or to determine cost-effectiveness of the treatment options by slight model adaptations.

6. TABLES & FIGURES

6.1 Literature review table

Table 1: Post-kidney transplantation studies on tacrolimus based steroid sparing versus steroid containing immunosuppressive regimens

Author	Date	Immunosuppression/study arms	Study type, length of follow-up, sample size	Outcome measures
Phelan P.[30]	2010	Tacrolimus, MMF; steroid withdrawal at 3 months vs steroid maintenance at <5mg vs steroid maintenance at >5mg doses	Clinical trial;1-2 years follow-up; N=241	AR: 11.3% vs 11.6% vs 10.1%, p=ns; GL: 3.8% vs 1.5% vs 4.2%, p=ns; NODM: 0% vs 7.2% vs 7.6%, p=ns; Mean BP: 130/80 vs 133/79 vs 130/74, p=ns; TC: 4.12 mmol/l vs 4.32 mmol/l vs 4.25 mmol/l p=ns; Serum creatinine:116 µM/l vs 116.5 µM/l vs 121 µM/l, p=ns
Miguel G.[91]	2010	Tacrolimus/cyclosporine, MMF; steroid withdrawal at mean time of 3 years vs steroid maintenance	Retrospective cohort study (Spain); 15 year follow-up; N=4,481	Mean GS time:13.6 years vs 12.6 years, p<0.001;Death:8.5% vs 12.5%, p<0.001;TC: 199.9 mg/dL vs. 211.7 mg/dL, p<0.01;TG: 138.7 mg/dL vs 152.2 mg/dL p=0.008
Meulen CG[34]	2004	Tacrolimus, MMF; steroid avoidance with daclizumab vs steroid maintenance till 4 months	Prospective multicenter study; 1 year follow-up; N=364	AR: 15% vs 14%, p=ns; Death due to cardiovascular events: 4% vs 2%, p=ns; PS: 95% vs 94%, p=ns; GS: 91% vs 90%, p=ns; NODM: 7% vs 12%, p=ns; Infections: 1.2% vs 1.4%, p=ns; Mean TC difference: −0.1 mmol/l, p=ns; Mean BP difference: -1.0 mmHg, p=ns
Helden M[34]	2004	Tacrolimus, MMF; 3 day steroid withdrawal with daclizumab vs steroid maintenance till 4 months	RCT; 1 year follow-up; N=364	Median AR time=11 vs 18 days, 15% vs 14%, p=ns; PS: 95% vs 94%; GS:91% vs 90%; NODM: 7% vs 12%;TC: 5.2 vs 5.3, mmol/L,

				p=ns; Mean BP: 98 vs 99, p=ns; TG: 2.1 vs 2.0 mmol/L, p=ns
Vitko S[38]	2005	Tacrolimus; 1 day steroid withdrawal with basiliximab vs 1 day steroid withdrawal with MMF vs steroid maintenance with MMF	Open label; 6 month follow-up; N=451	AR: 26.1% vs 30.5% vs 8.2%; p<0.001; PS:99.3% vs 99.3% vs 100%; p=ns GS: 94.7% vs 96.7% vs 95.9%; p=ns NODM:1.4% vs 7.1% vs 4.6%; p=0.056 Treatment with lipid lowering drugs at 1 year: 12.7% vs 12.6% vs 18.7%; p=ns Treatment with antihypertensive medication at 1 year: 70.6% vs 68.5% vs 79.1%; p=ns CMV: 7.8% vs 16.6% vs 11.6%; p=0.005 Median creatinine clearance: 55.1 ml/min vs 59.4 ml/min vs 65.3 ml/min, p=0.007
Woodle ES, Peddi VR[31]	2010	Tacrolimus; 6 day steroid withdrawal with MMF and rATG vs steroid maintenance at least upto 90 days with MFF	2:1 randomized prospective open label trial; 1 year follow-up, N=151	AR: 13.6% vs 18.8%, p=ns; GL: 1.9% vs 0%, p=ns; NODM: 8% vs 15.3%, p=ns; TC: 150 mg/dl vs 200 mg/dl, p=0.0139; TG: 151.9 mg/dL vs. 181.4 mg/dL, p = 0.073 No difference in cardiovascular risk score Serum creatinine: 1.3 mg/dL vs 1.2 mg/dL, p=ns
Kramer BK[13]	2010	Tarcolimus; 1 day steroid withdrawal with basiliximab vs 1 day steroid withdrawal with MMF vs steroid maintenance with MMF	Open label randomized multicenter trial; 1 year follow-up; N=501	AR: 35.3% vs 39.7% vs 12.9%, p<0.01; PS: 95.9% vs 92.8% vs 100%; GS: 92.8% vs 95.4% vs 95.9%, p=0.51;NODM: 0.7% vs 4.7% vs 3.2% p=0.249;Mean change in TC:-0.15 vs -0.07 vs -0.14, p=ns; BP: 133.3/82.3 vs 132.4 /81.4 vs 133.7 /82.3 mmHg, p=ns; Lipid lowering drugs: 17.9%, vs 20.4% vs 28.6%, p=ns; Antihypertensive medication:69.0% vs 74.2% vs 74.3% of patients; Serum creatinine: 141.9 μM vs144.0 μM vs 134.5, p=ns

Laftavi M[32]	2005	Tacrolimus, rALG and MMF; 7 day steroid withdrawal vs steroid maintenance	Randomized prospective trial; 1 year follow-up; N=60	AR:13% vs 11%,p=ns; Mean BP: 97.5 vs 95.9, p=ns; TC: 175.6 vs 168.6, p=ns; 64% of patients with subclinical rejection progressed to fibrosis while only 14% of patients without rejection progressed to fibrosis at 1 year; Risk of rejection higher in African Americans after steroid withdrawal
Mysore S[36]	2006	Tacrolimus, basiliximab, MMF/sirolimus; 2-day steroid withdrawal vs steroid maintenance	Randomized trial; 3 year follow-up; N=300	AR: 16% vs 14%; p=ns; PS: 89% vs 91%, ps=ns GS: 78% vs 79%, p=ns; NODM: 4% vs 21%, p<0.01;DGF: 56% vs 34%, p=0.0001; Incidence of CAN was equivalent; Serious infections: 18% vs 35%, p=0.05
Rostaing L[35]	2005	Tacrolimus, MMF; 1 day steroid withdrawal with daclizumab vs steroid maintenance	Open-label, multicenter, parallel-group; 6-month; N=538	AR: 16.5% vs 16.5%, p=ns; PS: 98.1% vs 99.9%, p=ns; GS: 91.9% vs 95.7%, p=0.064; NODM: 0.4% vs 5.4%, p=0.003; Mean change in TC: -0.19 mmol/L vs +0.19 mmol/L, p=0.005; Antihypertensive treatment: 51.4% vs 61.5%; Median serum creatinine: 125.0 μM vs 131.0 μM, p=ns; Mean total cholesterol change from baseline: BMD: t score change: -0.15, z score change: -0.13; p=0.03 in maintenance group, p=NS in withdrawal group
Shihab FS[33]	2013	Tacrolimus, MMF; 7 day steroid withdrawal vs steroid maintenance	Prospective multicenter double blind study;5 year follow-up; N=397	CMV disease: 7.3% vs 10.3%, p = 0.37; Serum creatinine level ≥ 6.0 mEq/L:22.5% vs 12.3, p=0.01
Cantarovich D[37]	2013	Tacrolimus/cyclosporine, MMF and basiliximab; 2-3 month steroid withdrawal vs steroid avoidance,	Prospective observational study (DIVAT database); 10 year	3 month AR: HR: 1.23, p=.5349;Late AR: HR: 4.06, p=.0585; GL in diabetes recipients: HR:8.18; p=0.0065 (steroid withdrawal vs steroid avoidance);Median time to GL(including death with functioning graft): 3.6 years

			follow-up; N=572 patients	Death: 20.59% vs 20.00%, p=ns; NODM: 11% vs 9%, p=.5437

PS: patient survival; GS: graft survival; GL: graft loss; BP: blood pressure; NODM: new-onset diabetes mellitus; TC: total cholesterol; TG: total triglycerides; CAN: chronic allograft nephropathy; CMV: cytomegalovirus; MMF: mycophenolate mofetil; ALG: anti-lymphoblast globulin; ATG: anti-thymocyte globulin

6.2 Patient transition tables for post-kidney transplantation simulation model

Table 2: Patient transitions in the simulation model

Table 2.1: Allowed events

Event	Allowed Next Event												
	AR	GL[a]	MI	Stroke	CVD[b]	NODM[c]	Cancer[d]	BI	CMV	Fx	D-GL	D-Cardio[e]	D-Other
AR	x	x	x	x	x	x	x	x	x	x			x
GL			x	x	x	x	x	x	x	x	x		X
MI	x	x	x	x	x	x	x	x	x	x		x	x
Stroke	x	x	x	x	x	x	x	x	x	x		x	x
CVD	x	x	x	x		x	x	x	x	x		x	x
NOD	x	x	x	x	x		x	x	x	x		x	x
Cancer	x	x	x	x	x	x		x	x	x		x	x
BI	x	x	x	x	x	x	x	x	x	x			x
CMV	x	x	x	x	x	x	x	x	x	x			x
Fx	x	x	x	x	x	x	x	x	x	x			x
D-GL	na	na	na	na	na	na	na	na	na	na	na	na	na
D-Cardio	na	na	na	na	na	na	na	na	na	na	na	na	na
D-Other	na	na	na	na	na	na	na	na	na	na	na	na	na

[a] Patients who have had a GL (and are now on dialysis) will not be allowed to have a GL event.
[b] CVD does not include MI or Stroke. Patients with CVD already (either pre-existing or as an event post-transplant) will not be allowed to have CVD as an event.
[c] Patients with pre-existing diabetes or who have had NODM as an event will not be allowed to have NOD as an event.
[d] Patients with a prior malignancy will not be allowed to have cancer as an event.
[e] Patients with pre-existing CVD, pre-existing diabetes, or pre-existing cancer will be allowed to go to D-Cardio without first having MI, Stroke, NODM, cancer, or CVD.
na: not applicable.
MI: myocardial infarction; CVD: other cardiovascular diseases; NODM: new-onset diabetes mellitus; BI: bacterial infection; CMV: cytomegalovirus infection; FX: fracture; GL: graft loss; D-GL: death due to graft loss; D-Cardio: death due to cardiovascular diseases; D-Other=death due to other reasons

Table 2.2: Updating for personal Weibull curves

Attribute Description	Event												
	AR	**GL**	**MI**	**Str**	**CVD**	**NODM**	**Cancer**	**BI**	**CMV**	**Fx**	**D-GL**	**D-Cardio**	**D-Other**
Steroid Avoidance													
7 Day Withdrawal													
3 month Withdrawal													
6 month Withdrawal													
12 month Withdrawal													
Steroid Maintenance													
Young (18-40)													
Middle-Aged (40-60)	x	x	x	x	x	x	x	x		x		x	x
Elderly (60+)	x	x	x	x	x	x	x	x		x		x	x
White													
Black													
Other Race													
Hispanic													
Male													
Female													
Low Weight (BMI<18.5)													
Normal Weight (18.5-35)													
Obese (BMI≥35)													
Diabetes			>3y	>3y	>3y		>3y	>3y		>3y		>3y	>3y
HTN													

HPL													
CVD History	>1y	>1y	>1y	>1y		>1y		>1y	>1y	>1y		>1y	>1y
Malignancy		x	x										x
CMV													
EBV													
HCV or HIV													
Creatinine >1.4mg/dl													
Prior Dialysis Period (0-1 years)													
Prior Dialysis Period (1-3 years)		>1y			>1y	>1y		>1y	>1y	>1y		>1y	>1y
Prior Dialysis Period (>3 years)		>3y			>3y	>3y		>3y	>3y	>3y		>3y	>3y
HLA mismatch 0-1													
HLA mismatch 2													
HLA mismatch >2													
Live Donor													
Cadaveric Donor													
Cold Ischemia Time (0-12 hours)													
Cold Ischemia Time (12-24 hours)													
Cold Ischemia Time (>24 hours)													
IL2 Induction													

Polyclonal Induction													
Monoclonal Induction													
Alemtuzumab Induction													
Induction Switch													
Acute Rejection		x	x	x	x	x	x	x	x	x	x	x	x

Notes: Personal Weibulls will not be updated often. However, if a patient moves into another age category (middle-aged or elderly), is diagnosed with cancer, or has an acute rejection, his/her Weibulls will be updated immediately to reflect that change (for the events where an "x" is shown, where "x" signifies a statistically significant effect except in the case of AR for which the coefficient may or may not be significant). If a patient is diagnosed with diabetes or CVD, his/her Weibulls will be updated with a lag to reflect the fact that newly diagnosed patients do not immediately reach the full event risks that come with a longer time with the disease. Finally, once a patient starts dialysis following graft loss, his/her Weibulls will be updated after 1 year and then again after 3 years for those events for which length of time on dialysis has a statistically significant impact.

MI: myocardial infarction; Str: stroke; CVD: other cardiovascular diseases; NODM: new-onset diabetes mellitus; BI: bacterial infection; CMV: cytomegalovirus infection; FX: fracture; GL: graft loss; D-GL: death due to graft loss; D-Cardio: death due to cardiovascular diseases; D-Other=death due to other reasons; HTN: hypertension; HPL: hyperlipidemia; EBV: Epstein Barr virus

6.3 Cohort description and summary time to event tables for various events

Table 3: Cohort description for events 'graft loss', 'acute rejection', 'death due to graft loss', 'death due to cardiovascular diseases', and 'death due to other reasons'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total (%)[b]					
55,028 (100)	333 (0.6)	1,809 (3.3)	2,444 (4.4)	2,328(4.2)	48,114 (87.4)
Age group					
18-40 years	98 (29.4)	515 (28.5)	585(23.9)**	601 (25.8)	13,263 (27.6)
40-60 years	153 (45.9)	878 (48.5)	1,253 (51.3)	1,217(52.3)	24,526 (50.9)
=>60 years	82 (24.6)	416 (23.0)	606(24.8)**	510(21.9)	10,325 (21.5)
Race					
White	216 (64.9)	1,155 (63.8)	1,650(67.5)**	1,634(70.2)**	29,941 (62.2)
Black	84 (25.2)	464 (25.6)	510(20.9)**	495(21.3)**	13,240 (27.5)
Other	33 (9.9)	190 (10.5)	284 (11.6)*	199 (8.5)	4,930 (10.2)
Ethnicity					
Hispanic	27 (8.1)*	253 (12.99)*	238 (9.7)**	237 (10.2)**	7,501 (15.6)
Non-Hispanic	306 (91.9)	1,574 (87.0)	2,206(90.3)	2,091 (90.3)	40,613(84.4)
Sex					
Male	196 (58.9)	1,061 (58.6)	1,426 (58.3)	1,286 (55.2)*	27,918 (58.0)
Female	137 (41.1)	748 (41.3)	1,018 (41.6)	1,042 (44.8)	20,196 (42.0)
BMI					
<18	9 (2.7)	49 (2.7)	61 (2.5)	61 (2.6)	1,380 (2.9)
18- 34	254 (76.3)	1,304(72.1)*	1,915(78.4)**	1,673 (71.9)*	35,704 (74.2)
=>35	25 (7.5)	176 (9.7)**	226 (9.3)**	166 (7.1)	3,445 (7.2)
Diabetes history					
Yes	106 (31.8)	612 (33.8)*	828 (33.9)*	734 (31.5)	15,237 (31.7)
No	222 (66.7)	1,119 (61.9)	1,510 (61.8)	1,417 (60.9)	29,721 (61.8)
Hypertension history					
Yes	293(87.9)*	1,633 (90.3)	2,206 (90.3)	2,086 (89.6)	43,743(90.9)
No	17 (5.1)	83 (4.6)	84 (3.4)	105 (4.5)	2,137 (4.4)

Hyperlipidemia history					
Yes	11(3.3)*	41(2.3)*	89 (3.6)*	41 (1.8)	731 (1.5)
No	29 (8.7)*	130 (7.2)*	199 (8.1)	127 (5.5)	2,312 (4.8)
Other CVD history					
Yes	86 (25.8)	442 (24.4)	600 (24.5)	522 (22.4)	11,230 (23.3)
No	241 (72.4)	1,277 (70.6)	1,726 (70.6)	1,599 (68.7)	33,456 (69.5)
Malignancy history					
Yes	19 (5.7)	83 (4.6)	123 (5.0)	108 (4.6)	2,044 (4.2)
No	308 (92.5)	1,634 (90.3)	2,193 (89.7)	2,000 (85.9)	42,413 (88.2)
CMV history					
Yes	0 (0.0)**	20 (1.1)**	51 (2.1)**	153 (6.6)	2,766 (5.75)
No	0 (0.0)	19 (1.1)	48 (1.9)	118 (5.6)	1,609 (3.3)
EBV history					
Yes	44 (13.2)*	363 (20.1)*	358 (14.6)**	409 (17.6)**	10,689 (22.2)
No	177 (53.1)	782 (43.2)	1,231 (50.4)	1,048 (45.0)	21,929 (45.6)
HCV/HIV history					
Yes	65(19.5)**	258 (14.3)**	300 (12.3)**	246 (10.6)	4,455 (9.3)
No	211 (63.4)	1,167 (64.5)	1,667 (68.2)	1,750 (75.2)	37,292 (77.5)
Serum creatinine post kidney transplantation					
<1.4 mg/dl	163 (48.9)	817 (45.2)	1,278 (52.3)	1,202 (51.6)	23,771 (49.4)
=>1.4 mg/dl	170 (51.1)	992 (54.8)*	1,166 (47.7)*	1,126 (48.4)*	24,343 (50.6)
Dialysis time					
0-1 years	62 (18.7)	323 (17.9)	475 (19.5)*	432 (18.6)*	8,126 (16.9)
1-3 years	79 (23.8)*	543 (30.0)	742 (30.4)	734 (31.6)	14,289 (29.7)
>3 years	79 (23.8)*	525 (29.0)*	573 (23.5)**	563 (24.2)**	15,679 (32.6)
Cold ischemic time					
0-12 hours	121 (36.3)	634 (35.1)*	923 (37.8)	940 (40.4)*	18,350 (38.1)
12-24 hours	95 (28.5)	469 (25.9)*	621 (25.4)**	610 (26.2)*	14,196 (29.5)
>24 hours	39 (11.7)	283 (15.6)*	281 (11.5)*	345 (14.8)*	6,310 (13.1)

Donor type					
Live	141 (42.3)	772 (42.7)*	1,140(46.6)**	990 (42.5)*	18,705 (38.9)
Cadaveric	192 (57.7)	1,037 (57.3)	1,304 (53.4)	1,338 (57.5)	29,409 (61.1)
HLA mismatch					
0-1	51 (15.3)	227 (12.6)*	420 (17.2)*	403 (17.3)*	7,114 (14.8)
2	39 (11.7)	187 (10.3)	277 (11.3)	293 (12.6)*	5,095 (10.6)
>2	242 (72.7)	1,371(75.8)*	1,693(69.3)**	1,607(69.0)**	35,111 (72.9)
Induction agent					
IL2 Induction	17 (5.1)**	282 (15.6)**	499 (20.4)**	553 (23.7)**	14,082(29.3)
Polyclonal Induction	126 (37.8)*	789 (43.6)**	1,042(42.6)**	647 (27.8)**	15,756 (32.7)
Monoclonal Induction	0(0.0)**	19(1.1)**	31(1.3)**	65(2.8)	1,620(2.9)
Alemtuzumab Induction	37 (11.1)**	345 (19.1)**	149 (6.1)**	95 (4.1)**	694 (1.4)
Switch from tacrolimus to cyclosporine /sirolimus					
Yes	111(33.3)**	569 (31.4)**	646 (26.4)*	653 (28.0)**	11,678 (24.3)
No	222 (66.7)	1,240 (68.5)	1,798 (73.6)	1,675 (71.9)	36,436 (75.7)
Acute rejection					
Yes	41 (12.3)	239 (13.2)	320 (13.1)	324 (13.9)	6,554 (13.6)
No	292 (87.7)	320 (13.1)	2,124 (86.9)	2,004 (86.1)	41,560 (86.4)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 4: Time to acute rejection (in months) and number of patients with acute rejection (AR)

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with AR (%)[b]
	47.9	5.9	55,028 (100)	9,042 (16.4)
Steroid avoidance	35.9	23.9	333 (0.6)	93 (27.9)
7-day steroid withdrawal	35.9	11.9	1,809 (3.3)	559 (30.9)
6 month steroid withdrawal	47.9	5.9	2,444 (4.4)	375 (15.3)
1 year steroid withdrawal	59.9	5.9	2,328 (4.2)	375 (16.1)
Steroid maintenance	48.7	5.9	48,114 (87.4)	7,640 (15.8)

[a] Percent of column total
[b] Percent of row total

Table 5. Time to graft loss (in months) and number of patients with graft loss

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with graft loss (%)[b]
	59.9	43.5	55,028 (100)	8,123 (14.8)
Steroid avoidance	47.9	26.7	333 (0.6)	68 (20.4)
7-day steroid withdrawal	47.9	30.5	1,809 (3.3)	379 (20.9)
6 month steroid withdrawal	59.9	45.5	2,444 (4.4)	225 (9.2)
1 year steroid withdrawal	47.9	46.2	2,328 (4.2)	337 (14.5)
Steroid maintenance	59.9	44.3	48,114 (87.4)	7,114 (14.8)

[a] Percent of column total
[b] Percent of row total

Table 6: Time to death due to graft loss (in months) and number of patients who died due to graft loss

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with death due to graft loss (%)[b]
	59.9	52.2	55,028 (100)	73 (0.1)
Steroid avoidance	35.9	16.7	333 (0.6)	1 (0.3)
7-day steroid withdrawal	35.9	76.9	1,809 (3.3)	1 (0.1)
6 month steroid withdrawal	47.9	154.6	2,444 (4.4)	1(0.1)
1 year steroid withdrawal	59.9	40.7	2,328 (4.2)	3 (0.1)
Steroid maintenance	48.7	52.4	48,114 (87.4)	67 (0.1)

[a] Percent of column total
[b] Percent of row total

Table 7: Time to death due to cardiovascular diseases (in months) and number of patients who died due to cardiovascular diseases (CVD)

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with death due to CVD (%)[b]
	59.9	50.2	55,028 (100)	1,379 (2.5)
Steroid avoidance	47.9	82.6	333 (0.6)	3 (0.9)
7-day steroid withdrawal	47.9	31.9	1,809 (3.3)	40 (2.2)
6 month steroid withdrawal	51.4	50.6	2,444 (4.4)	45 (1.8)
1 year steroid withdrawal	65.2	59.5	2,328 (4.2)	58 (2.5)
Steroid maintenance	59.9	50.6	48,114 (87.4)	1,233 (2.6)

[a] Percent of column total
[b] Percent of row total

Table 8: Time to death due to other reasons (in months) and number of patients who died due to other reasons

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients who died due to other reasons (%)[b]
	59.9	49.3	55,028 (100)	2,028 (3.7)
Steroid avoidance	47.9	44.0	333 (0.6)	11 (3.3)
7-day steroid withdrawal	47.9	31.1	1,809 (3.3)	60 (3.3)
6 month steroid withdrawal	51.4	56.4	2,444 (4.4)	66 (2.7)
1 year steroid withdrawal	65.2	52.4	2,328 (4.2)	74 (3.2)
Steroid maintenance	59.9	49.6	48,114 (87.4)	1,817 (3.8)

[a] Percent of column total
[b] Percent of row total

Table 9: Cohort description for the event 'myocardial infarction'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total (%)[b]					
16,795 (100)	163 (0.9)	761 (4.5)	1,216 (7.2)	594 (3.5)	14,061 (83.7)
Age group					
18-40 years	44 (26.9)	207 (27.2)	292 (24.0)	123 (20.7)	3,398 (24.2)
40-60 years	77 (47.2)	370 (48.6)	585 (48.1)	309 (52.0)	6,981 (49.6)
=>60 years	42 (25.8)	184 (24.2)	339 (27.9)	162 (27.3)	3,682 (26.2)
Race					
White	92 (56.4)	469 (61.6)*	769 (63.2)**	392 (65.9)**	7,688 (54.7)
Black	56 (34.4)	194 (25.5)*	267 (21.9)**	133 (22.4)**	2,166 (15.4)
Other	15 (9.2)*	98 (12.9)	180 (14.8)	69 (11.6)*	4,207 (29.9)
Ethnicity					
Hispanic	15 (9.2)*	100 (13.1)*	122 (10.0)**	60 (10.1)*	2,224 (15.8)
Non-Hispanic	148 (90.8)	661 (86.9)	1,094 (89.9)	534 (89.9)	11,837 (84.2)
Sex					
Male	73 (44.8)	303 (39.8)	508 (41.8)	254 (42.8)	5,778 (41.1)
Female	90 (55.2)	458 (60.2)	708 (58.2)	340 (57.2)	8,283 (58.9)
BMI					
<18	5 (3.1)	21 (2.8)	29 (2.4)*	14 (2.4)	10,996 (78.2)
18- 34	121 (74.2)	582 (76.5)	989 (81.3)	477 (80.3)	381 (2.7)
=>35	15 (9.2)	91 (11.9)*	132 (10.9)*	49 (8.2)	1,240 (8.8)
Diabetes history					
Yes	40 (24.5)	231 (30.3)	363 (29.8)	174 (29.3)	3,933 (27.9)
No	122 (74.8)	526 (69.1)	846 (69.6)	418 (70.4)	10,083 (71.7)
Hypertension history					
Yes	141 (86.5)	700 (91.9)	1,088 (89.5)*	551 (92.8)	12,903 (91.8)
No	8 (4.9)	20 (2.6)	34 (2.8)	9 (1.5)	451 (3.2)
Hyperlipidemia history					
Yes	17 (10.4)	83 (10.9)*	156 (12.8)*	63 (10.6)	1,252 (8.9)
No	7 (4.3)	30 (3.9)	59 (4.8)	21 (3.5)	466 (3.3)

Other CVD history					
Yes	28 (17.2)	156 (20.5)	255 (20.9)*	113 (19.0)	2,523 (17.9)
No	39 (23.9)	206 (27.1)	364 (29.9)	149 (25.1)	2,980 (21.2)
Malignancy history					
Yes	8 (4.9)	43 (5.6)	74 (6.1)	28 (4.7)	713 (5.1)
No	152 (93.2)	701 (92.1)	1,120 (92.1)	556 (93.6)	13,044 (92.8)
HCV/HIV history					
Yes	83 (50.9)	407 (53.5)	646 (53.1)	380 (63.9)	8,202 (58.3)
No	39 (23.9)	112 (14.7)	204 (16.8)	84 (14.1)	2,511 (17.9)
Serum creatinine					
<1.4 mg/dl	320 (42.0)	617 (50.7)	298 (50.2)	6,911 (49.1)	75 (46.0)
=>1.4 mg/dl	434 (57.0)	594 (48.8)	289 (48.6)	7,057 (50.2)	84 (51.5)
Dialysis time					
0-1 years	29 (17.9)	147 (19.3)**	378 (31.1)**	106 (17.8)*	1,989 (14.2)
1-3 years	36 (22.2)	218 (28.6)	222 (18.3)	175 (29.5)	4,169 (29.7)
>3 years	43 (26.5)*	242 (31.8)**	322 (26.5)**	168 (28.3)*	5,182 (36.9)
Cold ischemic time					
0-12 hours	60 (36.8)	271 (35.6)*	473 (38.9)*	249 (41.9)	5,971 (42.5)
12-24 hours	49 (30.1)	224 (29.4)*	362 (29.8)*	167 (28.1)*	4,705 (33.5)
>24 hours	19 (11.7)	112 (14.7)*	131 (10.8)	62 (10.4)	1,600 (11.4)
Donor type					
Live	57 (34.9)	299 (39.3)*	497 (40.9)*	260 (43.8)**	4,988 (35.5)
Cadaveric	106 (65.0)	462 (60.7)	719 (59.1)	334 (56.2)	9,073 (64.5)
HLA mismatch					
0-1	15 (9.2)	72 (9.5)*	184 (15.1)*	86 (14.5)	15 (9.2)
2	133 (81.6)	603 (79.2)	886 (72.9)	441 (74.2)	133 (81.6)
>2	14 (8.6)	73 (9.6)*	117 (9.6)*	64 (10.8)	14 (8.6)
Induction agent					
IL2 Induction	4 (2.4)**	100 (13.1)**	206 (16.9)**	180 (30.3)	3,791 (26.9)
Polyclonal Induction	57 (34.9)*	393 (51.6)*	608 (50.0)*	228 (38.4)*	6,485 (46.1)

Monoclonal Induction	0 (0.0)	3 (0.4)	5 (0.4)	0 (0.0)	41 (0.3)
Alemtuzumab Induction	25 (15.3)**	206 (27.1)**	106 (8.7)**	43 (7.2)**	367 (2.6)
Switch from tacrolimus to cyclosporine /sirolimus					
Yes	33 (20.2)	190 (24.9)**	264 (21.7)**	112 (18.9)	2,382 (16.9)
No	130 (79.7)	571 (75.0)	952 (78.3)	482 (81.1)	11,679 (83.1)
Acute rejection					
Yes	8 (4.9)	39 (5.1)	130 (10.7)**	39 (6.6)	750 (5.3)
No	155 (95.1)	722 (94.9)	1,066 (89.3)	555 (93.4)	13,311 (94.7)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 10: Time to myocardial infarction (in months) and number of patients with myocardial infarction

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with myocardial infarction (%)[b]
	35.8	14.2	16,795 (100)	940 (5.6)
Steroid avoidance	36.0	18.7	163 (0.9)	11 (6.7)
7-day steroid withdrawal	33.6	23.1	761 (4.5)	48 (6.3)
6 month steroid withdrawal	34.6	12.1	1,216 (7.2)	56 (4.6)
1 year steroid withdrawal	37.2	3.6	594 (3.5)	23 (3.9)
Steroid maintenance	35.9	13.8	14,061 (83.7)	802 (5.7)

[a] Percent of column total
[b] Percent of row total

Table 11: Cohort description for the event 'stroke'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total (%)[b]					
16,658 (100)	163(0.9)	750 (4.5)	1,073 (6.4)	603 (3.6)	14,069 (84.5)
Age group					
18-40 years	43 (26.4)	205 (27.3)*	241 (22.5)	120 (19.9)*	3,400 (24.2)
40-60 years	77 (47.2)	357 (47.6)	534 (49.8)	315 (52.2)	7,032 (49.9)
=>60 years	43 (26.4)	188 (25.1)	298 (27.8)	168 (27.9)	3,637 (25.8)
Race					
White	94 (57.7)*	448 (59.7)	672 (62.6)*	399 (66.2)	7,818 (55.6)
Black	56 (34.4)	206 (27.5)	230 (21.4)**	132 (21.9)**	4,107 (29.2)
Other	13 (7.9)	96 (12.8)*	171 (15.9)**	72 (11.9)**	2,144 (15.2)
Ethnicity					
Hispanic	16 (9.8)*	90 (12.0)*	98 (9.1)**	64 (10.6)*	2,208 (15.7)
Non-Hispanic	147 (90.2)	660 (88.0)	975 (90.9)	539 (89.4)	11,861 (84.3)
Sex					
Male	88 (53.9)	458 (61.1)	627 (58.4)	354 (58.7)	8,441 (60.0)
Female	75 (46.0)	292 (38.9)	446 (41.6)	249 (41.3)	5,628 (40.0)
BMI					
<18	5 (3.1)	23 (3.1)	27 (2.5)	13 (2.2)	366 (2.6)
18- 34	120 (73.6)	579 (77.2)	868 (80.9)*	476 (78.9)	11,008 (78.2)
=>35	16 (9.8)	86 (11.5)*	121 (11.3)*	58 (9.6)	1,245 (8.8)
Diabetes history					
Yes	43(26.4)	221 (29.5)	331 (30.8)	187 (31.0)	4,020 (28.6)
No	120 (73.6)	526 (70.1)	735 (68.5)	414 (68.7)	10,009 (71.1)
Hypertension history					
Yes	142 (87.1)*	692 (92.3)	967 (90.1)	559 (92.7)	12,933 (91.9)
No	8 (4.9)	19 (2.5)	26 (2.4)	9 (1.5)	449 (3.2)
Hyperlipidemia history					
Yes	17 (10.4)	83 (11.1)	126 (11.7)	61 (10.1)	1,226 (8.7)
No	7 (4.3)	28 (3.7)	50 (4.7)	22 (3.6)	453 (3.2)

Other CVD history					
Yes	34 (20.9)	181 (24.1)	270 (25.2)	144 (23.9)	3,008 (21.4)
No	127 (77.9)	554 (73.9)	786 (73.2)	451 (74.8)	10,773 (76.6)
Malignancy history					
Yes	7 (4.3)	37 (4.9)	65 (6.1)	31 (5.1)	706 (5.0)
No	154 (94.5)	698 (93.1)	991 (92.4)	563 (93.4)	13,073 (92.9)
EBV history					
Yes	79 (48.5)	300 (40.0)	484 (45.1)	303 (50.2)	6,345 (45.1)
No	21 (12.9)	131 (17.5)	134 (12.5)	102 (16.9)	2,510 (17.8)
HCV/HIV history					
Yes	88 (53.9)*	412 (54.9)*	395 (65.5)*	88 (53.9)*	8,456 (60.1)
No	35 (21.5)	112 (14.9)	79 (13.1)	35 (21.5)	2,444 (17.4)
Serum creatinine					
<1.4 mg/dl	85 (52.1)	426 (56.8)*	522 (48.6)	303 (50.2)	7,137 (50.7)
=>1.4 mg/dl	75 (46.0)	317 (42.3)	545 (50.8)	295 (48.9)	6,838 (48.6)
Dialysis time					
0-1 years	29 (17.9)	142 (18.9)	197 (18.4)	105 (17.4)	2,032 (14.5)
1-3 years	38 (23.5)	223 (29.7)	336 (31.4)	185 (30.7)	4,213 (30.0)
>3 years	39 (24.1)**	229 (30.5)*	277 (25.9)*	161 (26.7)**	5,064 (36.1)
Cold ischemic time					
0-12 hours	60 (36.8)	267 (35.6)	416 (38.8)	260 (43.1)	5,992 (42.6)
12-24 hours	49 (30.1)	212 (28.3)	317 (29.5)	163 (27.0)	4,642 (32.9)
>24 hours	23 (14.1)	115 (15.3)	117 (10.9)	64 (10.6)	1,599 (11.4)
Donor type					
Live	59 (36.2)	301 (40.1)*	451 (42.0)**	267 (44.3)**	5,085 (36.1)
Cadaveric	104 (63.8)	449 (59.9)	622 (57.9)	336 (55.7)	8,984 (63.9)
HLA mismatch					
0-1	15 (9.2)	69 (9.2)*	172 (16.0)*	90 (14.9)*	1,751 (12.4)
2	16 (9.8)	69 (9.2)	116 (10.8)*	67 (11.1)*	1,207 (8.6)
>2	131 (80.4)	599 (79.9)	763 (71.1)**	443 (73.5)*	10,962 (77.9)

Induction agent					
IL2 Induction	4 (2.4)**	90 (12.0)**	185 (17.2)**	177 (29.3)	3,817 (27.1)
Polyclonal Induction	57 (34.9)*	393 (52.4)*	525 (48.9)*	238 (39.5)*	6,443 (45.8)
Monoclonal Induction	0 (0.0)	2 (0.3)	4 (0.4)	0 (0.0)	42 (0.3)
Alemtuzumab Induction	27(16.6)**	207 (27.6)**	88 (8.2)**	44 (7.3)**	387 (2.7)
Switch from tacrolimus to cyclosporine /sirolimus					
Yes	34 (20.9)	192 (25.6)	226 (21.1)**	113 (18.7)	2,384 (16.9)
No	129 (79.1)	558 (74.4)	847 (78.9)	490 (81.3)	129 (79.1)
Acute rejection					
Yes	9 (5.5)	38 (5.1)	102 (9.5)**	34 (5.6)	765 (5.4)
No	154 (94.5)	712 (94.9)	971 (90.5)	569 (94.4)	13,304 (94.6)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 12: Time to stroke (in months) and number of patients with stroke

	Median follow-up time	Median time to event	# of censored patients (%)[a]	# of patients with stroke (%)[b]
	35.4	20.2	16,658 (100)	1,929 (7.4)
Steroid avoidance	35.6	18.2	163 (0.9)	17 (10.4)
7-day steroid withdrawal	32.3	19.6	750 (4.5)	101 (13.5)
6 month steroid withdrawal	34.5	14.6	1073 (6.4)	114 (10.6)
1 year steroid withdrawal	36.2	18.9	603 (3.6)	68 (11.3)
Steroid maintenance	35.5	20.7	14,069 (84.5)	1,629 (11.6)

[a] Percent of column total
[b] Percent of row total

Table 13: Cohort description for the event 'other cardiovascular diseases'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total (%)[b]					
7,319 (100)	77 (1.0)	329 (4.5)	563 (7.7)	284 (3.9)	6,066 (82.9)
Age group					
18-40 years	28 (36.4)	124 (37.7)*	103 (18.3)	73 (25.7)	1,874 (30.9)
40-60 years	35 (45.4)	150 (45.6)	289 (51.3)	162 (57.0)	3,101 (51.1)
=>60 years	14 (18.2)	55 (16.7)	171 (30.4)	49 (17.3)	1,091 (17.9)
Race					
White	45 (58.4)	225 (68.4)*	402 (71.4)**	208 (73.2)**	3,645 (60.1)
Black	26 (33.8)	66 (20.1)	78 (13.8)**	36 (12.7)**	1,521 (25.1)
Other	6 (7.8)	38 (11.6)	83 (14.7)	40 (14.1)	900 (14.8)
Ethnicity					
Hispanic	6 (7.8)	31 (9.4)*	49 (8.7)*	31 (10.9)	833 (13.7)
Non-Hispanic	833 (13.7)	298 (90.6)	514 (91.3)	253 (89.1)	5,233 (86.3)
Sex					
Male	42 (54.6)*	134 (40.7)	249 (44.2)	142(50.0)	2,626 (43.3)
Female	35 (45.4)	195 (59.3)	314 (55.8)	142 (50.0)	3,440 (56.7)
BMI					
<=18	2 (2.6)	11 (3.3)	14 (2.5)	8 (2.8)	170 (2.8)
18- 34	61 (79.2)	254 (77.2)*	461 (81.9)*	228 (80.3)	4,834 (79.7)
=>35	4 (5.2)	38 (11.5)*	53 (9.4)*	22 (7.7)	484 (7.9)
Diabetes history					
Yes	17 (22.1)	78 (23.7)	110 (19.5)	66 (23.2)	1,266 (20.9)
No	59 (76.6)	246 (74.8)	444 (78.9)	214 (75.3)	4,668 (76.9)
Hypertension history					
Yes	62 (80.5)*	292 (88.7)	484 (85.9)	254 (89.4)	62 (80.5)
No	5 (6.5)	10 (3.0)	16 (2.8)	5 (1.8)	5 (6.5)
Hyperlipidemia history					
Yes	12 (15.6)	45 (13.7)	83 (14.7)	34 (11.9)	725 (11.9)
No	7 (9.1)	16 (4.9)	38 (6.7)	17 (5.9)	261 (4.3)

Malignancy history					
Yes	2 (2.6)	24 (7.3)	27 (4.8)	13 (4.6)	282 (4.6)
No	74 (96.1)	300 (91.2)	527 (93.6)	267 (94.0)	5,655 (93.2)
HCV/HIV history					
Yes	41 (53.2)*	186 (56.5)*	304 (54.0)**	195 (68.7)*	3,841 (63.3)
No	8 (10.4)	39 (11.8)	68 (12.1)	29 (10.2)	741 (12.2)
Serum creatinine					
<1.4 mg/dl	37 (48.0)	136 (41.3)*	297 (52.7)	158 (55.6)	3,005 (49.5)
=>1.4 mg/dl	38 (49.3)	188 (57.1)	263 (46.7)	125 (44.0)	3,025 (49.9)
Dialysis time					
0-1 years	19 (24.7)*	83 (25.2)*	127 (22.6)*	63 (22.2)*	1,158 (19.1)
1-3 years	14 (18.2)	90 (27.4)	172 (30.6)	84 (29.6)	1,823 (30.1)
>3 years	11 (14.3)*	57 (17.3)*	84 (14.9)**	38 (13.4)**	1,396 (23.1)
Cold ischemic time					
0-12 hours	27 (35.1)	131 (39.8)*	248 (44.1)	138 (48.6)	2,816 (46.4)
12-24 hours	21 (27.3)	79 (24.0)*	150 (26.6)	59 (20.8)*	1,735 (28.6)
>24 hours	9 (11.7)	38 (11.5)	54 (9.6)	29 (10.2)	574 (9.5)
Donor type					
Live	34 (44.2)	172 (52.3)*	273 (48.5)	159 (55.9)**	2,749 (45.3)
Cadaveric	43 (55.8)	157 (47.7)	290 (51.5)	125 (44.0)	3,317 (54.7)
HLA mismatch					
0-1	11(14.3)	30 (9.1)*	108 (19.2)*	47 (16.6)	815 (13.4)
2	57 (74.0)	247 (75.1)	385 (68.4)*	196 (69.0)	4,604 (75.9)
>2	9 (11.7)	45 (13.7)**	61 (10.8)*	39 (13.7)**	580 (9.6)
Induction agent					
IL2 Induction	2 (2.6)**	53 (16.1)**	96 (17.1)**	94 (33.1)**	1,747 (28.8)
Polyclonal Induction	25 (32.5)*	167 (50.8)*	167 (50.8)*	103 (36.3)*	2,683 (44.2)
Monoclonal Induction	0 (0.0)	1 (0.3)	3 (0.5)	0 (0.0)	19 (0.3)
Alemtuzumab Induction	15 (19.5)**	82 (24.9)**	58 (10.3)**	21 (7.4)**	149 (2.5)

Switch from tacrolimus to cyclosporine/ sirolimus					
Yes	16 (20.8)	102 (31.0)	120 (21.3)*	48 (16.9)	1,057 (17.4)
No	61 (79.2)	227 (69.0)	443 (78.7)	236 (83.1)	5,009 (82.6)
Acute rejection					
Yes	5 (6.5)	12 (3.6)	46 (8.2)**	15 (5.3)	283 (4.7)
No	72 (93.5)	317 (96.3)	517 (91.8)	269 (94.7)	5,783 (95.3)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 14: Time to other cardiovascular diseases (in months) and number of patients with other cardiovascular diseases

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with other cardiovascular diseases (%)[b]
	23.8	8.9	7,319 (100)	2,913 (39.8)
Steroid avoidance	24.2	15.2	77 (1.0)	36 (46.7)
7-day steroid withdrawal	20.8	11.7	329 (4.5)	151 (45.9)
6 month steroid withdrawal	24.4	9.7	563 (7.7)	179 (31.8)
1 year steroid withdrawal	26.7	9.6	284 (3.9)	116 (40.8)
Steroid maintenance	23.7	8.4	6,066 (82.9)	2,431 (40.1)

[a] Percent of column total
[b] Percent of row total

Table 15: Cohort description for the event 'new-onset diabetes mellitus'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total (%)[b]					
9,973 (100)	97 (0.9)	430 (4.3)	717 (7.2)	377 (3.8)	8,352 (83.7)
Age group					
18-40 years	33 (34.0)	148 (34.4)	208 (29.0)	94 (24.9)	4,071 (48.7)
40-60 years	40 (41.2)	190 (44.2)	342 (47.7)	193 (51.2)	2,502 (29.9)
=>60 years	24 (24.7)	92 (21.4)	167 (23.3)	90 (23.9)	1,779 (21.3)
Race					
White	65 (67.0)	279 (64.9)	510 (71.1)	265 (70.3)	4,834 (57.9)
Black	23 (23.7)	107 (16.7)	120 (16.7)	71 (18.8)	2,369 (28.4)
Other	9 (9.3)	44 (10.2)	87 (12.1)	41 (10.9)	1,149 (13.8)
Ethnicity					
Hispanic	10 (10.3)	43 (10.0)	50 (6.9)	36 (9.6)	1,060 (12.7)
Non-Hispanic	87 (89.7)	387 (90.0)	667 (93.0)	341 (90.4)	7,292 (87.3)
Sex					
Male	47 (48.4)	172 (40.0)	319 (44.5)	170 (45.1)	3,511 (42.0)
Female	50 (51.5)	258 (60.0)	398 (55.5)	207 (54.9)	4,841 (57.9)
BMI					
<=18	3 (3.1)	15 (3.5)	23 (3.2)	14 (3.7)	276 (3.3)
18- 34	74 (76.3)	349 (81.2)	586 (81.7)	303 (80.4)	6,692 (80.1)
=>35	6 (6.2)	32 (7.4)	64 (8.9)	22 (5.8)	529 (6.3)
Hypertension history					
Yes	6 (6.2)	389 (90.5)	631 (86.0)	349 (92.6)	7,595 (90.9)
No	81 (83.5)	13 (3.0)	25 (3.5)	6 (1.6)	296 (3.5)
Hyperlipidemia history					
Yes	12 (12.4)	47 (10.9)	92 (12.8)	38 (10.1)	737 (8.8)
No	3 (3.1)	16 (3.7)	41 (5.7)	17 (4.5)	275 (3.3)

Other CVD history					
Yes	12 (12.3)	78 (18.1)	122 (17.0)	71 (18.8)	1,201 (14.4)
No	85 (87.6)	352 (81.9)	595 (82.9)	306 (81.2)	7,151 (85.6)
Malignancy history					
Yes	3 (3.1)	29 (6.7)	41 (5.7)	20 (5.3)	456 (5.5)
No	92 (94.8)	393 (91.4)	662 (92.3)	350 (92.8)	7,679 (91.9)
HCV/HIV history					
Yes	250 (58.1)	250 (58.1)	420 (58.6)	253 (67.1)	5,153 (61.7)
No	58 (13.5)	58 (13.5)	87 (12.1)	45 (11.9)	1,339 (16.0)
Serum creatinine					
<1.4 mg/dl	49 (50.5)	172 (40.0)	373 (52.0)	189 (50.1)	4,069 (48.7)
=>1.4 mg/dl	45 (46.4)	252 (58.6)	341 (47.6)	186 (49.3)	4,238 (50.7)
Dialysis time					
0-1 years	18 (18.6)	88 (20.5)	147 (20.6)	73 (19.4)	1,295 (15.6)
1-3 years	23 (23.7)	121 (28.1)	209 (20.2)	107 (28.4)	2,401 (28.8)
>3 years	21 (21.6)	116 (26.9)	155 (21.7)	94 (24.9)	2,831 (33.9)
Cold ischemic time					
0-12 hours	165 (38.4)	165 (38.4)	320 (44.6)	164 (43.5)	3,770 (45.1)
12-24 hours	114 (26.5)	114 (26.5)	185 (25.8)	100 (26.5)	2,583 (30.9)
>24 hours	54 (12.6)	54 (12.6)	69 (9.6)	36 (9.6)	820 (9.8)
Donor type					
Live	200 (46.5)	200 (46.5)	332 (46.3)	184 (48.8)	3327 (39.8)
Cadaveric	230 (53.5)	230 (53.5)	385 (53.7)	193 (51.2)	5,025 (60.2)
HLA mismatch					
0-1	8 (8.2)	40 (9.3)	115 (16.0)	57 (15.1)	1,026 (12.3)
2	78 (80.4)	329 (76.5)	510 (71.1)	271 (71.9)	757 (9.1)
>2	10 (10.3)	52 (12.1)	80 (11.2)	45 (11.9)	6,480 (77.6)
Induction agent					
IL2 Induction	3 (3.1)	52 (12.1)	115 (16.0)	83 (22.0)	2,298 (27.5)
Polyclonal Induction	38 (39.2)	225 (52.3)	330 (46.0)	146 (38.7)	3,818 (45.7)

Monoclonal Induction	0 (0.0)	3 (0.7)	4 (0.6)	0 (0.0)	25 (0.3)
Alemtuzumab Induction	18 (18.6)	118 (27.4)	82 (11.4)	26 (6.9)	220 (2.6)
Switch from tacrolimus to cyclosporine /sirolimus					
Yes	17 (18.6)	110 (25.6)	146 (20.4)	70 (18.6)	6,887 (82.5)
No	307 (81.4)	320 (74.4)	571 (79.6)	307 (81.4)	1,465 (17.5)
Acute rejection					
Yes	4 (4.1)	23 (5.3)	62 (8.6)	19 (5.0)	358 (4.3)
No	93 (95.9)	407 (94.6)	655 (91.3)	358 (94.9)	7,994 (95.7)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 16: Time to new-onset diabetes mellitus (NODM) (in months) and number of patients with new-onset diabetes mellitus

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with NODM (%)[b]
	24.8	5.3	9,973 (100)	4,288 (43.0)
Steroid avoidance	23.6	5.7	97 (0.9)	46 (47.4)
7-day steroid withdrawal	24.3	8.0	430 (4.3)	179 (41.6)
6 month steroid withdrawal	28.4	10.1	717 (7.2)	241 (33.6)
1 year steroid withdrawal	29.5	6.1	377 (3.8)	141 (37.4)
Steroid maintenance	24.4	4.9	8,352 (83.7)	3,681 (17.8)

[a] Percent of column total
[b] Percent of row total

Table 17: Cohort description for the event 'cancer'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total (%)[b]					
13,182 (100)	138 (1.0)	575 (4.4)	971 (7.4)	490 (3.7)	11,008 (83.5)
Age group					
18-40years	38 (27.5)	179 (31.1)*	480 (49.4)	269 (54.9)*	109 (22.2)
40-60 years	73 (52.9)	283 (49.2)	264 (27.2)	109 (22.2)	269 (54.9)
=>60 years	27 (19.6)	113 (19.6)	227 (23.4)	112 (28.9)	112 (22.9)
Race					
White	82 (59.4)	345 (60.0)	599 (61.7)	318 (64.9)	5,983 (54.3)
Black	44 (31.9)	157 (27.3)*	219 (22.5)**	60 (12.2)**	3,278 (29.8)
Other	12 (8.7)*	73 (12.7)	153 (15.8)	112 (22.9)*	1,747 (15.9)
Ethnicity					
Hispanic	12 (8.7)	77 (13.4)*	99 (10.2)**	51 (10.4)*	1,784 (16.2)
Non-Hispanic	126 (91.3)	498 (86.6)	872 (89.8)	439 (89.6)	9,224 (83.8)
Sex					
Male	61 (44.2)	237(41.2)	401 (41.3)	208 (42.4)	4,379 (39.8)
Female	77 (55.8)	338 (58.8)	570 (58.7)	282 (57.6)	6,629 (60.2)
BMI					
<18	3 (2.2)	17 (2.9)	22 (2.3)	13 (2.6)	298 (2.7)
18- 34	101 (73.2)	440 (76.5)	807 (83.1)*	388 (79.2)	8,608 (78.2)
=>35	15 (10.9)	65 (11.3)*	96 (9.9)*	46 (9.4)	975 (8.9)
Diabetes history					
Yes	34 (24.6)	181 (31.5)	290 (29.9)	150 (30.6)	3,259 (29.6)
No	103 (74.6)	391 (68.0)	676 (69.6)	339 (69.2)	7,716 (70.1)
Hypertension history					
Yes	118 (85.5)	528 (91.8)	867 (89.3)*	457 (93.3)*	10,091 (91.7)
No	7 (5.1)	12 (2.1)	25 (2.6)	6 (1.2)	341 (3.1)
Hyperlipidemia history					
Yes	14 (10.1)	62 (10.8)	127 (13.1)*	55 (11.2)	1,028 (9.3)
No	7 (5.1)	22 (3.8)	49 (5.0)	19 (3.9)	380 (3.4)

Other CVD history					
Yes	31 (22.5)	139 (24.2)	232 (23.9)	111 (22.6)	2,382 (21.6)
No	104 (75.4)	422 (73.4)	724 (74.6)	374 (76.3)	8,412 (76.4)
HCV/HIV history					
Yes	75 (54.3)	330 (57.4)	555 (57.2)	338 (68.9)*	6,822 (61.9)
No	28 (20.3)	73 (12.7)	134 (13.8)	55 (11.2)	1,722 (15.6)
Serum creatinine					
<1.4 mg/dl	69 (50.0)	490 (50.5)	236 (48.2)	65 (47.1)	5,579 (50.7)
=>1.4 mg/dl	65 (47.1)	475 (48.9)	249 (50.8)	69 (50.0)	5,355 (48.6)
Dialysis time					
0-1 years	27 (19.7)	123 (21.4)	199 (20.5)	88 (17.9)	1,737 (15.8)
1-3 years	28 (20.4)	164 (28.5)*	297 (30.6)	153 (31.2)	3,617 (32.9)
>3 years	34 (24.8)	160 (27.8)	224 (23.1)	120 (24.5)	3,327 (30.3)
Cold ischemic time					
0-12 hours	48 (34.8)	207 (36.0)	403 (41.5)	221 (45.1)	4,768 (43.3)
12-24 hours	42 (30.4)	149 (25.9)*	271 (27.9)*	129 (26.3)*	3,557 (32.3)
>24 hours	19 (13.8)	91 (15.8)*	88 (9.1)	49 (10.0)	1,196 (10.9)
Donor type					
Live	49 (35.5)	332 (57.7)*	443 (45.6)*	226 (46.1)*	4,174 (37.9)
Cadaveric	89 (64.5)	243 (42.3)	528 (54.4)	264 (53.9)	6,834 (62.1)
HLA mismatch					
0-1	13 (9.4)	53 (9.2)*	153 (15.8)*	77 (15.7)*	1,391 (12.6)
2	110 (79.7)	449 (78.1)	692 (71.3)	360 (73.5)	8,540 (77.6)
>2	14 (10.1)	62 (10.8)	105 (10.8)**	50 (10.2)	961 (8.7)
Induction agent					
IL2 Induction	2 (1.40)**	71 (12.3)**	158 (16.3)**	143 (29.2)	3,009 (27.3)
Polyclonal Induction	48 (34.8)*	297 (51.6)*	480 (49.4)*	184 (37.5)*	5,033 (45.7)
Monoclonal Induction	0 (0.0)	3 (0.5)	4 (0.4)	0 (0.0)	32 (0.3)
Alemtuzumab Induction	21 (15.2)**	163(28.3)**	96 (9.9)**	36 (7.3)**	279 (2.5)**

Switch from tacrolimus to cyclosporine /sirolimus					
Yes	26 (18.8)	149 (25.9)	209 (21.5)*	96 (19.6)	1,850 (16.8)
No	112 (81.2)	426 (74.1)	762 (78.5)	394 (80.4)	9,158 (83.2)
Acute rejection					
Yes	7 (5.1)	25 (4.3)	98 (10.1)**	31 (6.3)	540 (4.9)
No	131 (94.9)	550 (95.6)	873 (89.9)	459 (93.7)	10,468 (95.1)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 18: Time to cancer (in months) and number of patients with cancer

	Median follow-up time	Median time to event	# of censored patients (%)[a]	# of patients with cancers (%)[b]
	27.5	15.3	13,182 (100)	5,276 (66.7)
Steroid avoidance	27.1	15.4	138 (1.0)	67 (48.5)
7-day steroid withdrawal	26.4	16.4	575 (4.4)	212 (36.9)
6 month steroid withdrawal	27.4	15.6	971 (7.4)	369 (38.1)
1 year steroid withdrawal	28.2	15.6	490 (3.7)	216 (44.1)
Steroid maintenance	27.6	15.2	11,008 (83.5)	4,412 (40.1)

[a] Percent of column total
[b] Percent of row total

Table 19: Cohort description for the event 'bacterial infection'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total (%)[b]					
15,853 (100)	150 (0.9)	721 (4.5)	1,174 (7.4)	582 (3.7)	13,226 (83.4)
Age group					
18-40 years	35 (23.3)	178 (24.7)	259 (22.1)	112 (19.2)	2,950 (22.3)
40-60 years	69 (46.0)	342 (47.4)	573 (48.8)	300 (51.6)	6,534 (49.4)
=>60 years	46 (30.7)	201 (27.9)	342 (29.1)	170 (29.2)	3,742 (28.3)
Race					
White	7,421 (56.1)	448 (62.1)*	762 (64.9)**	387 (66.5)**	89 (59.3)
Black	3,782 (28.6)	179 (24.8)*	242 (20.6)**	120 (20.6)**	47 (31.3)
Other	2,023(15.3)	94 (13.0)*	170 (14.5)**	75 (12.9)**	14 (9.8)
Ethnicity					
Hispanic	13 (8.7)**	91 (12.6)*	113 (9.6)**	62 (10.6)**	2,008 (15.2)
Non-Hispanic	137 (91.3)	630 (87.4)	1,061 (90.4)	520 (89.4)	11,218 (84.8)
Sex					
Male	66 (44.0)	278 (38.6)	478 (40.7)	241 (41.4)	5,253 (39.7)
Female	84 (56.0)	443 (61.4)	696 (59.3)	341 (58.6)	7,973 (60.3)
BMI					
<18	4 (2.7)	20 (2.8)	25 (2.1)	14 (2.4)	348 (2.6)
18- 34	112 (74.7)	554 (76.8)	955 (81.3)*	463 (79.6)	10,390 (78.6)
=>35	15 (10.0)	81 (11.2)*	131 (11.2)*	53 (9.1)	1,134 (8.6)
Diabetes history					
Yes	42 (28.0)	225 (31.2)	360 (30.7)	181 (31.1)	3,892 (29.4)
No	107 (71.3)	492 (68.2)	808 (68.8)	399 (68.6)	9,297 (70.3)
Hypertension history					
Yes	129 (86.0)	666 (92.4)	1,052 (89.6)	541 (92.9)	12,165 (91.9)
No	6 (4.0)	17 (2.4)	29 (2.5)	7 (1.2)	400 (3.0)

Hyperlipidemia history					
Yes	7 (4.7)	80 (11.1)	150 (12.8)*	59 (10.1)	1,189 (8.9)
No	14 (9.3)	27 (3.7)	59 (5.0)	21 (3.6)	448 (3.4)
Other CVD history					
Yes	35 (23.3)	181 (25.1)	309 (26.3)	137 (23.5)	3,022 (22.8)
No	112 (74.7)	526 (72.9)	847 (72.1)	437 (75.1)	9,945 (75.2)
Malignancy history					
Yes	10 (6.7)	43 (5.7)	71 (6.1)	27 (4.6)	697(5.3)
No	137 (91.3)	665 (92.1)	1,083 (92.2)	546 (93.8)	12,271 (92.8)
HCV/HIV history					
Yes	79 (52.7)*	410 (56.7)*	657 (55.9)*	381 (65.5)*	8,025 (60.7)
No	32 (21.3)	99 (13.7)	169 (14.4)	76 (13.1)	2,164 (16.4)
Serum creatinine					
<1.4 mg/dl	69 (46.0)	308 (42.7)*	590 (50.3)	288 (49.5)	6,441 (48.7)
=>1.4 mg/dl	77 (51.3)	406 (56.3)	578 (49.2)	287 (49.3)	6,688 (50.6)
Dialysis time					
0-1 years	28 (18.8)	138 (19.1)*	224 (19.1)*	101 (17.3)	1,972 (14.9)
1-3 years	35 (23.5)	215 (29.8)	372 (31.8)	176 (30.2)	3,997 (30.3)
>3 years	33 (22.1)*	216 (29.9)*	283 (24.2)**	155 (26.6)**	4,576 (34.7)
Cold ischemic time					
0-12 hours	52 (34.7)	263 (36.5)*	459 (39.1)*	257 (44.2)	5,704 (43.1)
12-24 hours	47 (31.3)	200 (27.7)*	340 (28.9)*	153 (26.3)*	4,330 (32.7)
>24 hours	19 (12.7)	112 (15.5)*	133 (11.3)	61 (10.5)	1,463 (11.1)
Donor type					
Live	53 (35.3)	287 (39.8)	489 (41.6)	260 (44.7)	53 (35.3)
Cadaveric	97 (64.7)	434 (60.2)	685 (58.3)	322 (55.3)**	97 (64.7)
HLA mismatch					
0-1	12 (8.0)	71 (9.8)	187 (15.9)*	83 (14.3)	1,643 (12.4)

2	122 (81.3)	586 (78.5)	848 (72.2)	434 (74.6)	10,305 (77.9)
>2	15 (10.0)	71 (9.8)	117 (9.9)**	61 (10.5)	1,141 (8.6)
Induction agent					
IL2 Induction	3 (2.0)**	97 (13.4)**	196 (16.7)	176 (30.2)**	3,599 (27.2)
Polyclonal Induction	47 (31.3)**	373 (51.7)*	572 (48.7)*	41 (7.0)**	6,050 (45.7)
Monoclonal Induction	0 (0.0)	3 (0.4)	5 (0.4)	0 (0.0)	41 (0.3)
Alemtuzumab Induction	30 (20.0)**	194 (26.9)**	117 (9.9)**	224 (38.5)**	338 (2.6)
Switch from tacrolimus to cyclosporine /sirolimus					
Yes	33 (22.0)	187 (25.9)	261 (22.2)**	105 (18.0)	2,287 (17.3)
No	117 (78.0)	534 (74.1)	913 (77.8)	477 (81.9)	10,939 (82.7)
Acute rejection					
Yes	7 (4.7)	31 (4.3)	105 (8.9)**	31 (5.3)	632 (4.8)
No	143 (95.3)	690 (95.7)	1,069 (91.1)	551 (94.7)	12,594 (95.2)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 20: Time to bacterial infection (in months) and number of patients with bacterial infection

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with bacterial infection (%)[b]
	30.7	11.7	15,853 (100)	4,532 (28.6)
Steroid avoidance	31.9	13.2	150 (0.9)	53 (35.3)
7-day steroid withdrawal	28.8	11.8	721 (4.5)	212 (29.4)
6 month steroid withdrawal	30.8	12.6	1,174 (7.4)	281 (23.9)
1 year steroid withdrawal	34.7	15.6	582 (3.7)	134 (23.0)
Steroid maintenance	30.5	11.4	13,226 (83.4)	3,852 (29.1)

[a] Percent of column total
[b] Percent of row total

Table 21: Cohort description for the event 'cytomegalovirus infection'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total (%)[b]					
7,319 (100)	181 (0.9)	850 (4.5)	1,359 (7.3)	680 (3.6)	15,623 (83.6)
Age group					
18-40 years	46 (25.4)	212 (24.9)	299 (22.0)	125 (18.4)*	3500 (22.4)
40-60 years	83 (45.9)	401 (47.2)	652 (47.9)	351 (51.6)	7715 (49.4)
=>60 years	52 (28.7)	237 (27.9)	408 (30.0)	204 (30.0)	4408 (28.2)
Race					
White	106 (58.6)	517 (60.8)*	861 (63.4)**	445 (65.4)**	8,586 (64.9)
Black	60 (33.1)	222 (26.1)*	300 (22.1)**	153 (22.5)**	4,621 (29.6)
Other	15 (8.3)*	111 (13.1)	198 (14.6)	82 (12.1)*	2,416 (15.5)
Ethnicity					
Hispanic	17 (9.4)*	110 (12.9)*	132 (9.7)**	72 (10.6)**	2,471 (15.8)
Non-Hispanic	164 (90.6)	740 (87.1)	1,227 (90.3)	608 (89.4)	1,3152 (84.2)
Sex					
Male	79 (43.6)	331 (38.9)	554 (40.8)	283 (41.6)	6,278 (40.2)
Female	102 (56.3)	519 (61.1)	805 (59.2)	397 (58.4)	9,345 (59.8)
BMI					
<18	5 (2.8)	23 (2.7)	32 (2.3)	17 (2.5)	404 (2.6)
18- 34	136 (75.1)	654 (76.9)*	1,105 (81.3)	539 (79.3)	12,233 (78.3)
=>35	18 (9.9)	98 (11.5)*	148 (10.9)*	62 (9.1)	1,385 (8.9)
Diabetes history					
Yes	51 (28.2)	275 (32.3)	434 (31.9)	225 (33.1)	4,800 (30.7)
No	129 (71.3)	571 (67.2)	918 (67.5)	453 (66.6)	10,777 (68.9)
Hypertension history					
Yes	158 (87.3)	787 (92.6)	1,228 (90.4)	634 (93.2)	14,414 (92.3)
No	8 (4.4)	21 (2.5)	35 (2.6)	9 (1.3)	485 (3.1)

Hyperlipidemia history					
Yes	17 (9.4)	84 (9.9)	158 (11.6)	65 (9.6)	1,291 (8.3)
No	7 (3.9)	31 (3.6)	61 (4.5)	23 (3.4)	474 (3.0)
Other CVD history					
Yes	43 (23.8)	230 (27.1)*	372 (27.4)*	182 (26.8)*	3,674 (23.5)
No	135 (74.6)	603 (70.9)	966 (71.1)	498 (71.9)	11,635 (74.5)
Malignancy history					
Yes	11 (6.1)	46 (5.4)	87 (6.4)	36 (5.3)	809 (5.2)
No	167 (92.3)	787 (92.6)	1,250 (91.9)	634 (93.2)	14,498 (92.8)
HCV/HIV history					
Yes	95 (52.5)	461 (54.2)	747 (54.9)	441 (64.8)*	9,145 (58.5)
No	43 (23.8)	136 (16.0)	235 (17.3)	98 (14.4)	2,918 (18.7)
Serum creatinine					
<1.4 mg/dl	82 (45.3)	360 (42.3)*	681 (50.1)	335 (49.3)	7,658 (49.0)
=>1.4 mg/dl	95 (52.5)	360 (42.3)	672 (49.4)	337 (49.6)	7,861 (50.3)
Dialysis time					
0-1 years	31 (17.2)	151 (17.8)*	239 (17.6)**	112 (16.5)*	2,136 (13.7)
1-3 years	43 (23.9)	255 (30.0)	430 (31.7)	216 (31.8)	4,657 (29.9)
>3 years	49 (27.2)*	282 (33.2)*	380 (28.0)**	190 (27.9)**	4,657 (29.9)
Cold ischemic time					
0-12 hours	65 (35.9)	296 (34.8)**	528 (38.8)*	291 (42.8)	6,560 (41.9)
12-24 hours	57 (31.5)	250 (29.4)*	409 (30.1)*	192 (28.2)*	5,298 (33.9)
>24 hours	23 (12.7)	137 (16.1)**	151 (11.1)	73 (10.7)	1,794 (11.5)
Donor type					
Live	61 (33.7)	317 (37.3)	544 (40.0)**	281 (41.3)*	5,394 (34.5)
Cadaveric	120 (66.3)	533 (62.7)	815 (59.9)	399 (58.7)	10,229 (65.5)
HLA mismatch					
0-1	16 (8.8)	83 (9.8)*	202 (14.9)*	98 (14.4)	1,948 (13.6)
2	16 (8.8)	80 (9.4)	133 (9.8)	71 (10.4)	1,304 (8.3)

>2	148 (81.8)	673 (79.2)	994 (73.1)**	507 (74.6)*	12,205 (78.1)
Induction agent					
IL2 Induction	4 (2.2)**	106 (12.5)**	227 (16.7)**	204 (30.0)	4,199 (26.9)
Polyclonal Induction	62 (34.2)*	442 (52.0)*	676 (49.7)*	263 (38.7)**	7,238 (46.3)
Monoclonal Induction	0 (0.0)	0 (0.0)	3 (0.3)	5 (0.4)	49 (0.3)
Alemtuzumab Induction	30 (16.6)**	234 (27.5)**	124 (9.1)**	49 (7.2)**	402 (2.6)
Switch from tacrolimus to cyclosporine /sirolimus					
Yes	37 (20.4)	212 (24.9)**	300 (22.1)**	127 (18.7)	2,621 (16.8)
No	144 (79.6)	638 (75.1)	1,059 (77.9)	553 (81.3)	13,002 (83.2)
Acute rejection					
Yes	7 (3.9)	38 (4.5)	142 (10.4)*	40 (5.9)	748 (4.8)
No	174 (96.1)	812 (95.5)	1,217 (89.5)	640 (94.1)	14,875 (95.2)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 22: Time to cytomegalovirus infection (CMV) (in months) and number of patients with cytomegalovirus infection

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with CMV infection (%)[b]
	34.5	5.1	7,319	2,458 (14.1)
Steroid avoidance	36.0	5.9	77 (1.0)	36 (1.2)
7-day steroid withdrawal	31.0	6.1	329 (4.5)	151 (5.2)
6 month steroid withdrawal	34.4	4.2	563 (7.7)	179 (6.1)
1 year steroid withdrawal	36.3	5.9	284 (3.9)	116 (3.9)
Steroid maintenance	34.5	5.1	6,066 (82.9)	2,431 (17.1)

[a] Percent of column total
[b] Percent of row total

Table 23: Cohort description for the event 'fracture'

	Steroid avoidance (%)[a]	7-day steroid withdrawal (%)[a]	6 month steroid withdrawal (%)[a]	1 year steroid withdrawal (%)[a]	Steroid maintenance (%)[a]
Total[b]					
17,392 (100)	169 (0.9)	786 (4.5)	1,268 (7.3)	644 (3.7)	14,525 (83.5)
Age group					
18-40 years	77 (45.6)	367 (46.7)*	611 (48.2)	335 (52.0)*	7,198 (49.6)
40-60 years	43 (25.4)	205 (26.1)	282 (22.2)	121 (18.8)	3,319 (22.8)
=>60 years	49 (28.9)	214 (27.2)	375 (29.6)	188 (29.2)	4,008 (27.6)
Race					
White	100 (59.2)	471 (59.9)	808 (63.7)**	419 (65.1)**	7,947 (54.7)
Black	55 (32.5)	211 (26.8)	278 (21.9)**	145 (22.5)**	4,334 (29.8)
Other	14 (8.3)	104 (13.2)	182 (14.3)	80 (12.4)*	2,244 (15.4)
Ethnicity					
Hispanic	14 (8.3)*	98 (12.5)*	126 (9.9)**	71 (11.0)*	2,273 (15.6)*
Non-Hispanic	155 (91.7)	688 (87.5)	1,142 (90.1)	573 (88.9)	12,252 (84.3)
Sex					
Male	75 (44.4)	509 (40.1)	267 (41.5)	94 (55.6)	5,751 (39.6)
Female	94 (55.6)	759 (59.9)	377 (58.5)	75 (44.4)	8,774 (60.4)
BMI					
<18	5 (2.9)	21 (2.7)	30 (2.4)	16 (2.5)	381 (2.6)
18- 34	125 (73.9)	606 (77.1)	1,037 (81.8)*	512 (79.5)	11,387 (78.4)
=>35	17 (10.1)	91 (11.6))*	129 (10.2)	56 (8.7)	1,278 (8.8)
Diabetes history					
Yes	47 (27.8)	246 (31.3)	389 (30.7)	209 (32.4)	4,289 (29.5)
No	121 (71.6)	536 (68.2)	872 (68.8)	433 (67.2)	10,194 (70.2)
Hypertension history					
Yes	147 (86.9)	729 (92.7)	1,142 (90.1)	600 (93.2)	13,383 (92.1)
No	7 (4.1)	18 (2.3)	33 (2.6)	8 (1.2)	447 (3.1)

Hyperlipidemia history					
Yes	17 (10.1)	83 (10.6)*	155 (12.2)*	64 (9.9)	1,251 (8.6)
No	6 (3.5)	29 (3.7)	59 (4.6)	23 (3.6)	457 (3.1)
Other CVD history					
Yes	38 (22.5)	210 (26.7)	338 (26.7)*	169 (26.2)*	3,330 (22.9)
No	128 (75.7)	561 (71.4)	911 (71.8)	466 (72.4)	10,900 (75.0)
Malignancy history					
Yes	11 (6.5)	43 (5.5)	76 (5.9)	33 (5.1)	752 (5.2)
No	155 (91.7)	728 (92.6)	1,170 (92.3)	601 (93.3)	13,479 (92.8)
EBV history					
Yes	82 (48.5)	314 (39.9)*	571 (45.0)	327 (50.8)*	6,444 (44.4)
No	22 (13.0)	137 (17.4)	151 (11.9)	103 (15.9)	2,563 (17.6)
HCV/HIV history					
Yes	92 (54.4)	432 (54.9)*	698 (55.0)*	420 (65.2)*	8,597 (59.2)
No	36 (21.3)	114 (14.5)	206 (16.2)	85 (13.2)	2,577 (17.7)
Serum creatinine					
<1.4 mg/dl	88 (52.1)	327 (41.6)**	627 (49.4)	318 (49.4)	7,372 (50.7)
=>1.4 mg/dl	77 (45.6)	452 (57.5)	635 (50.1)	318 (49.4)	7,059 (48.6)
Dialysis time					
0-1 years	30 (17.9)	149 (18.9)*	236 (18.7)**	105 (16.3)	2,075 (14.3)
1-3 years	42 (25.0)	247 (31.4)	403 (31.9)	204 (31.7)	4,385 (30.3)
>3 years	42 (25.0)*	234 (29.8)**	328 (25.9)**	174 (27.0)*	5,281 (36.5)
Cold ischemic time					
0-12 hours	63 (37.3)	276 (35.1)**	498 (39.3)*	280 (43.5)	6,146 (42.3)
12-24 hours	52 (30.8)	229 (29.1)*	373 (29.4)*	178 (27.6)*	4,851 (33.4)
>24 hours	21 (12.4)	119 (15.1)	140 (11.0)	68 (10.6)	1,659 (11.4)
Donor type					
Live	60 (35.5)	308 (39.2)*	524 (41.3)**	271 (42.1)**	5,159 (35.5)
Cadaveric	109 (64.5)	478 (60.8)	744 (58.7)	373 (57.9)	9,366 (64.5)

HLA mismatch					
0-1	16 (9.5)	79 (10.0)*	189 (14.9)*	94 (14.6)	1,804 (12.4)
2	137 (81.1)	618 (78.6)	924 (72.9)	476 (73.9)	11,333 (78.0)
>2	15 (8.9)	75 (9.5)	127 (10.0)**	70 (10.9)*	1,231 (8.5)
Induction agent					
IL2 Induction	4 (2.4)**	99 (12.6)**	213 (16.8)**	195 (30.3)*	3,919 (26.9)
Polyclonal Induction	59 (34.9)*	404 (51.4)*	625 (49.3)*	246 (38.2)**	6,691 (46.1)
Monoclonal Induction	0 (0.0)	3 (0.4)	5 (0.4)	0 (0.0)	44 (0.3)
Alemtuzumab Induction	29 (17.2)**	218 (27.7)**	119 (9.4)**	46 (7.1)**	371 (2.5)
Switch from tacrolimus to cyclosporine /sirolimus					
Yes	35 (20.7)	195 (24.8)**	277 (21.8)**	117 (18.2)	2,446 (16.8)
No	134 (79.3)	591 (75.2)	991 (78.1)	527 (81.8)	12,079 (83.2)
Acute rejection					
Yes	9 (5.3)	37 (4.7)	131 (10.8)**	40 (6.2)	769 (5.3)
No	160 (94.7)	749 (95.3)	1,131 (89.2)	604 (93.8)	13,756 (94.7)

[a] Percent of column total

[b] Percent of row total

* p-value<0.05; **p-value<0.0001 for chi-square test between steroid-sparing versus steroid maintenance regimen

Column totals may not add up to 100% due to missing data

Table 24: Time to fracture (in months) and number of patients with fractures

	Median follow-up time	Median time to event	Total # of patients (%)[a]	# of patients with fractures (%)[b]
	34.4	19.0	17,392 (100)	2,458 (14.1)
Steroid avoidance	36.0	13.6	169 (0.9)	21 (12.4)
7-day steroid withdrawal	32.6	17.4	786 (4.5)	111 (14.1)
6 month steroid withdrawal	33.8	17.1	1,268 (7.3)	142 (11.2)
1 year steroid withdrawal	36.3	18.1	644 (3.7)	72 (11.2)
Steroid maintenance	34.4	19.3	14,525 (83.5)	2,112 (14.5)

[a] Percent of column total
[b] Percent of row total

6.4 Parametric survival regression analysis tables (Prof Lifereg results)

Table 25. Acute rejection

	Parameter Estimate	**Confidence Interval**	**p-value**
Regimen			
7-day withdrawal	-1.03	-1.23 - -0.82	<0.0001
6 month withdrawal	0.05	0.11- 0.18	0.688
12 month withdrawal	0.20	0.11 - 0.03	0.087
Avoidance	-1.73	-2.19 - -1.26	<0.0001
Steroid maintenance			
Age group			
18-40 years	-0.78	-0.88 - 0.675	<0.0001
=>60 years	0.34	0.21- 0.47	<0.0001
40-60 years			
Race			0.695
Other	0.23	0.05 - 0.40	0.010
African-American	-0.27	-0.37 - -0.16	<.0001
White			
Hispanic	0.04	-0.09 - 0.18	0.552
Female	0.44	0.34 - 0.54	<0.0001
Diabetes history	-0.02	-0.07 - 0.02	0.242
Hypertension history	0.09	-0.13 - 031	0.408
Hyperlipidemia history	-0.61	-0.82 - -0.39	<0.0001
Other CVD history	-0.18	-0.29 - -0.06	0.002
Malignancy history	-0.05	-0.28 - 0.18	0.666
EBV history	-0.47	-0.59 - -0.34	<0.0001
HIV/HCV history	0.24	0.05-0.43	0.012
BMI			

<18.5	0.14	0.092 - 0.350	0.318
=>35	-0.32	-0.137 - 0.422	0.0001
18.5-35		-0.488 - -0.156	
Dialysis duration			
1-3 years	0.053	-0.083 - 0.189	0.442
=>3 years	0.150	0.001 - 0.299	0.048
HLA mismatch			
2	-0.31	-0.92 - -0.18	0.002
>2	-0.65	-0.50 - -0.11	<0.0001
0-1		-0.79 - -0.51	
Cadaveric donor	0.16	0.020 - 0.297	0.025
Cold ischemia time			
12-24 hours	-0.24	-0.379 - -0.095	0.001
>24 hours	-0.31	-0.473 - -0.147	0.0002
<=12 hours			
Induction regimen			
IL2 inhibitors	0.32	0.15 - 0.39	<0.0001
Monoclonal antibodies	-0.95	0.19 - 0.44	<0.0001
Other	-1.96	-1.16 - -0.74	<0.0001
Alemtuzumab			
Switch from tacrolimus to cyclosporine /sirolimus	-1.00	-1.09 - -0.90	<0.0001
Creatinine	-1.41	-1.51 - -1.30	<0.0001
Scale	2.17	2.13 - 2.22	
Shape	0.46	0.45 - 0.47	
Intercept	8.86	8.37 - 9.34	<0.0001

Table 26: Graft loss:

	Parameter Estimate	**Confidence Interval**	**p-value**
Regimen			
7-day withdrawal	-0.271	-0.348 - -0.194	<0.0001
6 month withdrawal	0.094	0.010 - 0.177	<0.0001
12 month withdrawal	0.050	-0.028 - 0.128	0.028
Avoidance	-0.573	-0.737 - -0.408	0.208
Steroid maintenance			
Age Group			
18-40 years	-0.285	-0.321 - -0.248	<0.0001
=>60 years	0.034	-0.012 - -0.081	0.148
40-60 years			
Race			
Other	0.072	0.003 - 0.140	0.039
African-American	-0.360	-0.397 - -0.324	<0.0001
White			
Hispanic	-0.037	-0.08 - 0.012	0.141
Female	0.141	0.107 - 0.175	<0.0001
Diabetes history	-0.002	-0.019 - 0.015	0.815
Hypertension history	-0.272	-0.359 - -0.184	<0.0001
Hyperlipidemia history	-0.604	-0.669 - -0.539	<0.0001
Other CVD History	-0.275	-0.311 - -0.239	<0.0001
Malignancy history	-0.207	-0.280 - -0.134	<0.0001
EBV history	-0.055	-0.098 - -0.012	0.012
HIV/HCV history	-0.145	-0.041 - 0.118	<0.0001
BMI			
<18.5	-0.089	-0.150 - -0.067	0.059
=>35	-0.011	-0.181 - 0.003	0.719
18.5-35			

Dialysis duration			
1-3 years	-0.043	-0.092-0.005	0.082
=>3 years	-0.107	-0.159 - -0.055	<0.0001
HLA mismatch			
2	-0.175	-0.241 - -0.108	<0.0001
>2	-0.142	-0.193 - -0.092	<0.0001
0-1			
Cadaveric donor	-0.177	-0.225 - - 0.120	<0.0001
Cold ischemia time			
12-24 hours	0.002	-0.046 - 0.049	0.929
>24 hours	-0.067	-0.121 - -0.013	0.014
<=12 hours			
Induction regimen			
IL2 inhibitors	0.086	0.045 - 0.128	<0.0001
Monoclonal antibodies	0.078	0.006 - 0.149	<0.0001
Other	-0.240	-0.329 - -0.152	0.032
Alemtuzumab	-0.113	-0.146 - -0.079	<0.0001
Switch from tacrolimus to cyclosporine /sirolimus			
Creatinine	-0.366	0.018 - -0.402	<0.0001
Acute rejection	-0.805	-0.838 - -0.764	<0.0001
Scale	0.716	0.006 - 0.703	
Shape	1.396	0.013 - 1.370	
Intercept	7.176	6.998 - 7.354	<0.0001

Table 27: Death due to graft loss

	Parameter Estimate	Confidence Interval	p-value
Regimen			
7-day withdrawal	-0.088	-0.665 - 0.488	0.764
6 month withdrawal	0.062	-0.494 - 0.618	0.828
12 month withdrawal	0.073	-0.485 - 0.631	0.798
Avoidance	-0.064	-1.879 - 1.752	0.945
Steroid maintenance			
Age group			
18-40 years	0.349	-0.003 - 0.701	0.052
=>60	-0.173	-0.428 - 0.083	0.185
40-60 years			
Race			
Other	-0.132	-0.555 - 0.290	0.539
African-American	-0.238	-0.494 - 0.019	0.069
White			
Hispanic	0.219	-0.187 - 0.626	0.290
Female	0.295	0.052 - 0.537	0.017
Diabetes history	-0.241	-1.33 - -0.038	0.038
Hypertension history	-0.563	-1.715 - 0.588	0.338
Hyperlipidemia history	4.202	-62.357 - 70.763	0.901
Other CVD history	-0.199	-0.447 - 0.049	0.115
Malignancy history	0.016	-0.375 - 0.630	0.619
EBV history	0.298	0.036 - 0.562	0.026
HIV/HCV history	-0.169	-0.695 - 0.356	0.527
BMI			
<18.5	-0.030	-0.725 - 0.664	0.932
=>35	0.148	-0.298 - 0.595	0.514
18.5-35	0.000		

Dialysis duration			
1-3 years	-0.118	-0.501 - 0.266	0.547
=>3 years	-0.239	-0.637 - 0.157	0.237
HLA mismatch			
2	-0.218	-0.605 - 0.169	0.270
>2	0.142	-0.178 - 0.463	0.384
0-1			
Cadaveric donor	-0.313	-0.651 - 0.025	0.069
Cold ischemia time			
12-24 hours	0.119	-0.183 - 0.423	0.439
>24 hours	0.254	-0.133 - 0.640	0.198
<=12 hours			
Induction regimen			
IL2 inhibitors	-0157	-0.490 - 0.177	0.357
Monoclonal antibodies	-0.518	-1.009 - -0.027	0.039
Other	-0.142	-1.221 - 0.936	0.796
Alemtuzumab	0.216	-0.057 - 0.489	0.121
Switch from tacrolimus to cyclosporine /sirolimus			
Creatinine	-0.382	-1.092 - 0.298	0.263
Acute rejection	-0.108	-0.437 - 0.220	0.518
Scale	0.482	0.399 - 0.582	
Shape	2.074	1.719 - 2.501	
Intercept	9.093	7.370 - 10.815	<0.0001

Table 28: Death due to cardiovascular diseases:

	Parameter Estimate	**Confidence Interval**	**p-value**
Regimen			
7-day withdrawal	0.06	-0.124 - 0.243	0.526
6 month withdrawal	0.105	-0.057 - 0.266	0.203
12 month withdrawal	0.111	-0.045 - 0.268	0.163
Avoidance	0.746	-0.167 - 1.658	0.109
Steroid maintenance			
Age group			
18-40 years	0.477	0.366 - 0.589	<0.0001
=>60 years	-0.377	-0.445 - -0.309	<0.0001
40-60 years			
Race			
Other	0.192	0.057 - 0.326	0.005
African-American	0.039	-0.037 - 0.114	0.315
White			
Hispanic	0.144	0.047 - 0.241	0.004
Female	-0.047	-0.114 - 0.019	0.165
Diabetes history	-0.483	-0.555 - -0.410	<0.0001
Hypertension history	0.159	0.009 - 0.310	0.038
Hyperlipidemia history	0.215	-0.043 – 0.474	0.103
Other CVD history	-0.319	-0.389 - -0.251	<.0001
Malignancy history	-0.052	-0.193 - 0.088	0.467
EBV history	-0.033	-0.114 - 0.047	0.420
HIV/HCV history	0.193	0.066 - 0.320	0.0029
BMI			
<18.5	0.028	-0.209 - 0.266	0.815
=>35	-0.115	-0.228 - -0.003	0.044
18.5-35			

Dialysis duration			
1-3 years	0.014	-0.082 - 0.111	0.771
>3 years	-0.15	-0.253 - -0.051	0.003
HLA mismatch			
2	0.047	-0.078 - 0.173	0.461
>2	-0.035	-0.123 - 0.053	0.434
0-1			
Cadaveric donor	-0.169	-0.263 - -0.075	0.0004
Cold ischemia time			
12-24 hours	-0.004	-0.095 - 0.087	0.937
>24 hours	-0.009	-0.114 – 0.095	0.862
<=12 hours			
Induction regimen			
IL2 inhibitors	-0.005	-0.087 - 0.078	0.913
Monoclonal antibodies	-0.081	-0.227 - 0.065	0.278
Other	0.043	-0.225 - 0.310	0.755
Alemtuzumab			
Switch from tacrolimus to cyclosporine /sirolimus	-0.013	-0.083 - 0.056	0.704
Creatinine	-0.112	-0.179 - -0.046	0.001
Acute rejection	-0.089	-0.183 - 0.004	0.059
Scale	0.575	0.549 - 0.600	
Shape	1.741	1.665 - 1.820	
Intercept	0.193	0.066 - 0.320	0.003

Table 29: Death due to other reasons:

	Parameter Estimate	Confidence Interval	p-value
Regimen			
7-day withdrawal	0.074	-0.078 - 0.227	0.338
6 month withdrawal	0.180	0.039 - 0.321	0.012
12 month withdrawal	0.180	0.043 - 0.317	0.010
Avoidance	0.131	-0.323 - 0.586	0.571
Steroid maintenance			
Age group			
18-40 years	0.503	0.413 - 0.593	<0.0001
=>60 years	-0.489	-0.547 - -0.433	<0.0001
40-60 years			
Race			
Other	0.250	0.134 - 0.366	<0.0001
African-American	0.124	0.059 - 0.189	0.0002
White			
Hispanic	0.157	0.075 - 0.240	0.0002
Female	-0.032	-0.087 - 0.023	0.258
Diabetes history	-0.282	-0.341 - -0.222	<0.0001
Hypertension history	0.029	-0.099 - 0.157	0.662
Hyperlipidemia history	0.168	-0.035 - 0.370	0.104
Other CVD history	-0.105	-0.163 - -0.047	0.0004
Malignancy history	-0.262	-0.359 - -0.165	<0.0001
EBV history	-0.145	-0.213 - -0.077	<0.0001
HIV/HCV history	0.115	0.005 - 0.226	0.041
BMI			
<18.5	-0.156	-0.317 - 0.005	0.057
=>35	-0.067	-0.166 - 0.031	0.181
18.5-35			
Dialysis duration			
1-3 years	-0.119	-0.200 - -0.038	0.004

>3 years	-0.179	-0.267 - -0.093	<0.0001
HLA mismatch			
2	0.039	-0.062 - 0.139	0.452
>2	0.017	-0.055 - 0.087	0.648
0-1			
Cadaveric donor	-0.125	-0.200 - -0.050	0.001
Cold ischemia time			
12-24 hours	0.049	-0.026 - 0.125	0.196
>24 hours	0.055	-0.033 - 0.143	0.217
<=12 hours			
Induction regimen			
IL2 inhibitors	0.091	0.024 - 0.157	0.007
Monoclonal antibodies	0.192	0.056 - 0.328	0.006
Other	0.169	-0.053 - 0.392	0.135
Alemtuzumab			
Switch from tacrolimus to cyclosporine /sirolimus	-0.030	-0.087 - 0.026	0.297
Creatinine	-0.075	-0.130 - -0.019	0.008
Acute rejection	-0.139	-0.216 - -0.063	0.0004
Scale	0.576	0.554 - 0.597	
Shape	1.737	1.674 - 1.802	
Intercept	6.381	6.110 - 6.652	<0.0001

Table 30: Myocardial infarction:

	Parameter Estimate	Confidence Interval	p-value
Regimen			
7-day withdrawal	-0.160	-0.746 - 0.425	0.591
6 month withdrawal	0..469	0.275 - -0.070	0.088
12 month withdrawal	0.534	0.397 - -0.244	0.178
Avoidance	0.199	-1.000 - 1.398	0.745
Steroid maintenance			
Age group			
18-40 years	1.450	0.992 - 1.908	<0.0001
=>60 years	-0.597	-0.875 - -0.319	<0.0001
40-60 years			
Race			
Other	0.161	-0.252 - 0.574	0.444
African-American	0.327	0.012 - 0.641	0.042
White			
Hispanic	0.277	-0.128 - 0.682	0.179
Female	-0.277	-0.559 - 0.004	0.053
Diabetes history	-1.189	-1.474 - -0.905	<0.0001
Hypertension history	-0.156	-0.962 - 0.649	0.703
Hyperlipidemia history	0.189	-0.400 - 0.779	0.529
Other CVD History	-0.844	-1.140 - -0.548	<0.0001
Malignancy history	-0.663	-1.147 - -0.178	0.007
EBV history	0.100	-0.234 - 0.435	0.555
HIV/HCV history	0.736	0.107 - 1.365	0.022
BMI			
<18.5	0.197	-0.729 - 1.22	0.677
=>35	0.010	-0.426 - 0.447	0.963
18.5-35			
Dialysis duration			
1-3 years	-0.488	-0.938 - -0.039	0.033

=>3 years	-0.592	-1.063 - -0.121	0.014
HLA Mismatch			
2	-0.321	-0.931 - 0.289	0.302
>2	-0.237	-0.651 - 0.176	0.261
0-1			
Cadaveric donor	-0.270	-0.659 - 0.119	0.174
Cold ischemia time			
12-24 hours	-0.141	-0.494 - 0.212	0.434
>24 hours	-0.164	-0.611 - 0.282	0.469
<=12 hours			
Induction Regimen			
IL2 inhibitors	0.417	0.091 - 0.742	0.012
Monoclonal antibodies	0.487	1.383 - -2.22	0.725
Other	-0.165	-0.769 - 0.439	0.593
Alemtuzumab	0.267	-0.582 - 0.047	0.096
Switch from tacrolimus to cyclosporine /sirolimus			
Creatinine	-0.176	-0.452 - 0.101	0.213
Acute rejection	0.705	0.059 - 1.351	0.032
Scale	1.972	1.853 - 2.099	
Shape	0.507	0.476 - 0.539	
Intercept	9.895	8.637 - 11.153	<0.0001

Table 31: Stroke

	Parameter Estimate	Confidence Interval	p-value
Regimen			
7-day withdrawal	-0.160	-0.745 - 0.425	0.591
6 month withdrawal	0.469	-0.070 - 1.008	0.088
12 month withdrawal	0.534	-0.244 - 1.312	0.178
Avoidance	0.199	-1.000 - 1.398	0.745
Steroid maintenance			
Age group			
18-40 years	1.450	0.992 - 1.908	<0.0001
=>60 years	-0.597	-0.875 - -0.319	<0.0001
40-60 years			
Race			
Other	0.161	-0.252 - 0.574	0.445
African-American	0.327	0.012 - 0.641	0.042
White			
Hispanic	0.277	-0.128 - 0.682	0.179
Female	-0.277	-0.559 - 0.004	0.053
Diabetes history	-1.189	-1.474 - -0.905	<0.0001
Hypertension history	-0.156	-0.962 - 0.649	0.703
Hyperlipidemia history	0.189	-0.400 - 0.779	0.529
Other CVD history	-0.844	-1.140 - -0.548	<0.0001
Malignancy history	-0.663	-1.147 - -0.178	0.007
EBV history	0.100	-0.234 - 0.435	0.555
HIV/HCV history	0.736	0.107 - 1.365	0.022
BMI			
<18.5 years	0.197	-0.729 - 1.122	0.677
=>35 years	0.010	-0.426 - 0.447	0.963
18.5-35			
Dialysis duration			
1-3 years	-0.488	-0.938 - -0.039	0.033

=>3 years	-0.592	-1.063 - -0.121	0.014
HLA mismatch			
2	-0.321	-0.931 - 0.289	0.302
>2	-0.237	-0.651 - 0.176	0.260
0-1			
Cadaveric donor	-0.270	-0.659 - 0.119	0.174
Cold ischemia time			
12-24 hours	-0.141	-0.494 - 0.212	0.434
>24 hours	-0.164	-0.611 - 0.282	0.469
<=12 hours			
Induction regimen			
IL2 inhibitors	0.417	0.091 - 0.742	0.012
Monoclonal antibodies	0.487	-2.223 - 3.197	0.725
Other	-0.165	-0.769 - 0.439	0.593
Alemtuzumab	-0.267	-0.582 - 0.047	0.096
Switch from tacrolimus to cyclosporine /sirolimus			
Creatinine	-0.176	-0.452 - 0.101	0.213
Acute rejection	0.132	-0.066	0.331
Scale	1.972	1.853 - 2.099	
Shape	0.507	0.476 - 0.539	
Intercept	9.895	8.637 - 11.153	<0.0001

Table 32: Other cardiovascular diseases

	Parameter Estimate	Confidence Interval	p-value
Regimen			
7-day withdrawal	-0.193	-0.484 - 0.097	0.193
6 month withdrawal	0.383	0.129 - 0.636	0.003
12 month withdrawal	-0.031	-0.359 - 0.296	0.852
Avoidance	-0.034	-0.607 - 0.539	0.908
Steroid maintenance			
Age group			
18-40 years	0.499	0.083 - 0.337	<0.0001
=>60 years	-0.782	0.081 - -0.942	<0.0001
40-60 years	0.000		
Race			
Other	0.177	-0.039 - 0.394	0.108
African-American	-0.158	-0.312 - 0.0002	0.050
White			
Hispanic	-0.015	-0.235 - 0.204	0.890
Female	0.130	-0.009 - 0.269	0.067
Diabetes history	-0.628	-0.778 - -0.479	<0.0001
Hypertension history	-0.299	-0.675 - 0.076	0.119
Hyperlipidemia history	-0.161	-0.395 - 0.073	0.178
Other CVD history			
Malignancy history	-0.222	-0.502 - 0.058	0.121
EBV history	-0.052	-0.222 - 0.118	0.551
HIV/HCV history	0.042	-0.306 - 0.390	0.815
BMI			

<18.5	-0.016	-0.431 - 0.399	0.939
=>35	-0.326	-0.543 - -0.108	0.003
18.5-35			
Dialysis duration			
1-3 years	-0.179	-0.383 - 0.023	0.082
=>3 years	-0.659	-0.883 - 0.435	<0.0001
HLA mismatch			
2	-0.150	-0.445 - 0.145	0.318
>2	-0.336	-0.536 - -0.135	0.001
0-1			
Cadaveric donor	-0.381	-0.569 - -0.193	<0.0001
Cold ischemia time			
12-24 hours	-0.077	-0.264 - 0.109	0.418
>24 hours	-0.175	-0.413 - 0.063	0.150
<=12 hours			
Induction regimen			
IL2 inhibitors	0.112	-0.046 - 0.270	0.166
Monoclonal antibodies	-0.458	-1.565 - 0.649	0.417
Other	-0.285	-0.588 - 0.018	0.066
Alemtuzumab	-0.326	-0.483 - -0.169	<0.0001
Switch from tacrolimus to cyclosporine /sirolimus			
Creatinine	-0.230	-0.372 - -0.089	0.001
Acute rejection	0.827	0.488 - 1.166	<0.0001
Scale	1.734	1.677 - 1.792	
Shape	0.577	0.558 - 0.596	
Intercept	5.973	5.388 - 6.558	<0.0001

Table 33: New-onset diabetes mellitus

	Parameter Estimate	Confidence Interval	p-value
Regimen			
7-day withdrawal	0.235	-0.065 - 0.535	0.125
6 month withdrawal	0.669	0.418 - 0.920	<0.0001
12 month withdrawal	0.339	0.017 - 0.661	0.038
Avoidance	0.044	-0.690 - 0.697	0.896
Steroid maintenance			
Age group			
18-40 years	0.875	0.721 - 1.029	<0.0001
=>60 years	-0.633	-0.781 - -0.485	<0.0001
40-60 years			
Race			
Other	-0.152	-0.352 - 0.047	0.134
African-American	-0.484	-0.632 - -0.336	<0.0001
White			
Hispanic	-0.689	-0.888 - -0.489	<0.0001
Female	-0.180	-0.312 - -0.048	0.007
Hypertension history	-0.129	-0.464 - 0.204	0.446
Hyperlipidemia history	-0.227	-0.483 - 0.029	0.082
Other CVD history	-0.295	-0.454 - -0.136	0.0003
Malignancy history	0.191	-0.076 - 0.458	0.162
CMV history			
EBV history	-0.228	-0.393 - -0.062	0.007
HIV/HCV history	-0.120	-0.465 - 0.225	0.495
BMI			
<18.5	0.567	0.178 - 0.954	0.004
=>35	-0.843	-1.059 - -0.626	<0.0001
18.5-35			
Dialysis duration			
1-3 years	-0.152	-0.352 - 0.385	0.135
=>3 years	-0.417	-0.628 - -0.206	0.0001

HLA mismatch			
2	-0.112	-0.387 - 0.163	0.424
>2	-0.164	-0.354 - 0.027	0.092
0-1			
Cadaveric donor	-0.326	-0.503 - -0.149	0.0003
Cold ischemia time			
12-24 hours	0.024	-0.143 - 0.191	0.780
>24 hours	-0.113	-0.333 - 0.106	0.312
<=12 hours			
Induction regimen	0.944	-0.363 - 2.251	0.157
IL2 inhibitors	0.485	0.172 - 0.797	0.002
Monoclonal antibodies			
Other			
Alemtuzumab	-0.342	-0.491 - -0.193	<0.0001
Switch from tacrolimus to cyclosporine /sirolimus	1.291	-0.109 - 2.691	0.071
Creatinine	-0.333	-1.106 - 0.439	0.398
Acute rejection	1.286	0.933 - 1.638	<0.0001
Scale	1.966	1.913 - 2.021	
Shape	0.508	0.494 - 0.523	
Intercept	5.787	5.240 - 6.333	<0.0001

Table 34: Cancer

	Parameter Estimate	Confidence Interval	p-value
Regimen			
7-day withdrawal	0.183	0.036 - 0.331	0.015
6 month withdrawal	0.054	-0.054 - 0.162	0.326
12 month withdrawal	-0.027	-0.169 - 0.115	0.708
Avoidance	-0.244	-0.499 - 0.011	0.061
Steroid maintenance			
Age group			
18-40 years	0.437	0.361 - 0.514	<0.0001
=>60 years	-0.321	-0.387 - -0.256	<0.0001
40-60 years			
Race			
Other	0.261	0.171 - 0.351	<0.0001
African-American	0.361	0.290 - 0.432	<0.0001
White			
Hispanic	0.210	0.120 - 0.300	<0.0001
Female	0.104	0.043 - 0.165	0.0008
Diabetes history	0.141	0.076 - 0.206	<0.0001
Hypertension history	0.872	-0.069 - 0.244	0.276
Hyperlipidemia history	-0.002	-0.114 - 0.109	0.966
Other CVD history	-0.587	-0.127 - 0.010	0.0951
CMV history			
EBV history	-0.036	-0.112 - 0.039	0.347
HIV/HCV history	-0.086	-0.243 - 0.070	0.279
BMI			
<18.5	-0.276	-0.436 - -0.116	0.0007
=>35	0.063	-0.038 - 0.163	0.222
18.5-35			
Dialysis duration			
1-3 years	-0.098	0.167 - -0.008	0.032
=>3 years	-0.054	-0.151 - 0.043	0.273

HLA mismatch			
2	-0.053	-0.177 - 0.071	0.403
>2	-0.071	0.043 - -0.156	0.099
0-1			
Cadaveric donor	-0.002	-0.085 - 0.081	0.955
Cold ischemia time	-0.114	-0.195 - -0.033	0.006
12-24 hours	-0.181	-0.283 - -0.079	0.0005
>24 hours			
<=12 hours			
Induction regimen	0.013	-0.056 - 0.082	0.721
IL2 inhibitors	0.309	-0.281 - 0.899	0.305
Monoclonal antibodies	0.011	-0.127 - 0.149	0.877
Other			
Alemtuzumab	-0.0414	-0.113 - 0.030	0.257
Switch from tacrolimus to cyclosporine /sirolimus	-0.006	-0.068 - 0.055	0.839
Creatinine	0.379	0.239 - 0.520	<0.0001
Acute rejection	1.018	0.993 - 1.043	
Scale	0.982	0.958 - 1.007	
Shape	4.217	3.966 - 4.468	<0.0001
Intercept			

Table 35: Bacterial infection:

	Parameter Estimate	**Confidence Interval**	**p-value**
Regimen			
7-day withdrawal	0.042	-0.161 - 0.245	0.685
6 month withdrawal	0.281	0.108 - 0.455	0.001
12 month withdrawal	0.456	0.203 - 0.709	0.0004
Avoidance	0.317	-0.109 - 0.744	0.145
Steroid maintenance			
Age group			
18-40 years	-0.166	-0.281 - -0.050	0.005
=>60 years	-0.097	-0.197 - 0.003	0.057
40-60 years			
Race			
Other	0.154	0.016 - 0.292	0.028
African-American	0.064	-0.040 - 0.168	0.230
White			
Hispanic	-0.133	-0.265 - -0.001	0.048
Female	0.706	0.612 0 - 0.799	<0.0001
Diabetes history	-1.063	-1.829 - -0.296	0.007
Hypertension history	0.134	-0.108 - 0.376	0.278
Hyperlipidemia history	0.032	-0.158 - 0.221	0.742
Other CVD history	-0.281	-0.381 - -0.181	<0.0001
Malignancy history	-0.033	-0.226 - 0.159	0.738
EBV history	-0.134	-0.249 - -0.019	0.023
HIV/HCV history	0.189	0.022 - 0.357	0.026
BMI			
<18.5	0.029	-0.254 - 0.312	0.839
=>35	-0.414	-0.550 - -0.278	<0.0001
18.5-35			

Dialysis duration			
1-3 years	-0.243	-0.387 - -0.098	0.001
=>3 years	-0.419	-0.572 - -0.267	<0.0001
HLA mismatch			
2	-0.148	-0.345 - 0.049	0.141
>2	-0.053	-0.187 - 0.081	0.437
0-1			
Cadaveric donor	-0.285	-0.414 - -0.156	<0.0001
Cold ischemia time	-0.079	-0.198 - 0.040	0.195
12-24 hours	-0.066	-0.218 - 0.086	0.393
>24 hours			
<=12 hours			
Induction regimen	0.102	-0.007 - 0.210	0.067
IL2 inhibitors	-0.739	-1.368 - -0.111	0.021
Monoclonal antibodies	-0.147	-0.348 - 0.055	0.154
Other			
Alemtuzumab	-0.303	-0.408 - -0.199	<0.0001
Switch from tacrolimus to cyclosporine /sirolimus	1.536	0.279 - 2.793	0.017
Creatinine	-0.307	-0.400 - -0.213	<0.0001
Acute rejection	0.535	0.317 - 0.752	<0.0001
Scale	1.450	1.411 - 1.490	
Shape	0.689	0.671 - 0.709	
Intercept	5.661	5.265 - 6.058	<0.0001

Table 36: CMV infection

	Parameter Estimate	Confidence Interval	p-value
Regimen			
7-day withdrawal	-0.011	-0.405 - 0.383	0.956
6 month withdrawal	0.758	0.378 - 1.138	<0.0001
12 month withdrawal	0.279	-0.186 - 0.744	0.239
Avoidance	-0.050	-0.843 - 0.742	0.901
Steroid maintenance			
Age group			
18-40 years	-0.227	-0.447 - -0.007	0.043
=>60 years	-0.143	-0.345 - 0.058	0.163
40-60 years			
Race			
Other	0.543	0.248 - 0.838	0.0003
African-American	0.198	-0.003 - 0.399	0.054
White			
Hispanic	0.937	0.631 - 1.243	<0.0001
Female	0.130	-0.055 - 0.312	0.168
Diabetes history	0.047	-0.149 - 0.243	0.635
Hypertension history	-0.431	-0.942 - 0.080	0.098
Hyperlipidemia history	0.385	-0.013 - 0.783	0.058
Other CVD history	0.293	0.081 - 0.506	0.007
Malignancy history	0.026	-0.350 - 0.403	0.891
EBV history	0.991	0.755 - 1.226	<0.0001
HIV/HCV history	0.035	-0.455 - 0.524	0.889
BMI			
<18.5	0.672	0.049 - 1.294	0.034
=>35	0.157	-0.144 - 0.458	0.306

18.5-35			
Dialysis duration			
1-3 years	-0.484	-0.792 - -0.176	0.002
=>3 years	-0.604	-0.924 - -0.283	0.0002
HLA mismatch			
2	-0.162	-0.585 - 0.260	0.451
>2	-0.383	-0.662 - -0.103	0.007
0-1			
Cadaveric donor	-0.403	-0.664 - -0.142	0.002
Cold ischemia time			
12-24 hours	-0.257	-0.488 - -0.023	0.029
>24 hours	-0.013	-0.317 - -0.290	0.931
<=12 hours			
Induction regimen			
IL2 inhibitors	0.285	0.066 - 0.504	0.011
Monoclonal antibodies	-1.298	-2.443 - -0.152	0.026
Other	-0.789	-1.145 - -0.415	<0.0001
Alemtuzumab			
Switch from tacrolimus to cyclosporine /sirolimus	0.131	-0.094 - 0.357	0.253
Creatinine	-0.601	-0.789 - -0.414	<0.0001
Acute rejection	1.444	0.957 - 1.99	<0.0001
Scale	2.126	2.047 - 2.208	
Shape	0.470	0.453 - 0.489	
Intercept	8.477	7.643 - 9.312	<0.0001

Table 37: Fracture

	Parameter Estimate	**Confidence Interval**	**p-value**
Regimen			
7-day withdrawal	0.049	-0.129 - 0.226	0.591
6 month withdrawal	0.171	0.023 - 0.319	0.024
12 month withdrawal	0.282	0.067 - 0.496	0.010
Avoidance	-0.512	-0.789 - -0.234	0.0003
Steroid maintenance			
Age group			
18-40 years	0.137	0.032 - 0.241	0.011
=>60 years	-0.125	-0.207 - -0.042	0.003
40-60 years			
Race			
Other	0.234	0.117 - 0.350	<0.0001
African-American	0.417	0.321 - 0.513	<0.0001
White			
Hispanic	-0.007	-0.116 - 0.103	0.906
Female	0.361	0.283 - 0.440	<0.0001
Diabetes history	-0.565	-0.656 - -0.483	<0.0001
Hypertension history	-0.030	-0.242 - 0.181	0.778
Hyperlipidemia History	-0.258	-0.402 - -0.114	0.0004
Other CVD history	-0.116	-0.199 - -0.032	0.007
Malignancy history	-0.179	-0.325 - -0.034	0.016
EBV history	0.011	-0.085 - 0.107	0.822
HIV/HCV History	-0.037	-0.240 - 0.166	0.722
BMI			
<18.5	0.082	-0.163 - 0.327	0.512
=>35	-0.051	-0.174 - 0.072	0.414
18.5-35			
Dialysis duration			
1-3 years	-0.225	-0.346 - -0.105	0.0002

=>3 years	-0.254	-0.383 - 0.125	0.0001
HLA mismatch			
2	0.019	-0.139 - 0.179	0.809
>2	0.071	-0.035 - 0.178	0.189
0-1			
Cadaveric donor	-0.032	-0.140 - 0.076	0.562
Cold ischemia time			
12-24 hours	-0.032	-0.136 - 0.071	0.541
>24 hours	-0.017	-0.148 - 0.114	0.798
<=12 hours			
Induction regimen			
IL2 inhibitors	-0.088	-0.177 - 0.002	0.054
Monoclonal antibodies	-0.570	-1.093 - 0.047	0.033
Other	-0.183	-0.355 - -0.012	0.036
Switch from tacrolimus to cyclosporine /sirolimus	-0.158	-0.247 - -0.069	0.0005
Serum creatinine level	0.006	-0.073 - 0.085	0.878
Acute rejection	0.082	-0.084 - 0.248	0.335
Scale	0.915	0.882 - 0.949	
Shape	1.093	1.054 - 1.134	
Intercept	5.515	5.175 - 5.855	<0.0001

6.5 Cumulative probability curves (cumulative density function (cdf)) for various events

Figure 1: Acute rejection

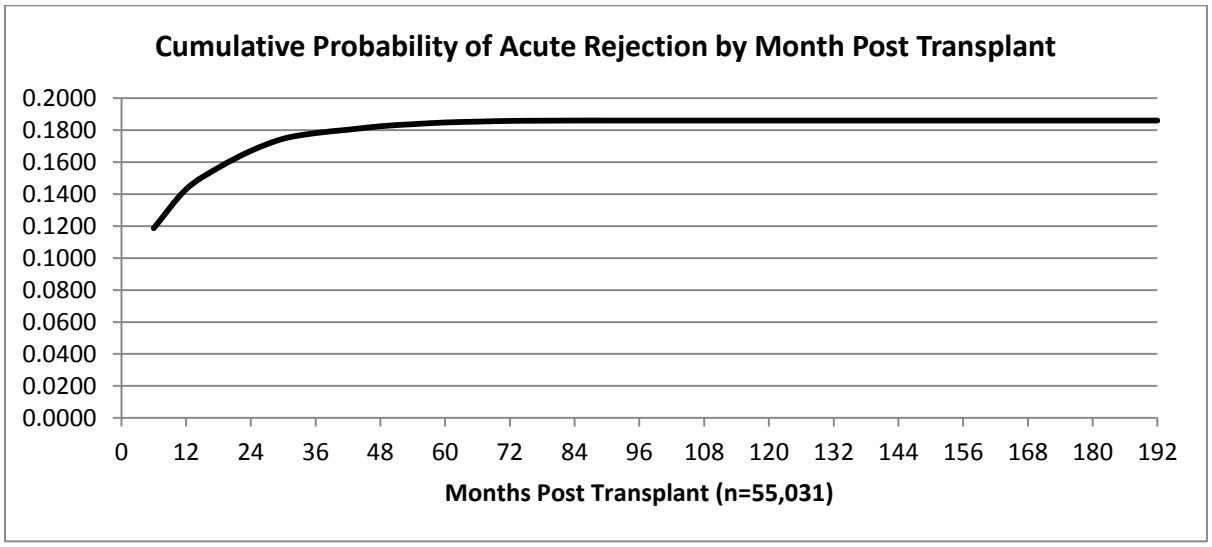


Figure 2: Graft loss

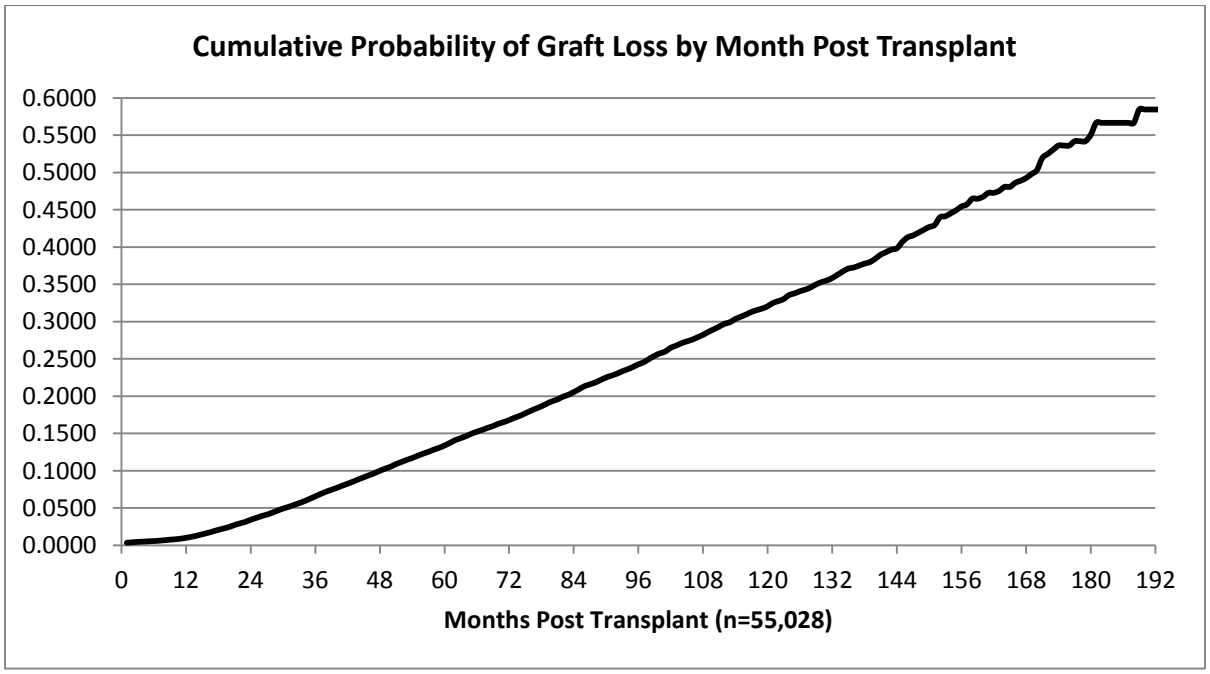


Figure 3: Myocardial infarction:

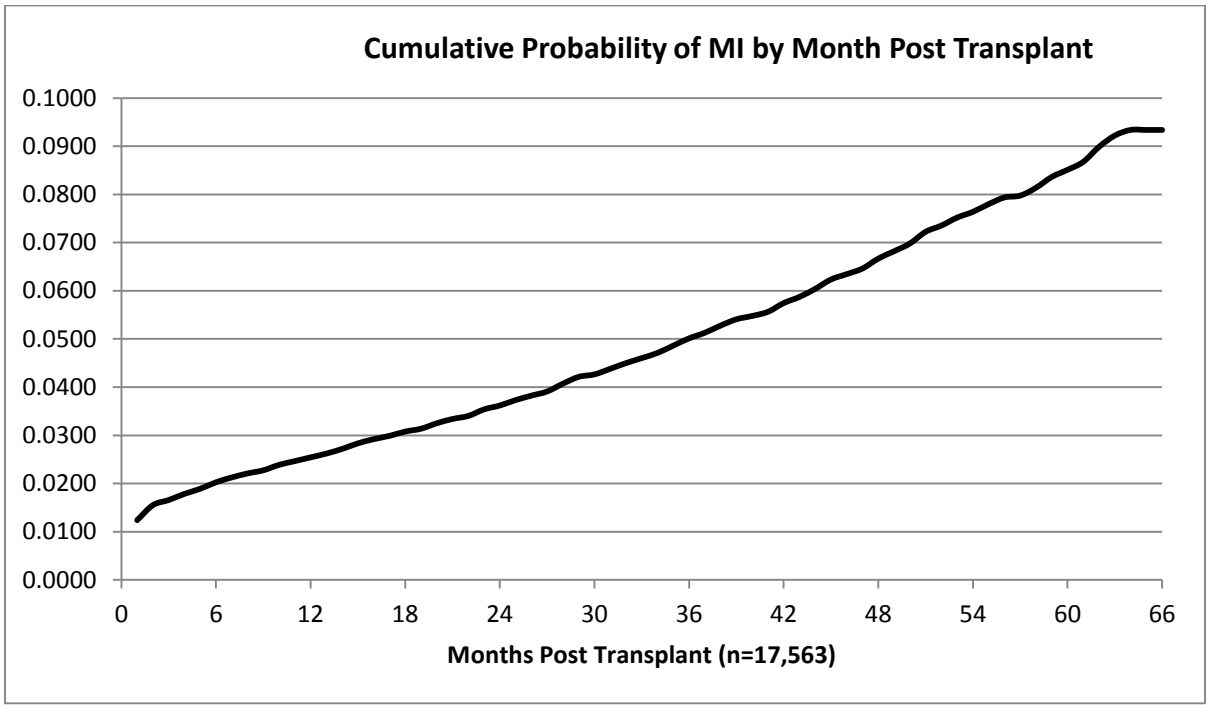


Figure 4: Stroke

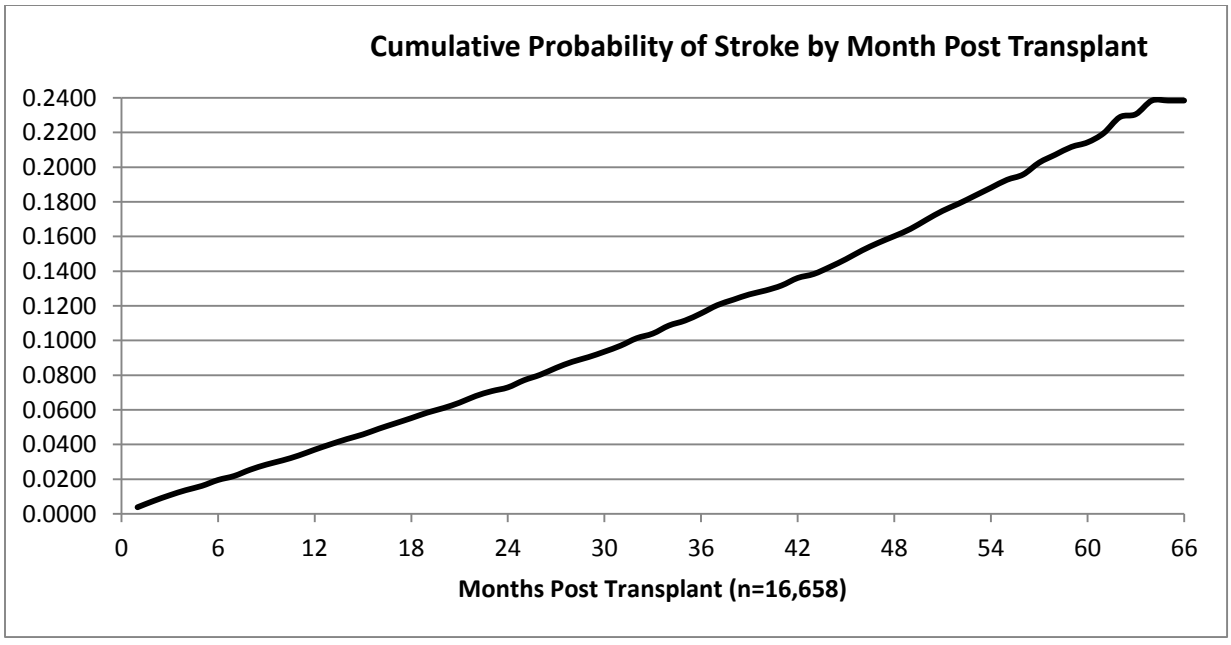


Figure 5: CVD:

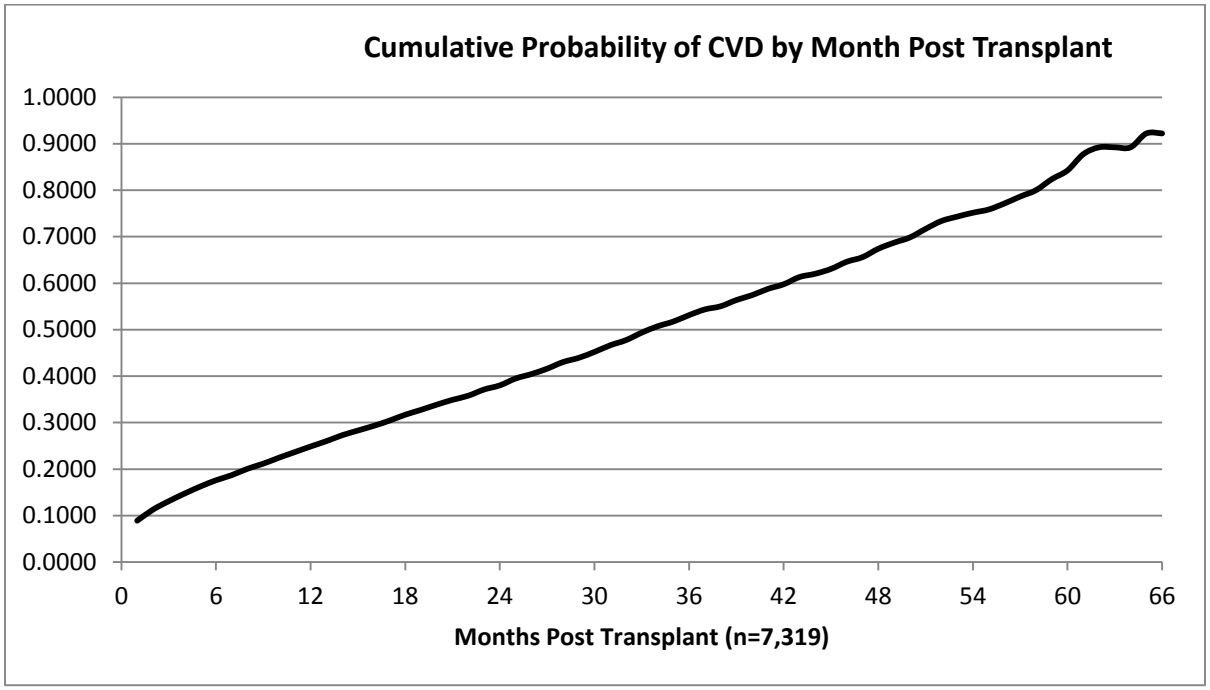


Figure 6: New-Onset Diabetes:

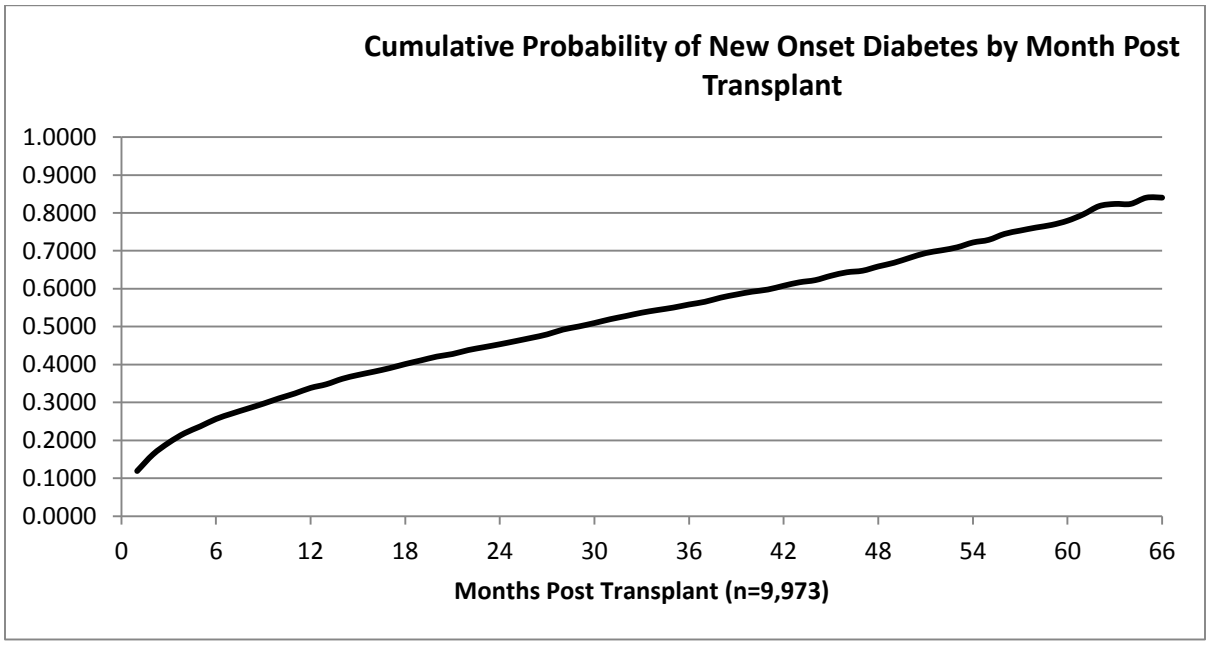


Figure 7: Cancer

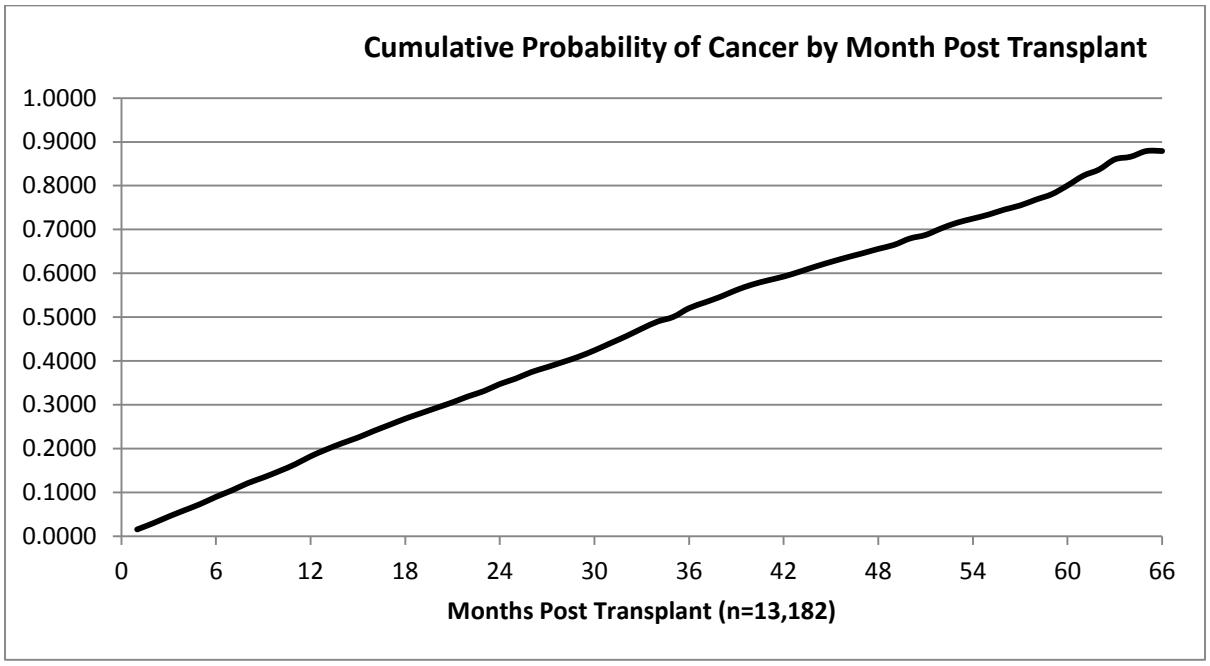


Figure 8: Bacterial infection

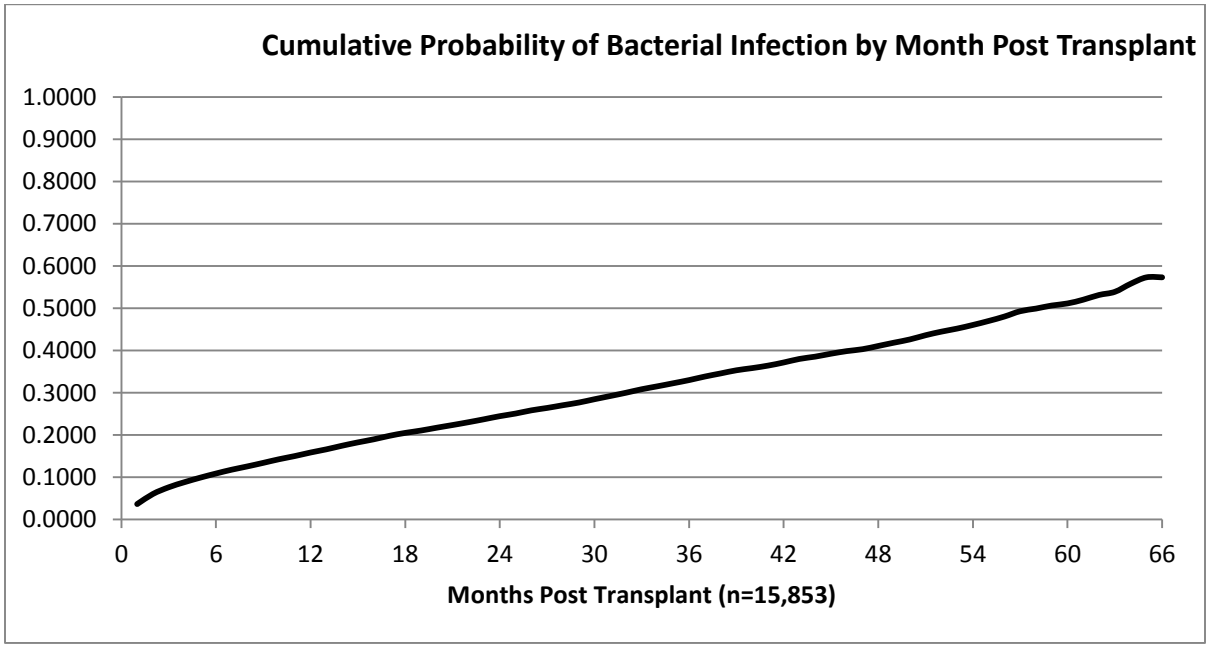


Figure 9: CMV infection:

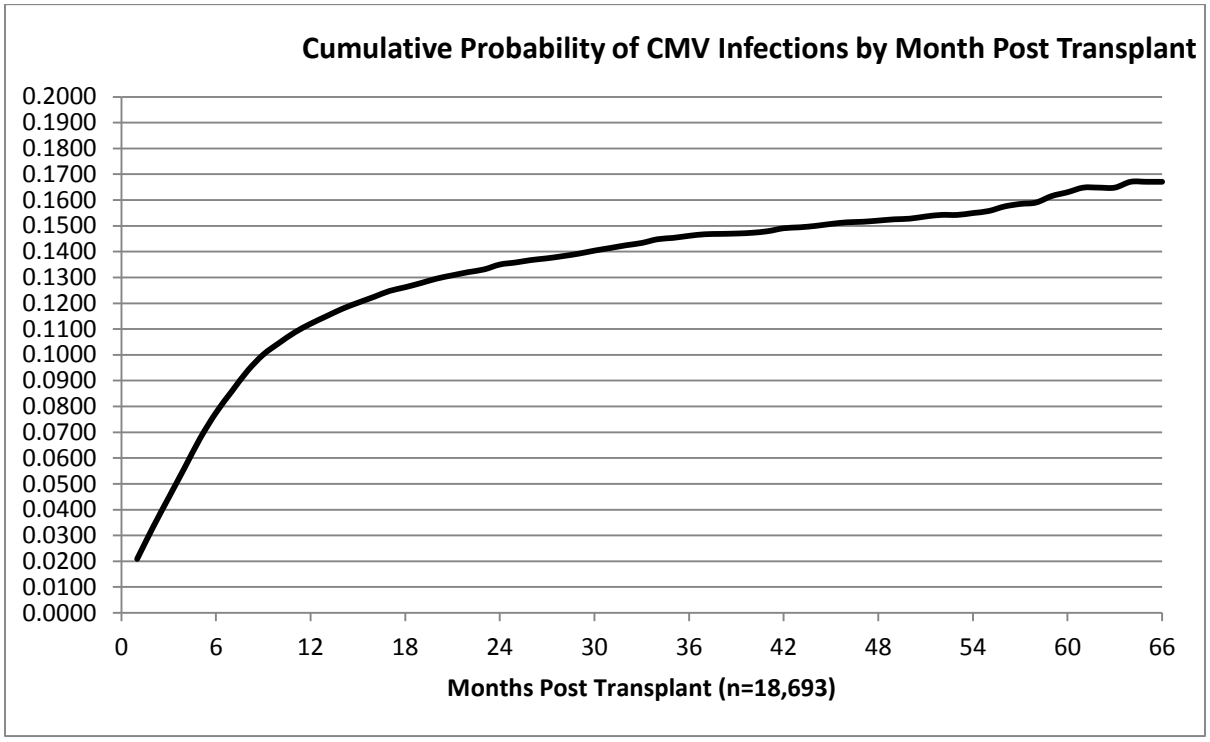


Figure 10: Fracture

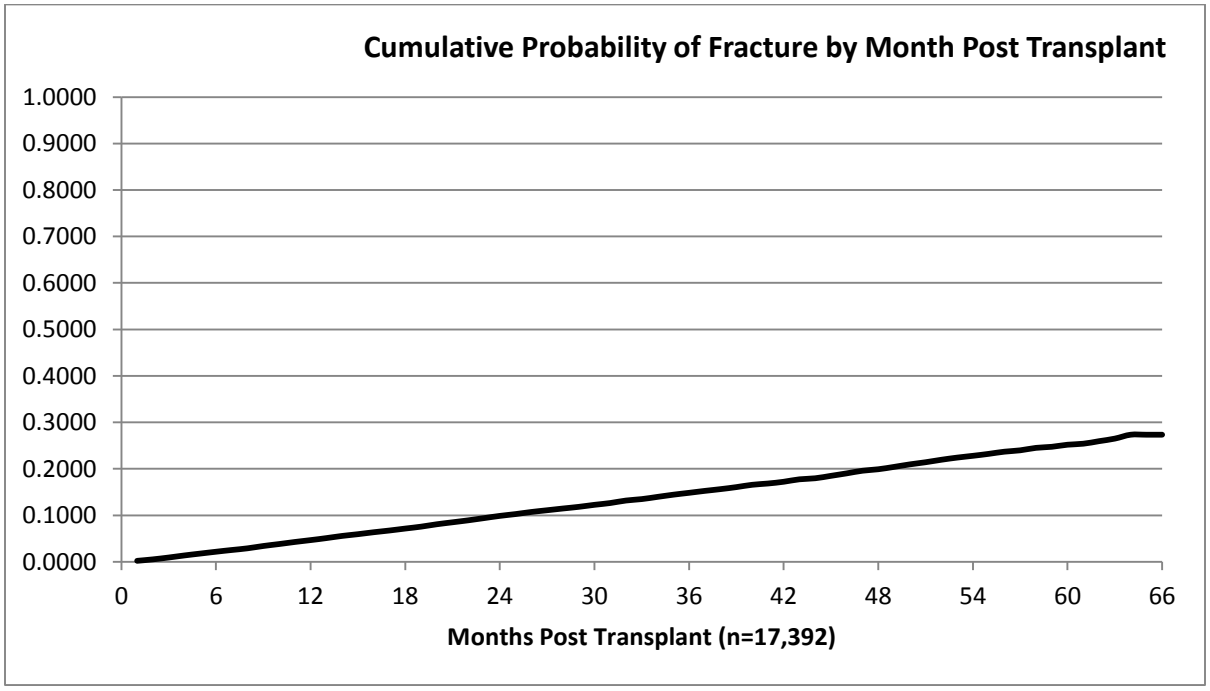


Figure 11: Death due to cardiovascular disease

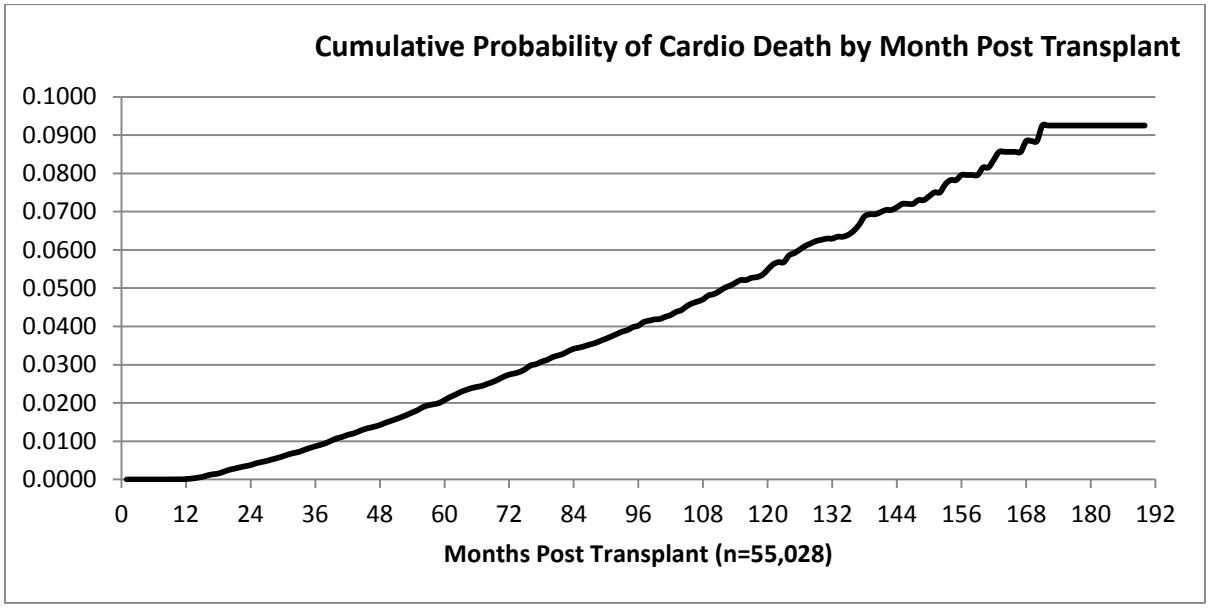


Figure 12: Death due to graft loss

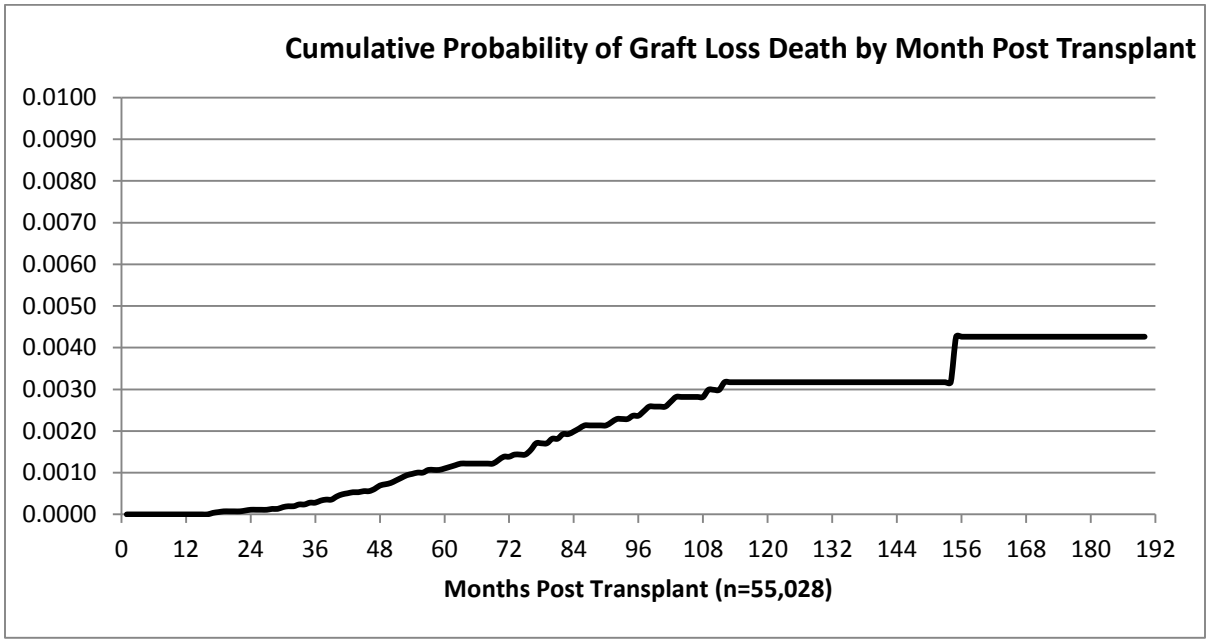
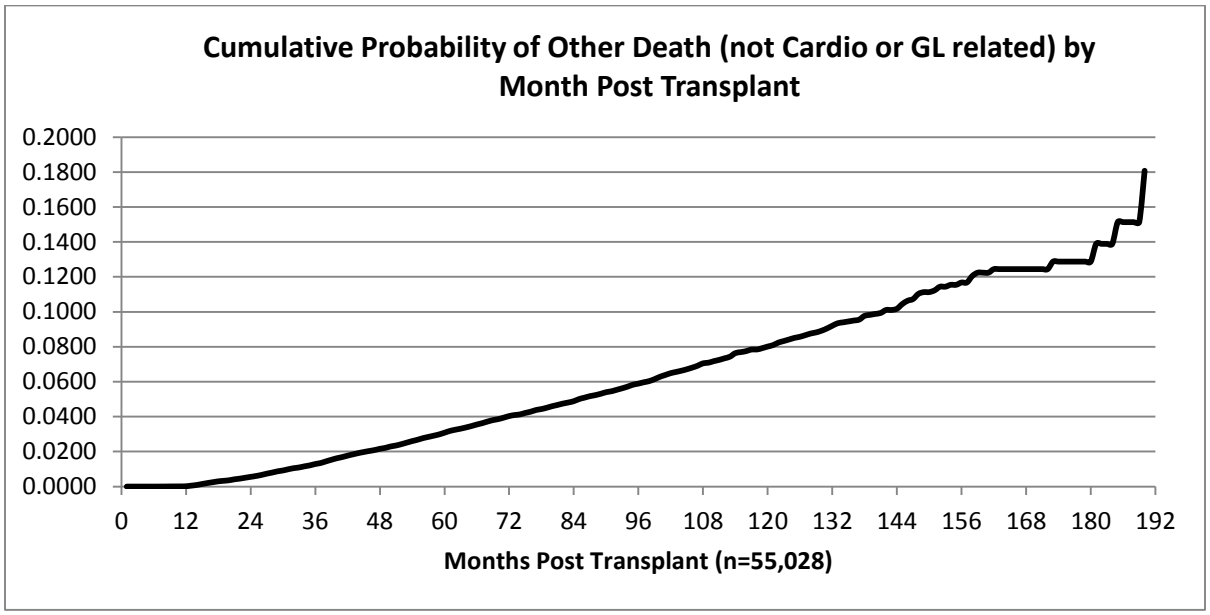


Figure 13: Death due to other reasons



6.6 Summary table of regression coefficients for various events

Table 38.1: 'Proc Lifereg' coefficients for various events (summary table)

Attribute Description	Event												
	AR	GL	MI	Str	CVD	NOD	Cancer	BI	CMV	Fx	D-GL	D-Cardio	D-Other
Steroid Avoidance	-1.73	-.57	.20	.21	-.03	.04	-.24	.32	-.05	-.51	-.06	.75	.13
7 Day Withdrawal	-1.03	-.27	-.16	-.24	-.19	.24	.18	.04	-.01	.05	-.09	.06	.07
6 Month Withdrawal	.05	.09	.47	.10	.38	.67	.05	.28	.76	.17	.06	.10	.18
12 Month Withdrawal	.20	.05	.53	.10	-.03	.34	-.03	.46	.28	.28	.07	.11	.18
Steroid Maintenance	0	0	0	0	0	0	0	0	0	0	0	0	0
Young (18-39)	-.78	-.28	1.45	.85	.50	.88	.44	-.17	.00	.14	.00	.48	.50
Middle-Aged (40-59)	0	0	0	0	0	0	0	0	0	0	0	0	0
Elderly (60+)	.34	.03	-.60	-.53	-.78	-.63	-.32	-.10	.00	-.12	.00	-.38	-.49
White	0	0	0	0	0	0	0	0	0	0	0	0	0
Black	-.27	-.36	.00	.05	.00	-.48	.36	.00	.20	.42	.00	.04	.12
Other Race	.23	.07	.00	.28	.00	-.15	.26	.00	.54	.23	.00	.19	.25
Hispanic	.00	.00	.00	.00	.00	-.69	.21	.00	.94	.00	.00	.14	.16
Male	.44	.14	.00	.13	.00	-.18	.11	.71	.00	.36	.00	.00	.00
Female	0	0	0	0	0	0	0	0	0	0	0	0	0
Low Weight (BMI<18.5)	.14	.00	.00	.00	-.02	.57	-.28	.03	.00	.00	.00	.00	.00
Normal Weight (18.5-35)	0	0	0	0	0	0	0	0	0	0	0	0	0

Obese (BMI≥35)	-.32	.00	.00	.00	-.33	-.84	.06	-.41	.00	.00	.00	.00	.00
Diabetes	.00	.00	-1.19	-.54	-.63	.00	.14	-.79	.00	-.56	.00	-.48	-.28
HTN	.00	-.27	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
HPL	-.61	-.60	.00	.00	.00	.00	.00	.00	.00	-.26	.00	.00	.00
CVD History	-.18	-.28	-.84	-.46	.00	-.30	.00	-.28	.29	-.12	.00	-.32	-.11
Malignancy	.00	-.21	-.66	.00	.00	.00	.00	.00	.00	.00	.00	.00	-.26
CMV	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
EBV	-.47	.00	.00	.00	.00	-.23	.00	.00	.99	.00	.00	.00	-.15
HCV or HIV	0	-.15	.00	.00	.00	.00	.00	.00	.00	.00	.00	.19	.00
Creatinine >1.4mg/dl	-1.41	-.37	.00	.00	-.23	.00	.00	-.31	-.60	.00	-.38	-.11	-.08
Dialysis time 0-1 years	0	0	0	0	0	0	0	0	0	0	0	0	0
Dialysis time 1-3 years	.00	-.04	.00	.00	-.18	-.15	.00	-.24	-.48	-.23	.00	.01	-.12
Dialysis time >3 years	.00	-.11	.00	.00	-.66	-.42	.00	-.42	-.60	-.25	.00	-.15	-.18
HLA mismatch (0-1)	0	0	0	0	0	0	0	0	0	0	0	0	0
HLA mismatch (2)	-.31	-.17	.00	.00	-.15	.00	.00	.00	-.16	.00	.00	.00	.00
HLA mismatch (>2)	-.66	-.14	.00	.00	-.34	.00	.00	.00	-.38	.00	.00	.00	.00
Live Donor	0	0	0	0	0	0	0	0	0	0	0	0	0
Cadaveric Donor	.00	-.18	.00	.00	-.38	-.33	.00	-.28	-.40	.00	.00	-.17	-.13
Cold Ischemia Time 0-12 hours	0	0	0	0	0	0	0	0	0	0	0	0	0
Cold Ischemia Time 12-24 hours	-.24	.00	.00	.00	.00	.00	-.11	.00	.00	.00	.00	.00	.00
Cold Ischemia Time >24 hours	-.31	.00	.00	.00	.00	.00	-.18	.00	.00	.00	.00	.00	.00

IL2 Induction	.32	.09	.00	.00	.00	.19	.00	.00	.29	.00	.00	.00	.09
Polyclonal Induction	-.95	.08	.00	.00	.00	.94	.00	.00	-1.30	.00	.00	.00	.19
Monoclonal Induction	-1.96	-.24	.00	.00	.00	.48	.00	.00	-.78	.00	.00	.00	.17
Alemtuzumab Induction	0	0	0	0	0	0	0	0	0	0	0	0	0
Induction Switch	-1.00	-.11	.00	-.16	-.33	-.34	.00	-.30	.00	-.16	.00	.00	.00
Acute Rejection	0	-.80	.71	.13	.83	1.29	.38	.53	1.44	.08	-.11	-.09	-.14

- An estimate of ".00" means that the estimated coefficient was statistically non-significant at the 0.01 level. A value of "0" is given for the reference group for categorical variables. Note that if one of the categories in a categorical variable had a significant (at the 0.01 level) estimated coefficient, then all estimates in the category are given as nonzero. For each regression, estimated coefficients for the steroid regimens AND for AR (which may serve as a proxy for change in immunosuppressant regimen) are given, whether or not they were statistically significant
- MI: myocardial infarction; Str: stroke; CVD: other cardiovascular diseases; NODM: new-onset diabetes mellitus; BI: bacterial infection; CMV: cytomegalovirus infection; FX: fracture; GL: graft loss; D-GL: death due to graft loss; D-Cardio: death due to cardiovascular diseases; D-Other=death due to other reasons; HTN: hypertension; HPL: hyperlipidemia; EBV: Epstein Barr virus

Table 38.2 'Proc Lifereg' exponentiated coefficients for various events (summary table)

	Event (Parametric regression estimates with exp(x) values)												
Attribute description	**AR**	**GL**	**MI**	**Str**	**CVD**	**NOD**	**Cancer**	**BI**	**CMV**	**Fx**	**D-GL**	**D-**	**D-**
Steroid Avoidance	0.18	0.57	1.22	1.23	0.97	1.04	0.79	1.38	0.95	0.6	0.94	2.12	1.14
7 Day Withdrawal	0.36	0.76	0.85	0.79	0.83	1.27	1.2	1.04	0.99	1.05	0.91	1.06	1.07
6 Month Withdrawal	1.05	1.09	1.6	1.11	1.46	1.95	1.05	1.32	2.14	1.19	1.06	1.11	1.2
12 Month Withdrawal	1.22	1.05	1.7	1.11	0.97	1.4	0.97	1.58	1.32	1.32	1.07	1.12	1.2
Steroid Maintenance	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Young (18-39)	0.46	0.76	4.26	2.34	1.65	2.41	1.55	0.84		1.15		1.62	1.65
Middle-aged(40-60)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Elderly (60+)	1.4	1.03	0.55	0.59	0.46	0.53	0.73	0.9		0.89		0.68	0.61
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	0.76	0.7		1.05		0.62	1.43		1.22	1.52		1.04	1.13
Other Race	1.26	1.07		1.32		0.86	1.3		1.72	1.26		1.21	1.28
Hispanic						0.5	1.23		2.56	1		1.15	1.17
Male	1.55	1.15		1.14		0.84	1.12	2.03		1.43			
BMI<18.5	1.15				0.98	1.77	0.76	1.03					
BMI 18.5-35	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
BMI≥35	0.73				0.72	0.43	1.06	0.66					
Diabetes			0.3	0.58	0.53	1	1.15	0.45		0.57		0.62	0.76
HTN		0.76											
HPL	0.54	0.55								0.77			
CVD History	0.84	0.76	0.43	0.63		0.74		0.76	1.34	0.89		0.73	0.9
Malignancy		0.81	0.52										0.77
CMV													

EBV	0.63					0.79			2.69				0.86
HCV or HIV		0.86										1.21	
Creatinine >1.4mg/dl	0.24	0.69			0.79			0.73	0.55		0.68	0.9	0.92
Dialysis time (0-1 year)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Dialysis time(1-3 years)		0.96			0.84	0.86		0.79	0.62	0.79		1.01	0.89
Dialysis time (>3 years)		0.90			0.52	0.66		0.66	0.55	0.78		0.86	0.84
HLA mismatch (0-1)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
HLA mismatch (2)	0.73	0.84			0.86				0.85				
HLA mismatch(>2)	0.52	0.87			0.71				0.68				
Live Donor	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Cadaveric Donor		0.84			0.68	0.72		0.76	0.67			0.84	0.88
Cold Ischemia Time	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Cold Ischemia Time	0.79						0.9						
Cold Ischemia Time	0.73						0.84						
IL2 Induction	1.38	1.09				1.21			1.34				1.09
Polyclonal Induction	0.39	1.08				2.56			0.27				1.21
Monoclonal Induction	0.14	0.79				1.62			0.46				1.19
Alemtuzumab Induction	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Switch from Tacrolimus to Cyclosporine /Sirolimus	0.37	0.9		0.85	0.72	0.71		0.74		0.85			
Acute Rejection		0.45	2.03	1.14	2.29	3.63	1.46	1.7	4.22	1.08	0.9	0.91	0.87

- Blank cells mean that the estimated coefficient was statistically non-significant at the 0.01 level. Note that if one of the categories in a categorical variable had a significant (at the 0.01 level) estimated coefficient, then all estimates in the category are given. For each regression, estimated coefficients for the steroid regimens AND for AR (which may serve as a proxy for change in immunosuppressant regimen) are given, whether or not they were statistically significant
- MI: myocardial infarction; Str: stroke; CVD: other cardiovascular diseases; NODM: new-onset diabetes mellitus; BI: bacterial infection; CMV: cytomegalovirus infection; FX: fracture; GL: graft loss; D-GL: death due to graft loss; D-Cardio: death due to cardiovascular diseases; D-Other=death due to other reasons; HTN: hypertension; HPL: hyperlipidemia; EBV: Epstein Barr virus

6.7 Discrete event simulation result tables

Table 39. DES results –Base patient

Regimen	Total Number of Events (out of 10,000 Patients)												
	1 AR	2 GL	3 MI	4 Stroke	5 CVD	6 NOD	7 Cancer	8 BI	9 CMV	10 Fx	11 D-GL	12 D-Cardio	13 D-Other
SM	3548	4099	1223	2465	6277	4644	8986	6744	5723	9713	0	2884	4212
12 M W	3338	4218	958	2361	6465	4245	9186	5175	5230	7576	0	2573	3407
6 M W	3605	4071	976	2266	5586	3721	9071	5762	4177	8410	1	2455	3350
7 Day W	5317	5799	1327	3267	6584	4174	8547	6500	5560	9289	1	2846	3945
SA	6776	7640	1180	2266	6404	4458	9416	5555	5651	18,806	2	1141	4593
	Number of Patients with ≥ 1 Event												
SM	3053	4099	1142	2112	6277	4644	8986	4789	4316	5913	0	2884	4212
12 M W	2906	4218	906	2025	6465	4245	9186	3968	4052	5114	0	2573	3407
6 M W	3118	4071	929	1976	5586	3721	9071	4302	3379	5485	1	2455	3350
7 Day W	4257	5799	1229	2675	6584	4174	8547	4669	4196	5767	1	2846	3945
SA	5140	7640	1101	1955	6404	4458	9416	4199	4273	7978	2	1141	4593
	Average Time to 1st Event in Months for Patients with ≥ 1 Event												
SM	46	112	83	118	61	58	58	72	48	92	NA	156	156
12 M W	49	119	88	123	63	63	58	79	52	100	NA	160	161
6 M W	50	119	88	122	68	64	61	77	53	99	141	160	162
7 Day W	41	107	84	117	60	59	65	74	47	93	83	159	159
SA	36	98	91	125	65	61	52	80	50	83	156	164	163

Base-Case Patient: White, 50-year-old male, with hyperlipidemia and hypertension, exposure to CMV pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor, HLA mismatch = 2, cold ischemic time between 12 and 24 hours, on a polyclonal antibody induction regimen

Steroid regimens: SM: Steroid maintenance; 12 M W**:** 12 month withdrawal; 6 M W: 6 month withdrawal; 7 Day W: 7 day withdrawal; SA: Steroid avoidance

Significantly more likely

Significantly less likely

Table 40. DES Results for BASE patient – Confidence Intervals

	1 AR	2 GL	3 MI	4 Stroke	5 CVD	6 NOD	7 Cancer	8 BI	9 CMV	10 Fx	11 D-GL	12 D-Cardio	13 D-Other
Events Lower													
SM	3448	3999	1123	2365	6177	4544	8886	6544	5523	9513	0	2784	4112
12 M W	3238	4118	858	2261	6365	4145	9086	5075	5130	7376	0	2473	3307
6 M W	3505	3971	876	2166	5486	3621	8971	5562	4077	8210	1	2355	3250
7 Day W	5217	5699	1227	3167	6484	4074	8447	6300	5460	9089	1	2746	3845
SA	6576	7540	1080	2166	6304	4358	9416	5455	5551	18506	2	1041	4493
Events Upper													
SM	3648	4199	1323	2565	6377	4744	9086	6944	5923	9913	0	2984	4312
12 M W	3438	4318	1058	2461	6565	4345	9286	5275	5330	7776	0	2673	3507
6 M W	3705	4171	1076	2366	5686	3821	9171	5962	4277	8610	1	2555	3450
7 Day W	5417	5899	1427	3367	6684	4274	8647	6700	5660	9489	1	2946	4045
SA	6976	7740	1280	2366	6504	4558	9416	5655	5751	19106	2	1241	4693
Patients Lower													
SM	2953	3999	1042	2012	6177	4544	8886	4689	4216	5813	0	2784	4112
12 M W	2806	4118	806	1925	6365	4145	9086	3868	3952	5014	0	2473	3307
6 M W	3018	3971	829	1876	5486	3621	8971	4202	3279	5385	1	2355	3250
7 Day W	4157	5699	1129	2575	6484	4074	8447	4569	4096	5667	1	2746	3845
SA	5040	7540	1001	1855	6304	4358	9416	4099	4173	7878	2	1041	4493
Patients Upper													
SM	3153	4199	1242	2212	6377	4744	9086	4889	4416	6013	0	2984	4312
12 M W	3006	4318	1006	2125	6565	4345	9286	4068	4152	5214	0	2673	3507
6 M W	3218	4171	1029	2076	5686	3821	9171	4402	3479	5585	1	2555	3450

7 Day W	4357	5899	1329	2775	6684	4274	8647	4769	4296	5867	1	2946	4045
SA	5240	7740	1201	2055	6504	4558	9416	4299	4373	8078	2	1241	4693
Time Lower													
SM	41.88	106.42	71.11	107.74	58.32	54.41	55.76	68.20	44.72	88.39	NA	145.92	148.42
12 M W	45.21	112.84	72.45	111.53	60.15	58.96	55.91	74.56	48.46	95.84	NA	148.43	151.46
6 M W	45.99	113.10	72.97	110.81	64.26	59.30	59.28	73.11	49.41	94.88	-159.00	148.18	152.87
7 Day W	38.05	103.32	72.12	108.82	57.71	55.49	62.63	70.19	44.41	89.66	-117.00	148.04	151.23
SA	33.75	94.69	77.59	113.85	62.24	57.14	51.03	75.90	46.87	80.37	-93.50	142.35	155.85
Time Upper													
SM	49.46	118.30	98.00	129.48	63.87	61.21	59.28	75.80	50.88	95.84	NA	167.18	163.71
12 M W	53.71	125.02	106.31	134.86	65.72	66.83	59.36	84.15	55.37	104.93	NA	172.32	170.42
6 M W	54.14	125.70	106.50	134.56	70.87	68.05	62.96	81.92	57.49	103.35	441.00	173.08	172.25
7 Day W	43.45	111.65	97.65	126.67	63.00	63.07	66.71	78.16	50.68	97.34	283.00	169.82	167.74
SA	38.03	100.51	107.48	138.31	67.99	64.54	53.05	85.16	53.38	85.51	406.50	190.45	170.53

Base-Case Patient: White, 50-year-old male, with hyperlipidemia and hypertension, exposure to CMV pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor, HLA mismatch = 2, cold ischemic time between 12 and 24 hours, on a polyclonal antibody induction regimen

Steroid regimens: SM: Steroid maintenance; 12 M W**:** 12 month withdrawal; 6 M W: 6 month withdrawal; 7 Day W: 7 day withdrawal; SA: Steroid avoidance

Significantly more likely

Significantly less likely

Table 41: DES Results for CVD patient

Regimen	Total Number of Events (out of 10,000 Patients)												
	1 AR	2 GL	3 MI	4 Stroke	5 CVD	6 NOD	7 Cancer	8 BI	9 CMV	10 Fx	11 D-GL	12 D-Cardio	13 D-Other
SM	3636	4619	1628	3114	NA	4907	8681	7511	4866	9834	0	3649	4198
12 M W	3386	4774	1303	3009	NA	4492	8929	5729	4443	7778	0	3303	3444
6 M W	3664	4661	1308	2978	NA	3962	8768	6381	3564	8606	0	3272	3401
7 Day W	5349	6243	1720	4143	NA	4406	8235	7193	4759	9468	0	3526	3963
SA	6749	8028	1553	2807	NA	4722	9314	6260	4922	19,611	2	1488	4766
	Number of Patients with ≥ 1 Event												
SM	3156	4619	1491	2591	NA	4907	8681	5081	3807	5877	0	3649	4198
12 M W	2965	4774	1225	2502	NA	4492	8929	4262	3558	5138	0	3303	3444
6 M W	3167	4661	1221	2483	NA	3962	8768	4609	2979	5513	0	3272	3401
7 Day W	4282	6243	1571	3235	NA	4406	8235	4940	3758	5775	0	3526	3963
SA	5130	8028	1433	2378	NA	4722	9314	4545	3837	8024	2	1488	4766
	Average Time to 1st Event in Months for Patients with ≥ 1 Event												
SM	43	103	72	106	NA	53	55	65	47	87	0	148	151
12 M W	45	110	78	110	NA	58	56	73	51	96	0	153	157
6 M W	45	111	76	110	NA	59	59	71	53	94	0	153	157
7 Day W	37	96	73	104	NA	54	62	66	48	89	0	150	154
SA	32	85	79	116	NA	56	51	75	51	78	155	157	159

CVD Patient: White, 50-year-old male, with hyperlipidemia and hypertension and history of cardiovascular disease (CVD), exposure to CMV pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor, HLA mismatch = 2, cold ischemic time between 12 and 24 hours, on a polyclonal antibody induction regimen

Steroid regimens: SM: Steroid maintenance; 12 M W**:** 12 month withdrawal; 6 M W: 6 month withdrawal; 7 Day W: 7 day withdrawal; SA: Steroid avoidance

Significantly more likely

Significantly less likely

Table 42: DES Results for patients with CVD – Confidence Intervals

	1 AR	2 GL	3 MI	4 Stroke	5 CVD	6 NOD	7 Cancer	8 BI	9 CMV	10 Fx	11 D-GL	12 D-Cardio	13 D-Other
Events Lower													
SM	3536	4519	1528	3014	NA	4807	8581	7311	4766	9634	0	3549	4098
12 M W	3286	4674	1203	2909	NA	4392	8829	5529	4343	7578	0	3203	3344
6 M W	3564	4561	1208	2878	NA	3862	8668	6181	3464	8406	0	3172	3301
7 Day W	5249	6143	1620	4043	NA	4306	8135	6993	4659	9268	0	3426	3863
SA	6549	7928	1453	2707	NA	4622	9314	6060	4822	19311	2	1388	4666
Events Upper													
SM	3736	4719	1728	3214	NA	5007	8781	7711	4966	10034	0	3749	4298
12 M W	3486	4874	1403	3109	NA	4592	9029	5929	4543	7978	0	3403	3544
6 M W	3764	4761	1408	3078	NA	4062	8868	6581	3664	8806	0	3372	3501
7 Day W	5449	6343	1820	4243	NA	4506	8335	7393	4859	9668	0	3626	4063
SA	6949	8128	1653	2907	NA	4822	9314	6460	5022	19911	2	1588	4866
Patients Lower													
SM	3056	4519	1391	2491	NA	4807	8581	4981	3707	5777	0	3549	4098
12 M W	2865	4674	1125	2402	NA	4392	8829	4162	3458	5038	0	3203	3344
6 M W	3067	4561	1121	2383	NA	3862	8668	4509	2879	5413	0	3172	3301
7 Day W	4182	6143	1471	3135	NA	4306	8135	4840	3658	5675	0	3426	3863
SA	5030	7928	1333	2278	NA	4622	9314	4445	3737	7924	2	1388	4666
Patients Upper													
SM	3256	4719	1591	2691	NA	5007	8781	5181	3907	5977	0	3749	4298
12 M W	3065	4874	1325	2602	NA	4592	9029	4362	3658	5238	0	3403	3544
6 M W	3267	4761	1321	2583	NA	4062	8868	4709	3079	5613	0	3372	3501
7 Day W	4382	6343	1671	3335	NA	4506	8335	5040	3858	5875	0	3626	4063

SA	5230	8128	1533	2478	NA	4822	9314	4645	3937	8124	2	1588	4866
Time Lower													
SM	39.47	97.89	62.92	97.46	NA	49.69	53.47	62.05	44.15	83.14	NA	139.73	143.93
12 M W	41.51	104.51	66.79	101.58	NA	54.38	53.92	68.54	47.36	91.41	NA	144.00	147.92
6 M W	41.51	105.37	65.59	101.24	NA	54.92	56.93	67.59	48.33	89.87	NA	143.53	148.30
7 Day W	34.40	92.22	63.88	97.46	NA	50.58	59.81	62.85	44.63	85.10	NA	141.40	146.16
SA	29.84	82.97	69.47	106.35	NA	53.18	50.19	70.86	47.37	75.37	-95.00	139.57	152.06
Time Upper													
SM	46.57	107.79	82.03	114.20	NA	55.71	56.97	68.75	50.90	90.25	NA	156.28	158.86
12 M W	49.29	114.72	90.76	119.53	NA	61.41	57.36	77.02	54.90	100.12	NA	162.66	166.28
6 M W	48.91	115.87	89.24	119.31	NA	62.68	60.60	75.42	57.11	97.92	NA	162.29	166.91
7 Day W	39.39	99.26	82.36	111.33	NA	57.29	63.86	69.78	51.50	92.47	NA	158.65	162.12
SA	33.73	87.94	90.99	125.79	NA	59.85	52.21	79.08	54.51	80.23	405.00	176.54	165.95

CVD Patient: White, 50-year-old male, with hyperlipidemia and hypertension and history of cardiovascular disease (CVD), exposure to CMV pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor, HLA mismatch = 2, cold ischemic time between 12 and 24 hours, on a polyclonal antibody induction regimen

Steroid regimens: SM: Steroid maintenance; 12 M W**:** 12 month withdrawal; 6 M W: 6 month withdrawal; 7 Day W: 7 day withdrawal; SA: Steroid avoidance

Significantly more likely

Significantly less likely

Table 43: DES Results for African-American Patients:

Regimen	AR	GL	MI	Stroke	CVD	NOD	Cancer	BI	CMV	Fx	D-GL	D-Cardio	D-Other
Number of Events													
SM	3779	5773	1245	2498	6372	5502	8174	7033	5293	6573	0	3003	3651
12 M W	3597	5803	981	2338	6556	5035	8455	5328	4781	5178	0	2675	2912
6 M W	3883	5629	986	2266	5697	4439	8291	5893	3852	5691	0	2499	2778
7 Day W	5644	7343	1335	3320	6702	4992	7616	6644	5159	6384	2	2952	3346
SA	6904	8803	1200	2228	6479	5250	8874	5854	5198	12,800	3	1174	3779
Number of Patients with >1 Event													
SM	3251	5773	1168	2132	6372	5502	8174	4927	4056	4635	0	3003	3651
12 M W	3115	5803	928	2015	6556	5035	8455	4038	3757	3936	0	2675	2912
6 M W	3317	5629	928	1967	5697	4439	8291	4345	3181	4212	0	2499	2778
7 Day W	4479	7343	1241	2693	6702	4992	7616	4719	3985	4539	2	2952	3346
SA	5242	8803	1117	1919	6479	5250	8874	4349	4008	6,825	3	1174	3779
Time to Event													
SM	42.62	107.31	86.85	121.83	63.48	56.89	69.08	73.64	49.52	101.49	NA	158.87	159.39
12 M W	46.08	112.42	91.46	124.84	64.92	60.31	70.01	81.15	52.82	109.36	NA	161.87	163.58
6 M W	46.17	114.00	90.18	125.34	69.76	62.27	73.52	78.34	55.43	108.03	NA	161.99	162.75
7 Day W	37.19	97.17	87.68	120.62	63.16	58.90	75.18	75.23	49.86	103.26	117.50	161.99	161.14
SA	30.12	83.53	95.20	127.64	67.59	59.54	65.61	84.27	51.43	95.98	153.33	166.36	164.53

African-American Patient: African-American, 50-year-old male, with hyperlipidemia and hypertension, exposure to CMV pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor, HLA mismatch = 2, cold ischemic time between 12 and 24 hours, on a polyclonal antibody induction regimen

Steroid regimens: SM: Steroid maintenance; 12 M W**:** 12 month withdrawal; 6 M W: 6 month withdrawal; 7 Day W: 7 day withdrawal; SA: Steroid avoidance

Significantly more likely

Significantly less likely

Table 44: DES Results for African-American Patients – Confidence Intervals:

	1 AR	2 GL	3 MI	4 Stroke	5 CVD	6 NOD	7 Cancer	8 BI	9 CMV	10 Fx	11 D-GL	12 D-Cardio	13 D-Other
Events Lower													
SM	3679	5673	1145	2398	6272	5402	8074	6833	5193	6373	0	2903	3551
12 M W	3497	5703	881	2238	6456	4935	8355	5228	4681	5078	0	2575	2812
6 M W	3783	5529	886	2166	5597	4339	8191	5693	3752	5491	0	2399	2678
7 Day W	5544	7243	1235	3220	6602	4892	7516	6444	5059	6184	2	2852	3246
SA	6704	8703	1100	2128	6379	5150	8774	5654	5098	12600	3	1074	3679
Events Upper													
SM	3879	5873	1345	2598	6472	5602	8274	7233	5393	6773	0	3103	3751
12 M W	3697	5903	1081	2438	6656	5135	8555	5428	4881	5278	0	2775	3012
6 M W	3983	5729	1086	2366	5797	4539	8391	6093	3952	5891	0	2599	2878
7 Day W	5744	7443	1435	3420	6802	5092	7716	6844	5259	6584	2	3052	3446
SA	7104	8903	1300	2328	6579	5350	8974	6054	5298	13000	3	1274	3879
Patients Lower													
SM	3151	5673	1068	2032	6272	5402	8074	4827	3956	4535	0	2903	3551
12 M W	3015	5703	828	1915	6456	4935	8355	3938	3657	3836	0	2575	2812
6 M W	3217	5529	828	1867	5597	4339	8191	4245	3081	4112	0	2399	2678
7 Day W	4379	7243	1141	2593	6602	4892	7516	4619	3885	4439	2	2852	3246
SA	5142	8703	1017	1819	6379	5150	8774	4249	3908	6725	3	1074	3679
Patients Upper													
SM	3351	5873	1268	2232	6472	5602	8274	5027	4156	4735	0	3103	3751
12 M W	3215	5903	1028	2115	6656	5135	8555	4138	3857	4036	0	2775	3012

6 M W	3417	5729	1028	2067	5797	4539	8391	4445	3281	4312	0	2599	2878
7 Day W	4579	7443	1341	2793	6802	5092	7716	4819	4085	4639	2	3052	3446
SA	5342	8903	1217	2019	6579	5350	8974	4449	4108	6925	3	1274	3879
Time Lower													
SM	39.29	103.18	74.33	111.26	60.69	53.97	66.87	69.93	46.29	96.60	NA	148.79	150.79
12 M W	42.40	108.15	75.94	113.55	62.12	57.05	67.84	76.43	49.19	103.38	NA	150.63	152.97
6 M W	42.65	109.55	74.89	113.76	66.49	58.61	71.22	74.02	51.18	102.42	NA	150.10	151.78
7 Day W	34.82	94.18	75.55	111.86	60.47	55.66	72.67	71.31	46.53	98.21	-32.50	151.60	151.79
SA	28.36	81.38	81.13	115.67	64.69	56.39	63.63	79.67	48.01	92.66	-46.67	144.67	155.93
Time Upper													
SM	46.16	111.58	101.73	133.43	66.36	59.93	71.35	77.51	52.92	106.60	NA	169.65	168.47
12 M W	49.99	116.85	110.71	137.31	67.80	63.70	72.24	86.10	56.64	115.65	NA	173.98	174.95
6 M W	49.90	118.61	109.16	138.16	73.15	66.11	75.88	82.88	59.95	113.92	NA	174.87	174.54
7 Day W	39.66	100.23	101.94	130.05	65.94	62.27	77.77	79.33	53.36	108.54	267.50	173.10	171.07
SA	31.95	85.73	112.04	140.92	70.58	62.81	67.63	89.07	55.02	99.40	353.33	192.09	173.60

African-American Patient: African-American, 50-year-old male, with hyperlipidemia and hypertension, exposure to CMV pre-transplant, 1-3 years of dialysis pre-transplant, cadaveric donor, HLA mismatch = 2, cold ischemic time between 12 and 24 hours, on a polyclonal antibody induction regimen

Steroid regimens: SM: Steroid maintenance; 12 M W**:** 12 month withdrawal; 6 M W: 6 month withdrawal; 7 Day W: 7 day withdrawal; SA: Steroid avoidance

Significantly more likely

Significantly less likely

6.8 Patient comparisons

Table 45: Patients on 6-month steroid withdrawal regimen:

	AR	GL	MI	Stroke	CVD	NODM	Cancer	BI	CMV	FX	D-GL	D-Cardio	D-Other
Base	3118	4071	929	1976	5586	3721	9071	4302	3379	5485	1	2455	3350
CVD	3167	4661	1221	2483	NA	3962	8768	4609	2979	5513	0	3272	3401
African American	3317	5629	928	1967	5697	4439	8291	4345	3181	4212	0	2499	2778

Table 46: Patients on 12-month steroid withdrawal regimen:

	AR	GL	MI	Stroke	CVD	NODM	Cancer	BI	CMV	FX	D-GL	D-Cardio	D-Other
Base	2906	4218	906	2025	6465	4245	9186	3968	4052	5114	0	2573	3407
CVD	2965	4774	1225	2502	NA	4492	8929	4262	3558	5138	0	3303	3444
African American	3115	5803	928	2015	6556	5035	8455	4038	3757	3936	0	2675	2912

Significantly more likely
Significantly less likely

7. APPENDICES

7.1 Appendix I: Validation of data fit for Weibull distributions

(Note: For all charts, the hypothetical patient characteristics vary; pdf: probability density function; cdf: cumulative density function)

Figure A.1

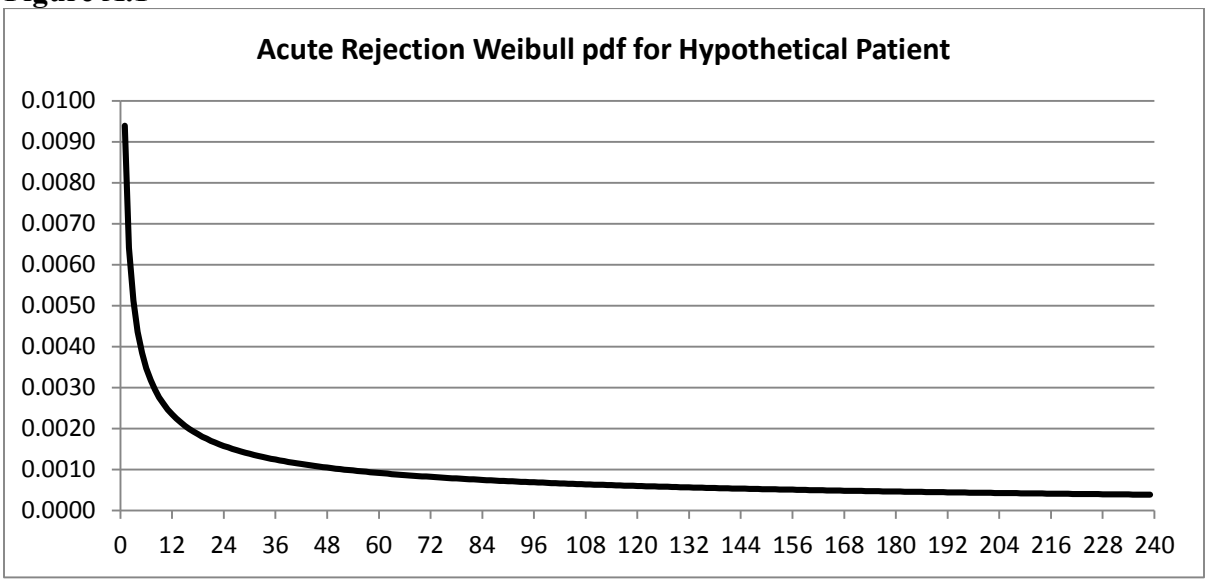


Figure A.2

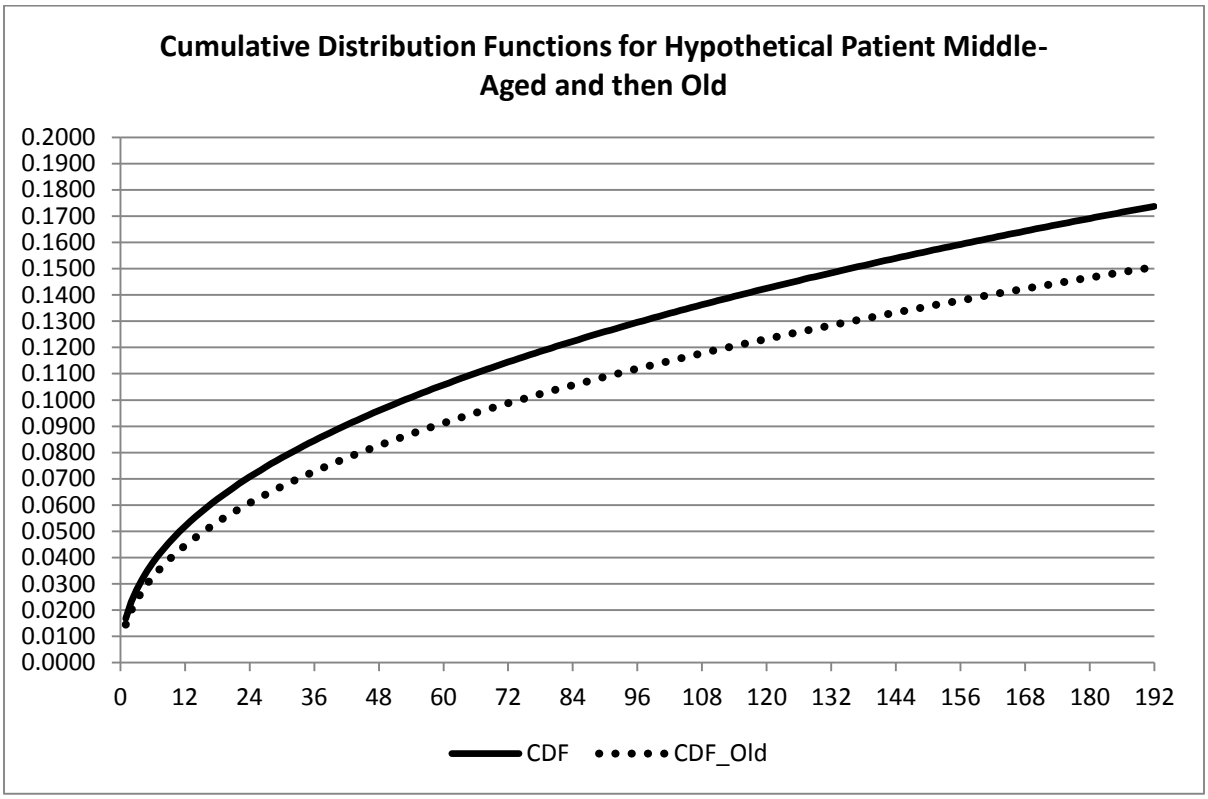


Figure B.1

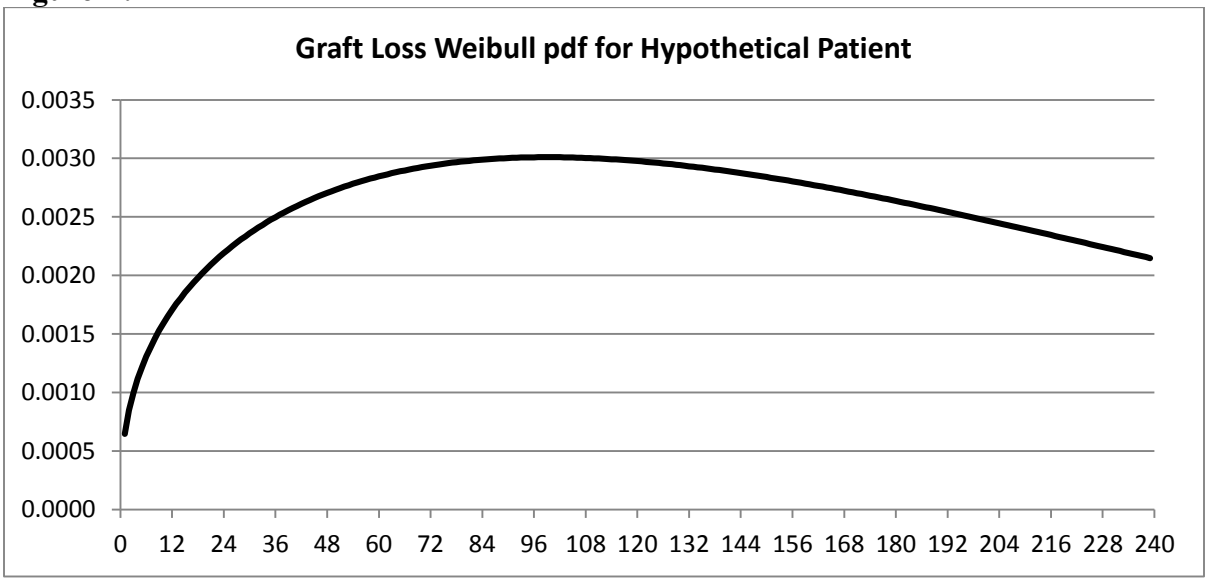


Figure B.2

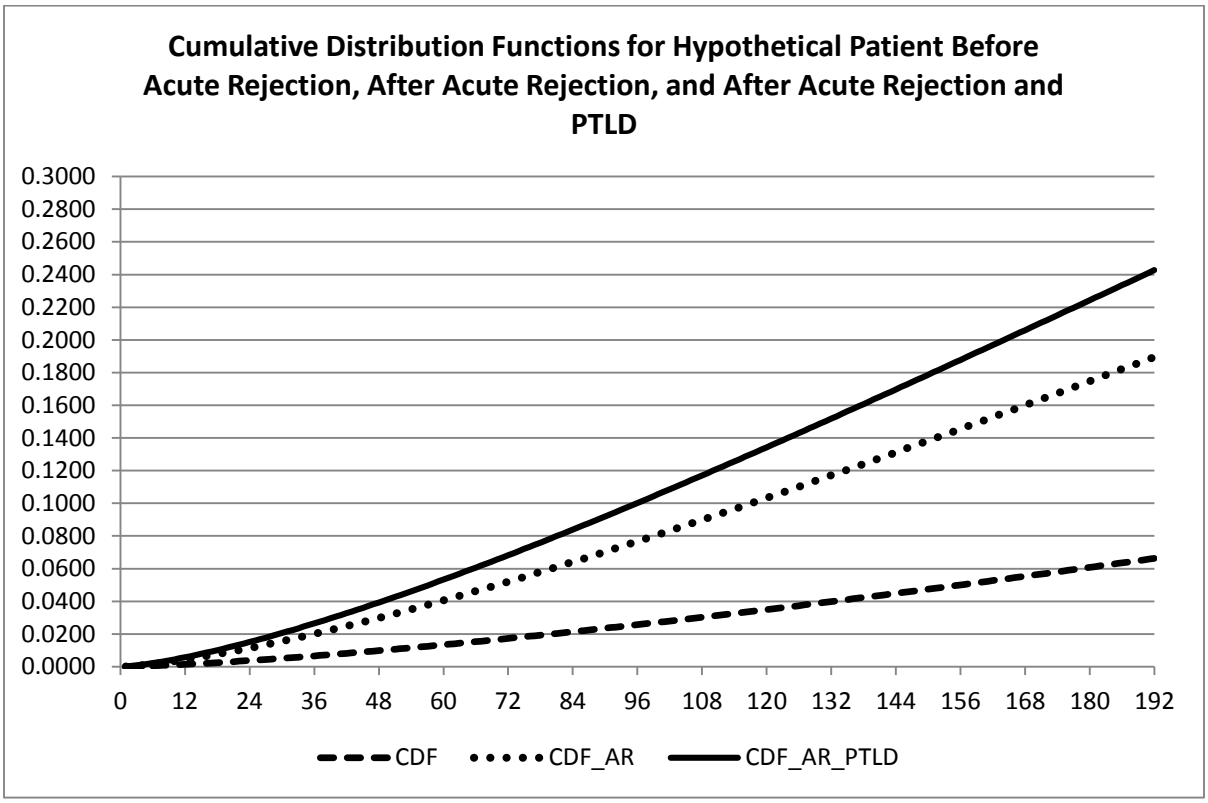


Figure C.1

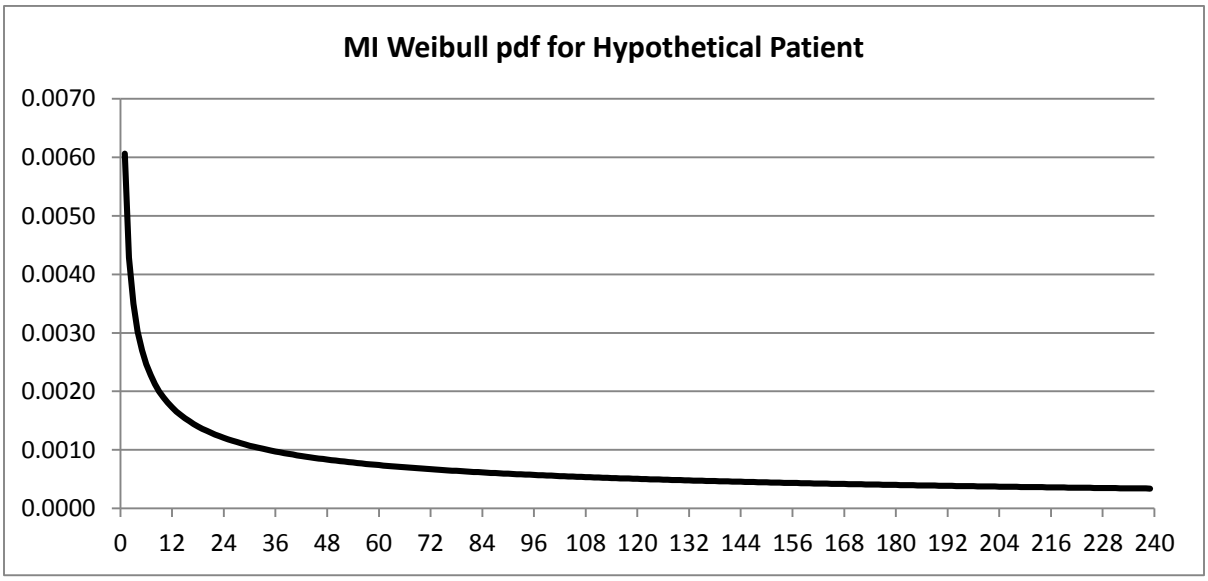


Figure C.2

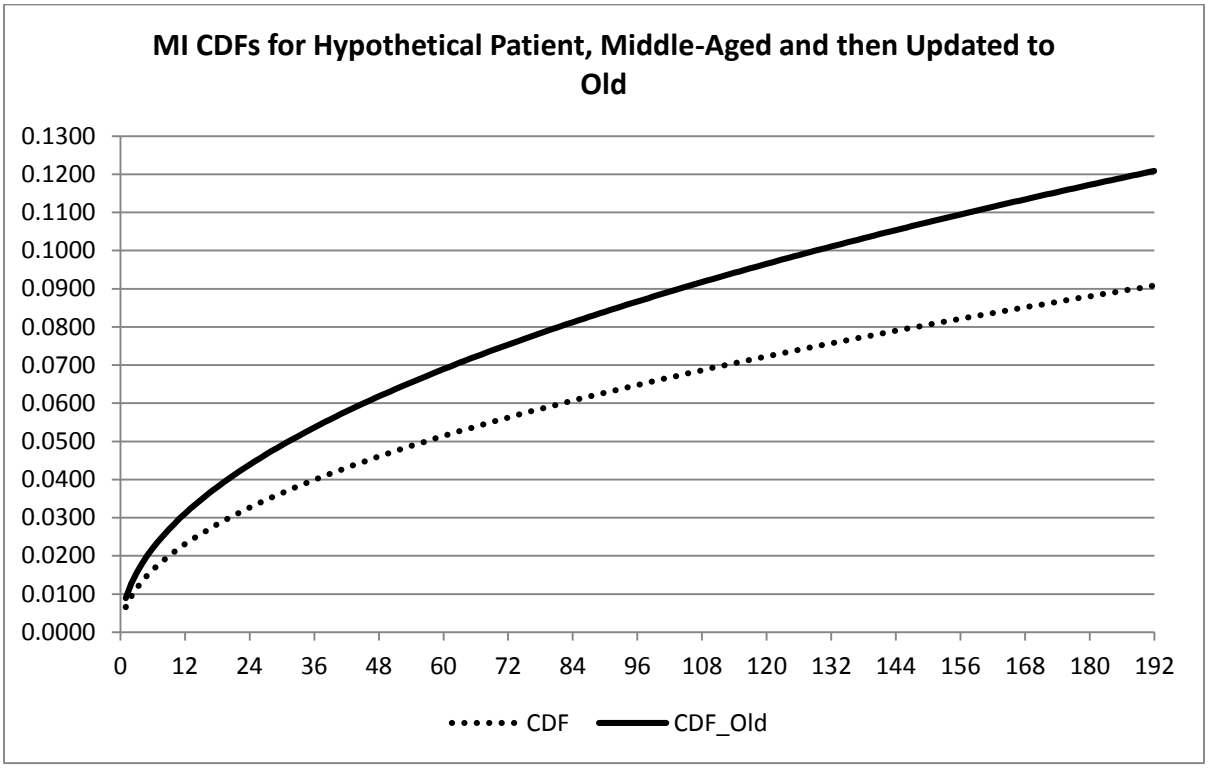


Figure D.1

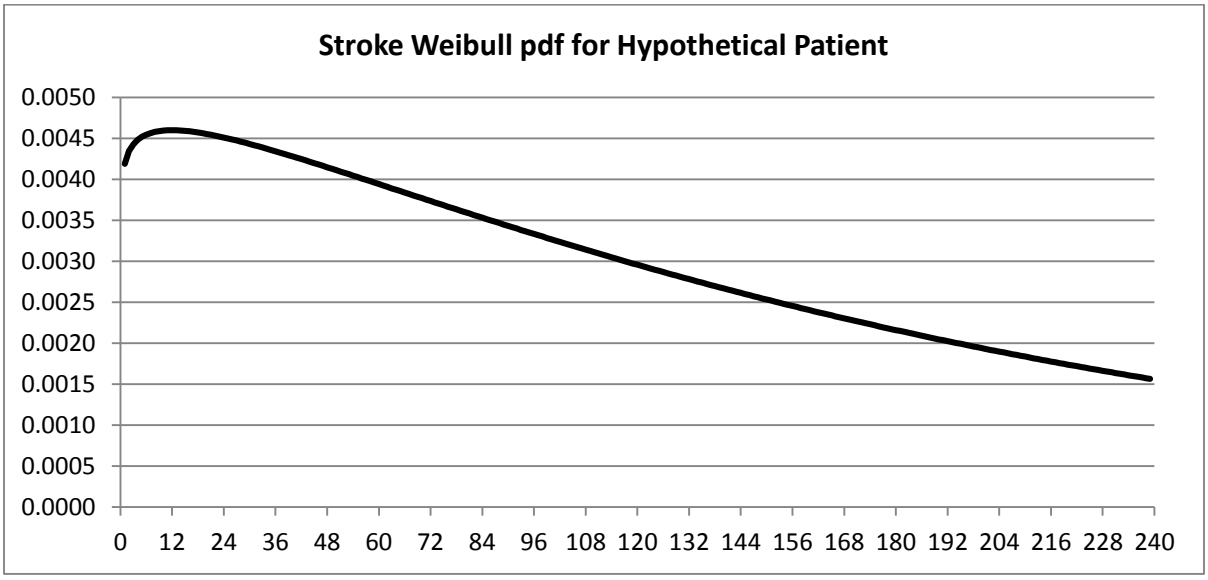


Figure D.2

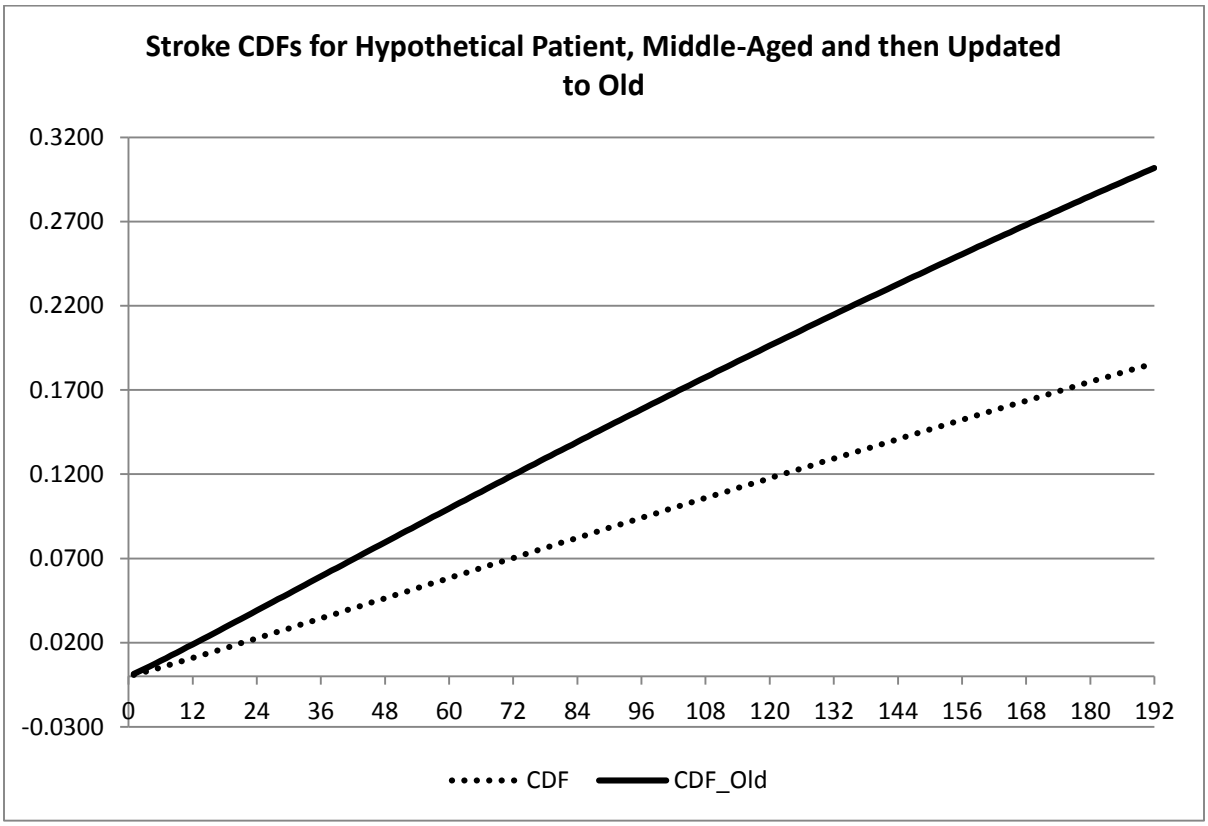
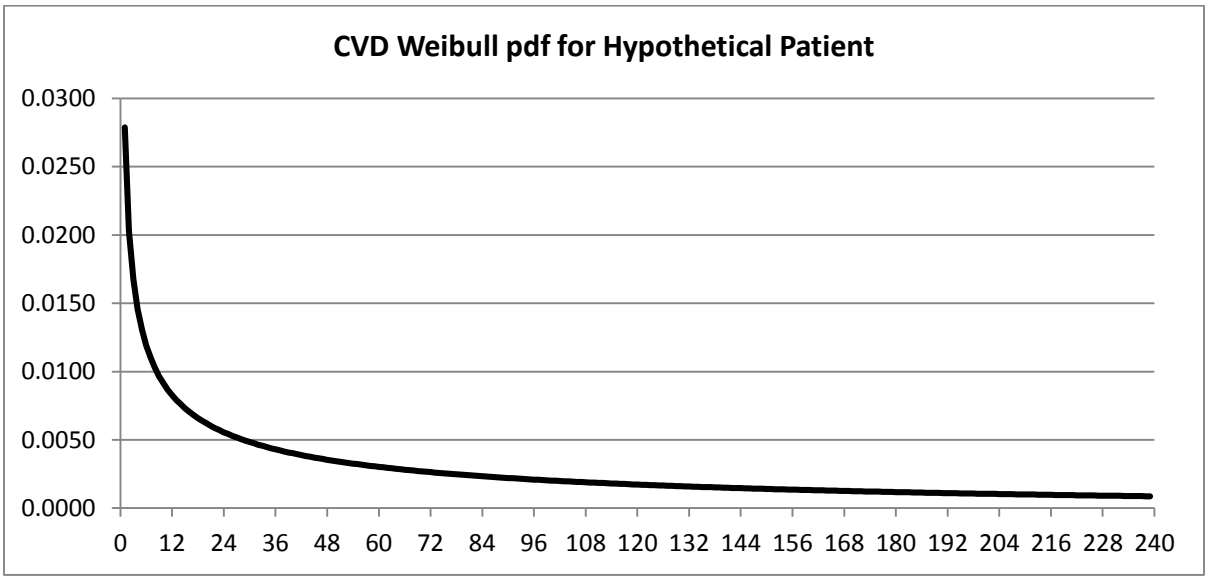


Figure E.1



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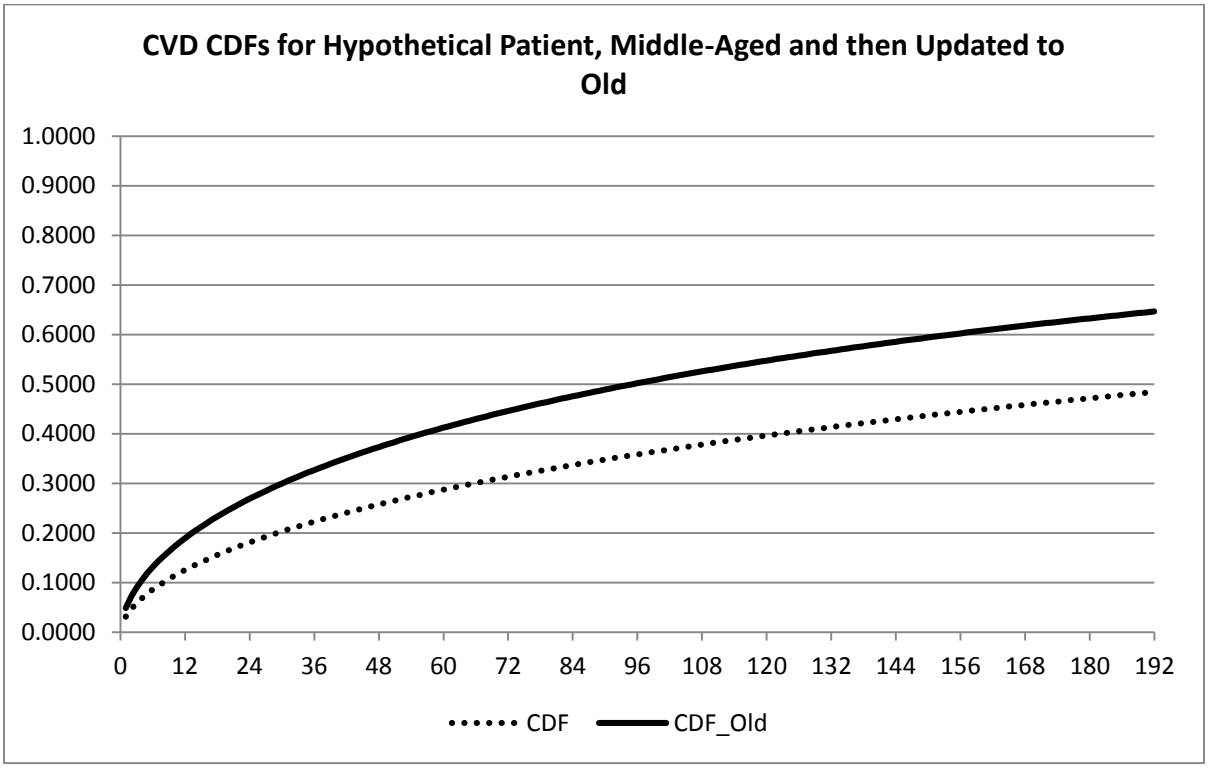


Figure F.1

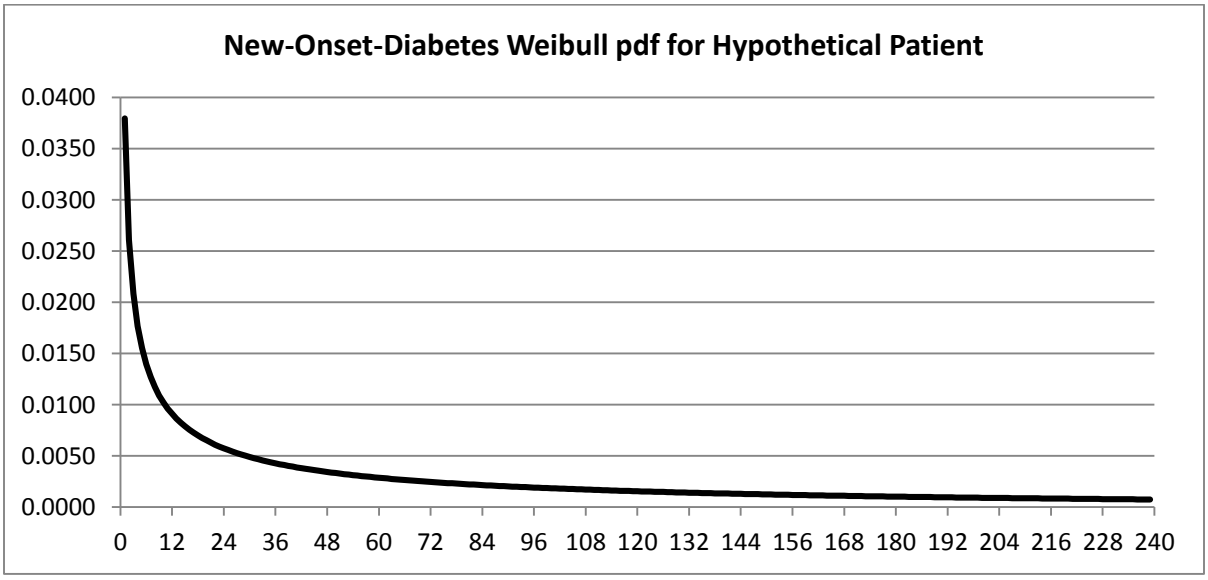


Figure F.2

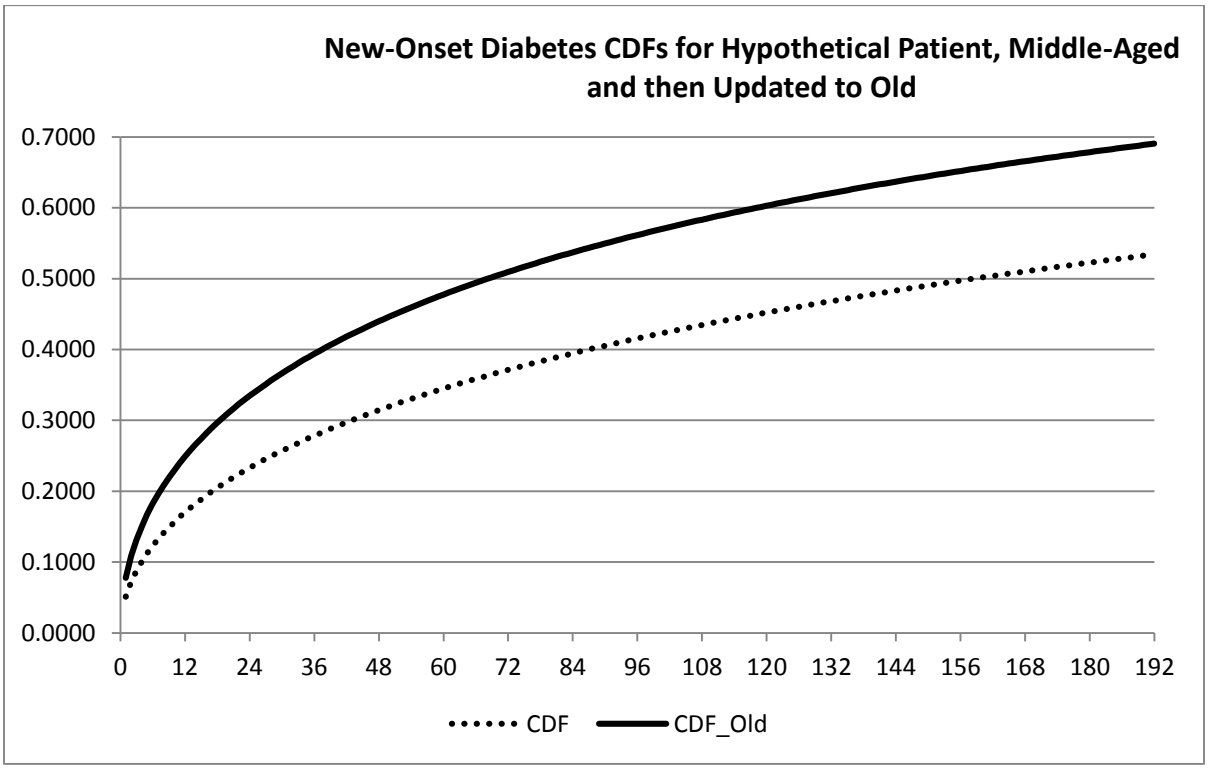


Figure G.1

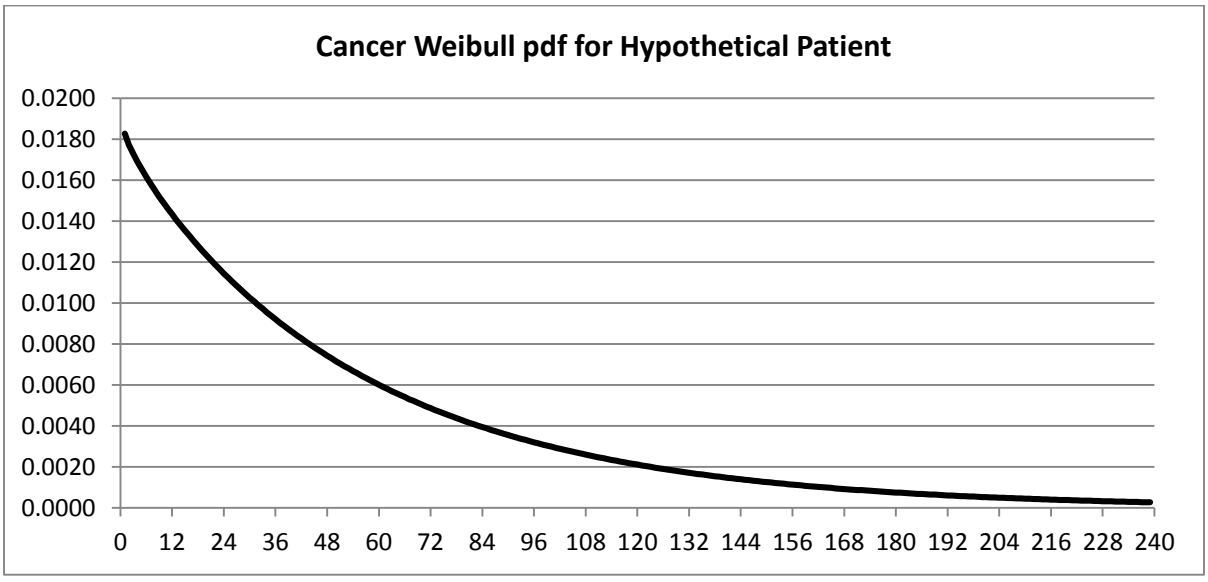


Figure G.2

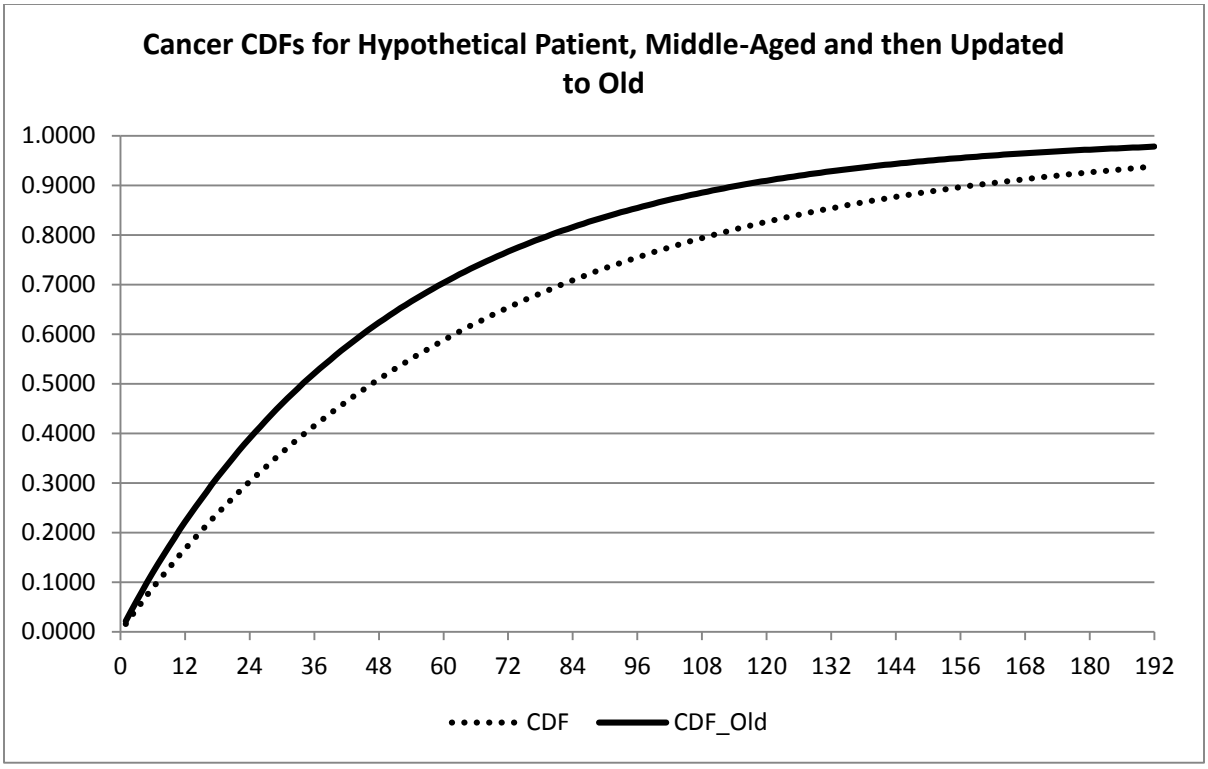


Figure H.1

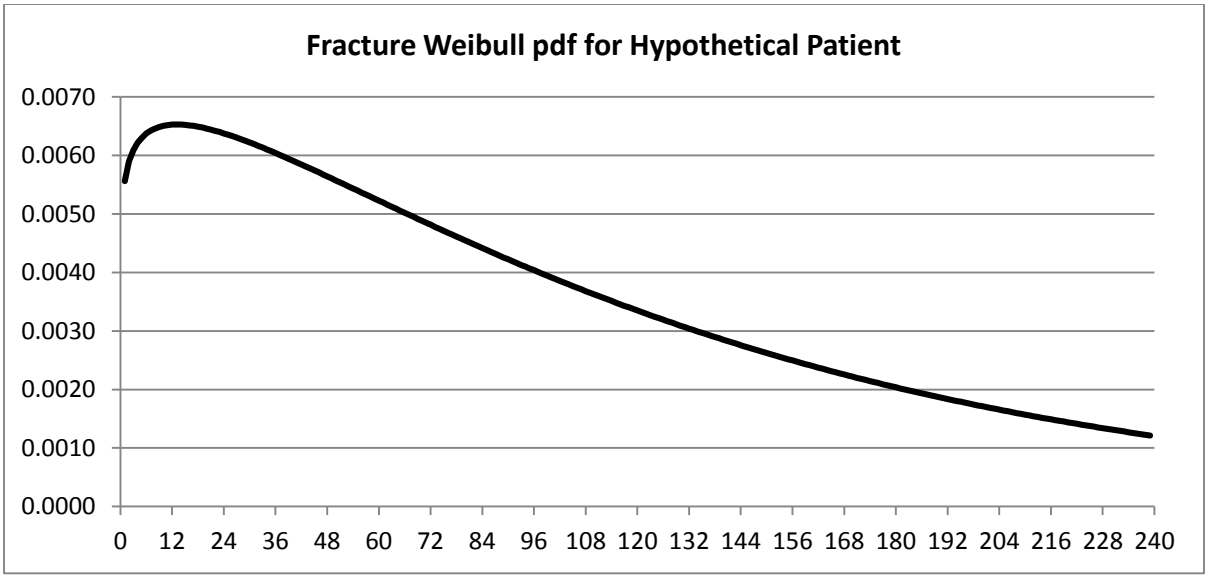


Figure H.2

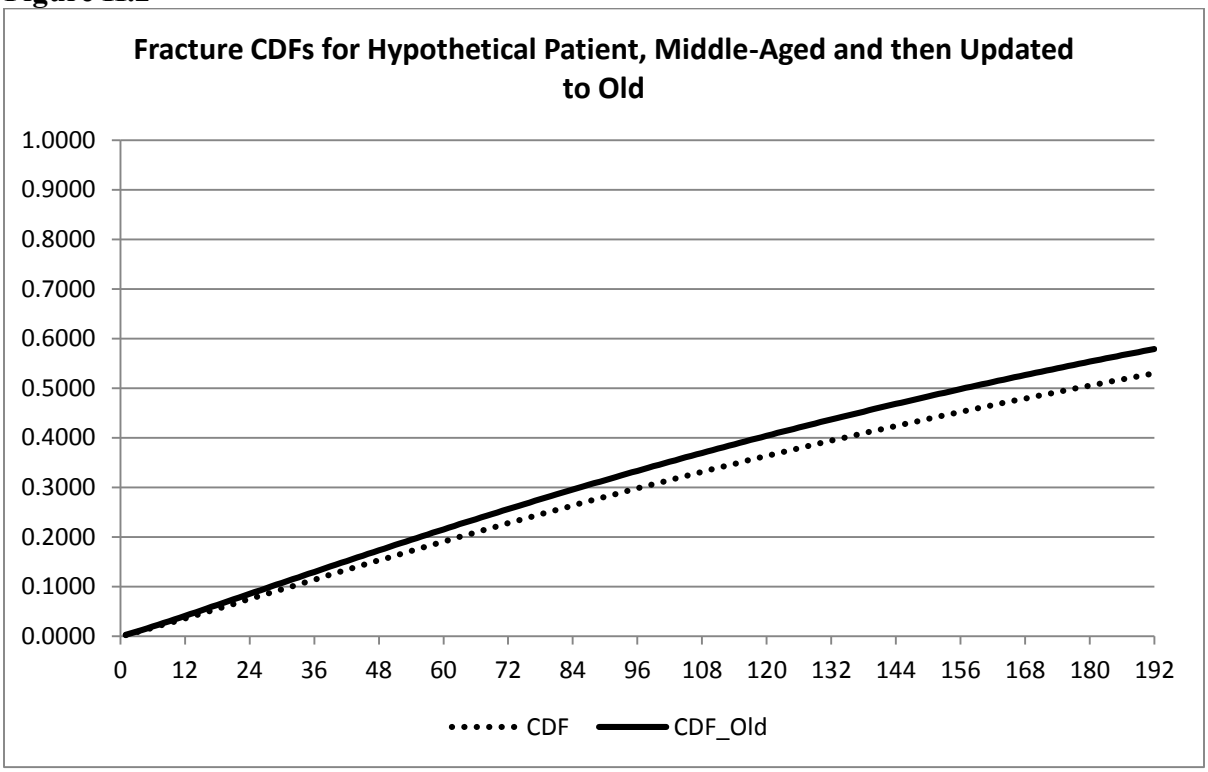


Figure I.1

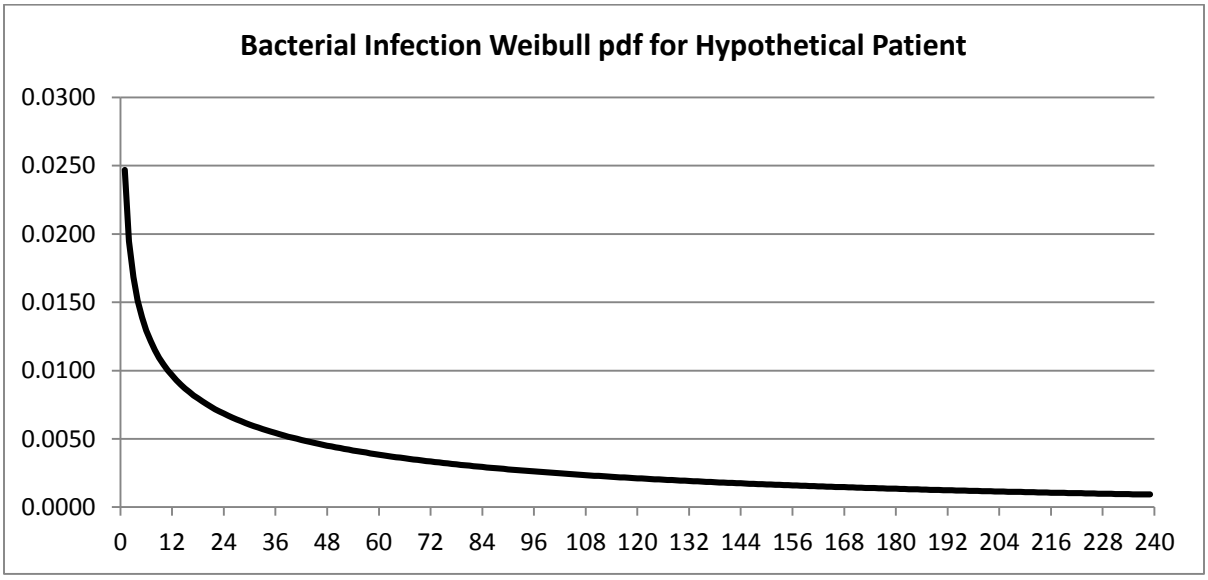


FIGURE I.2:

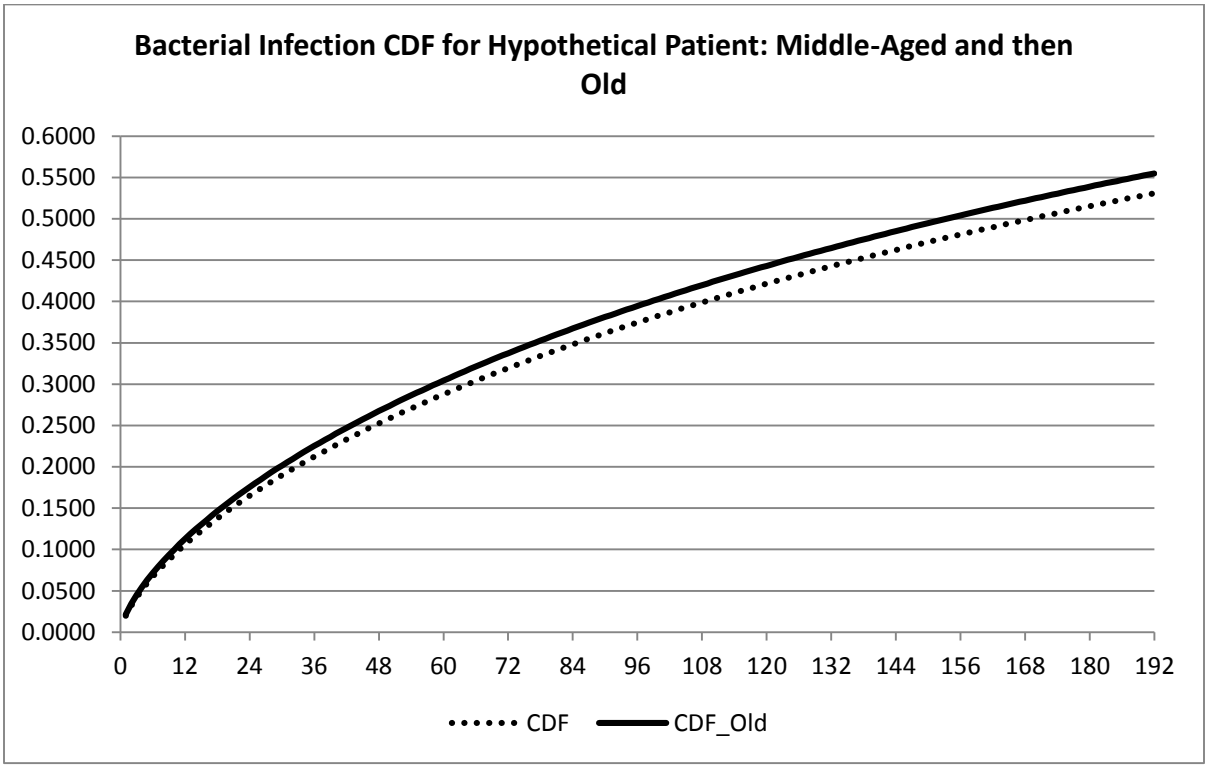


Figure J.1

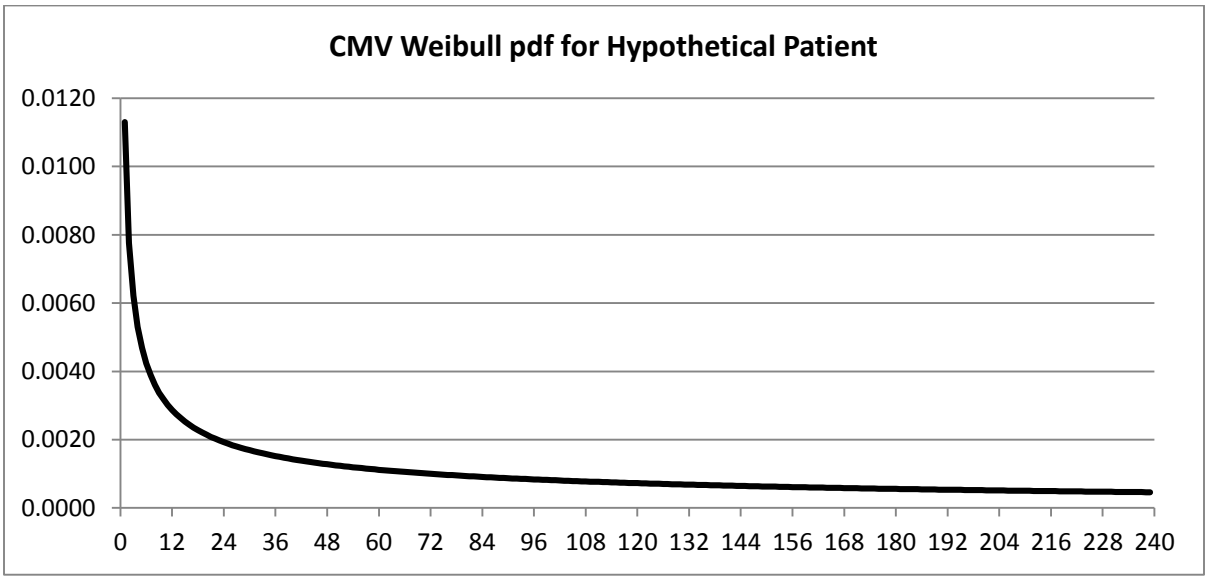


Figure J.2

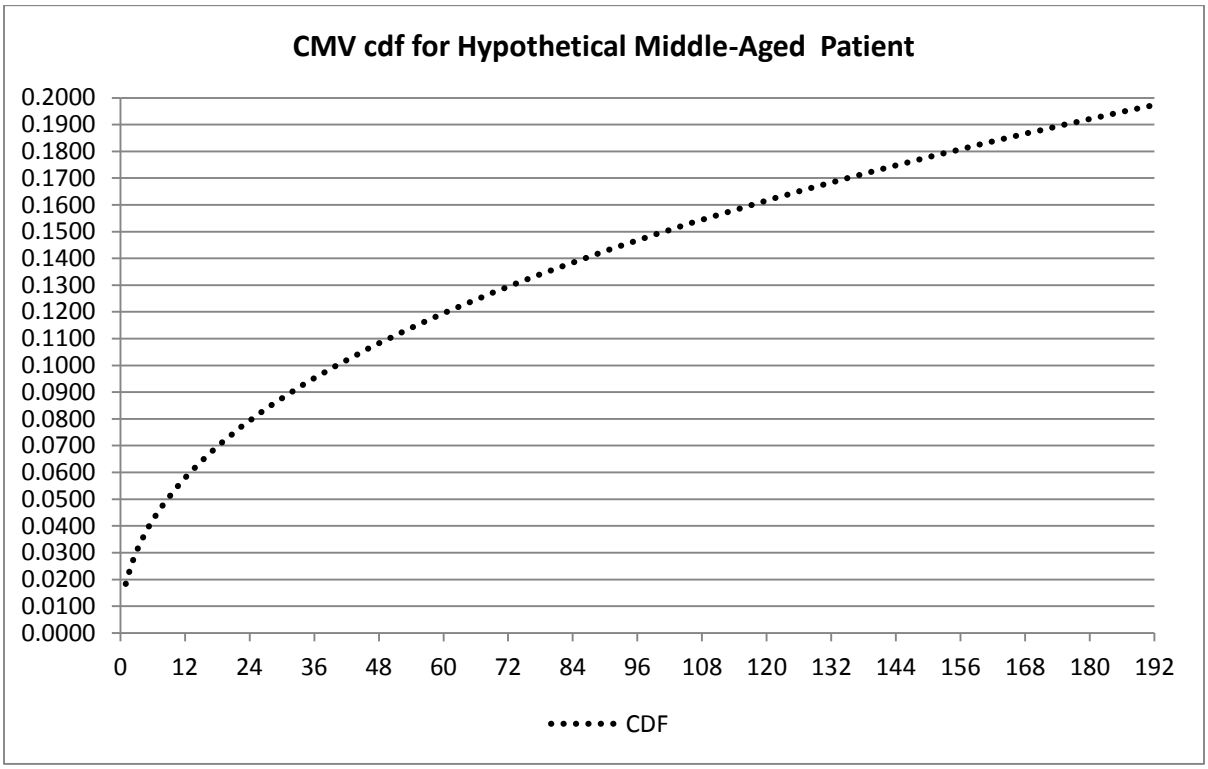


Figure K.1

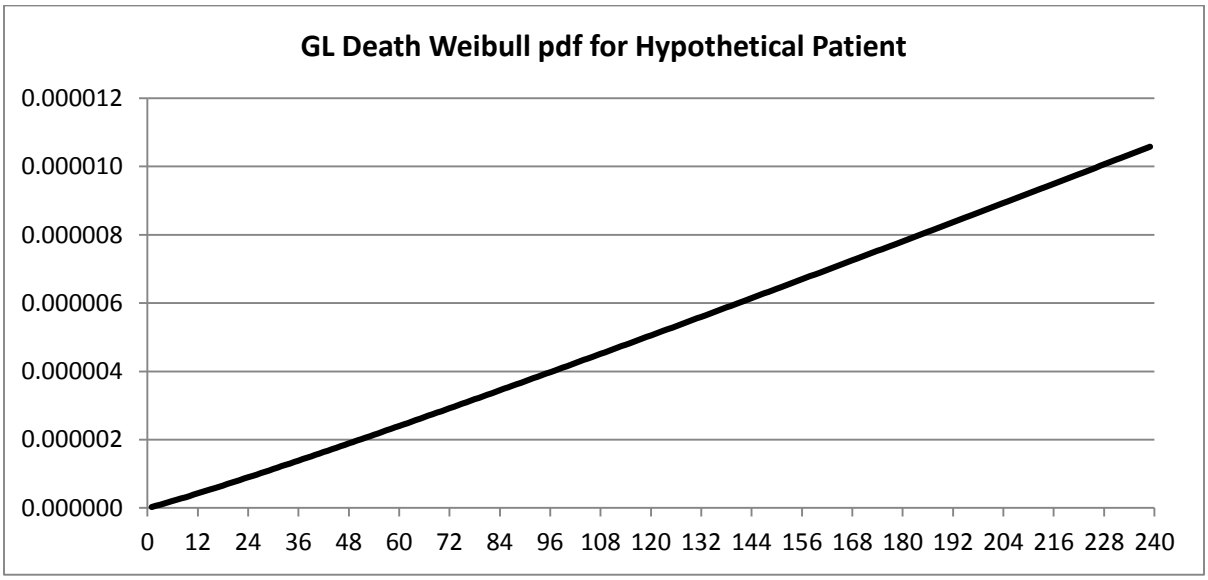


Figure K.2

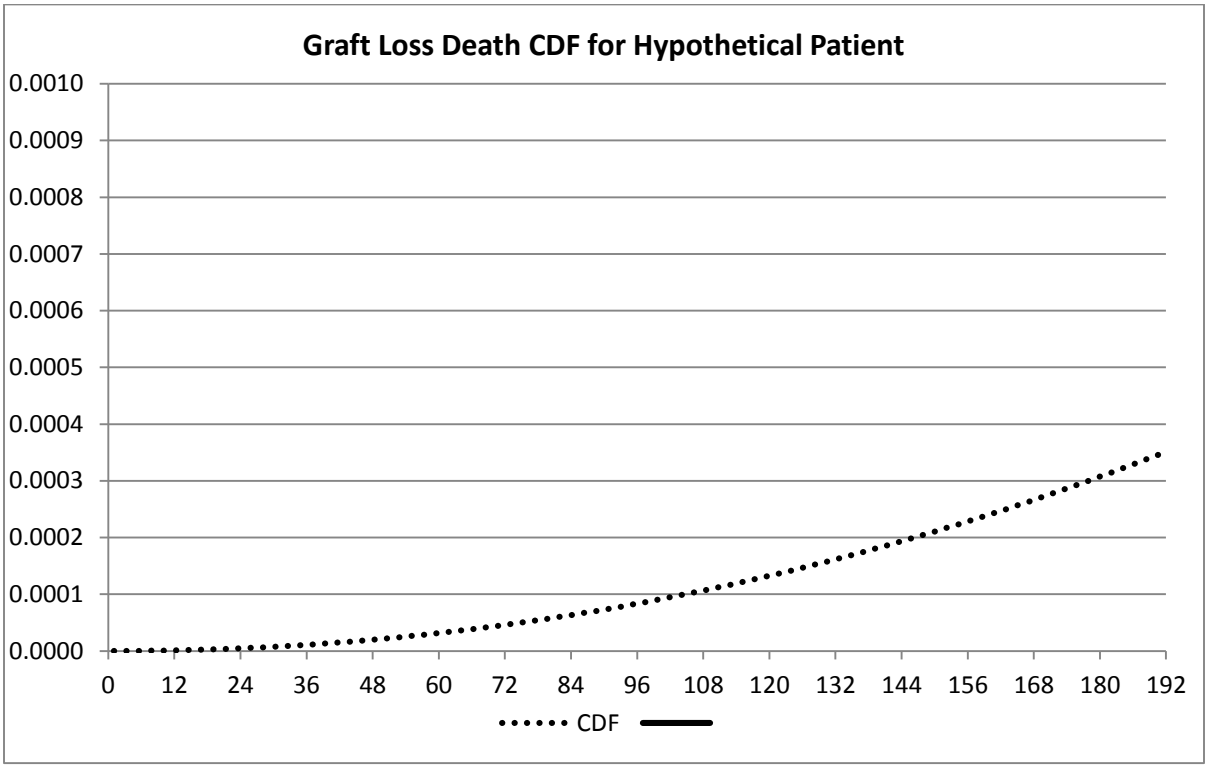


FIGURE L.1

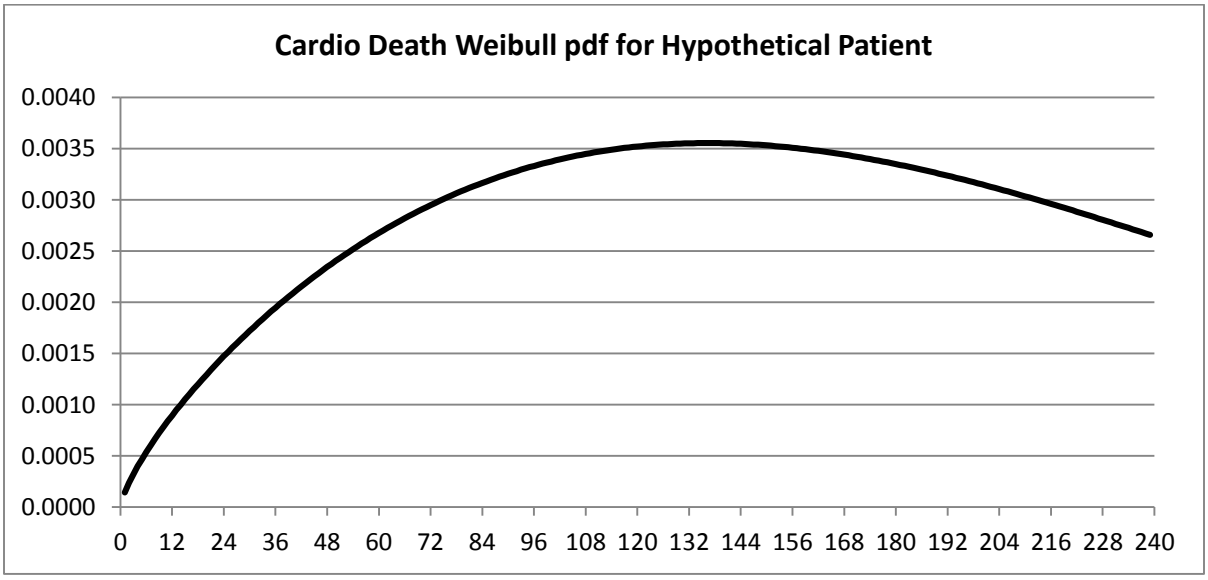


Figure L.2

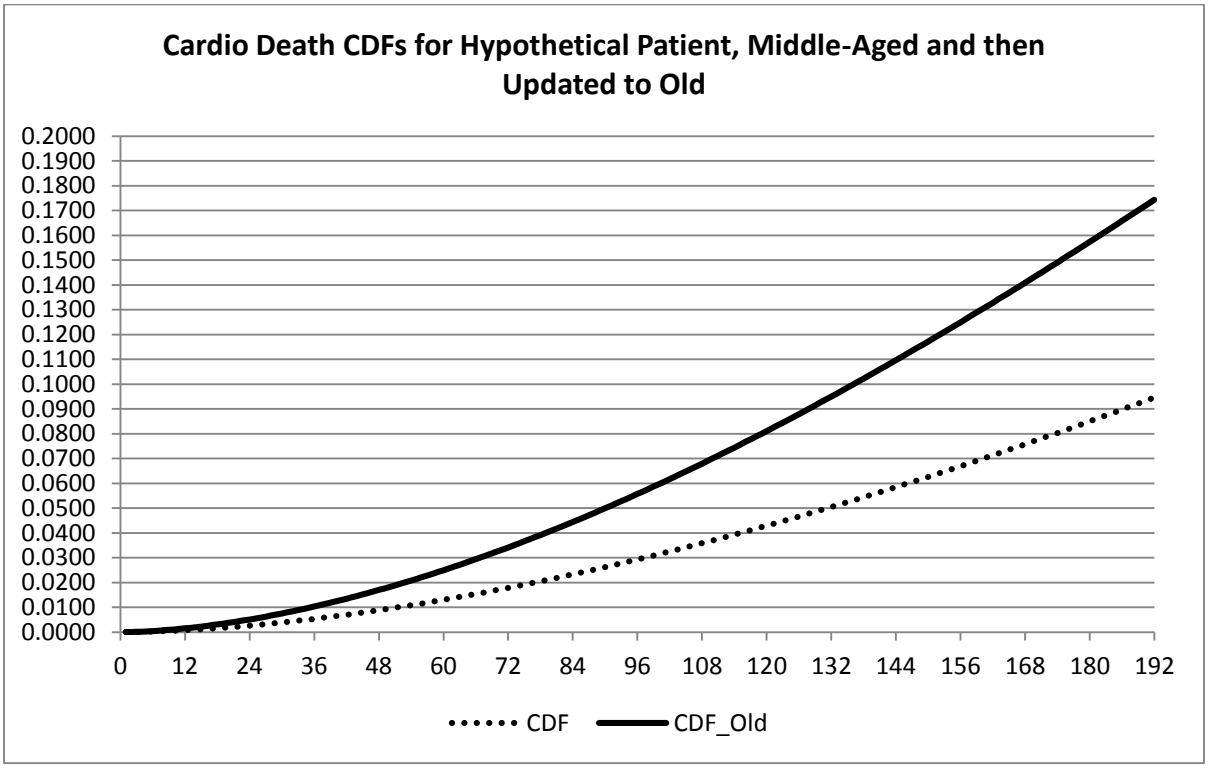


Figure J.1

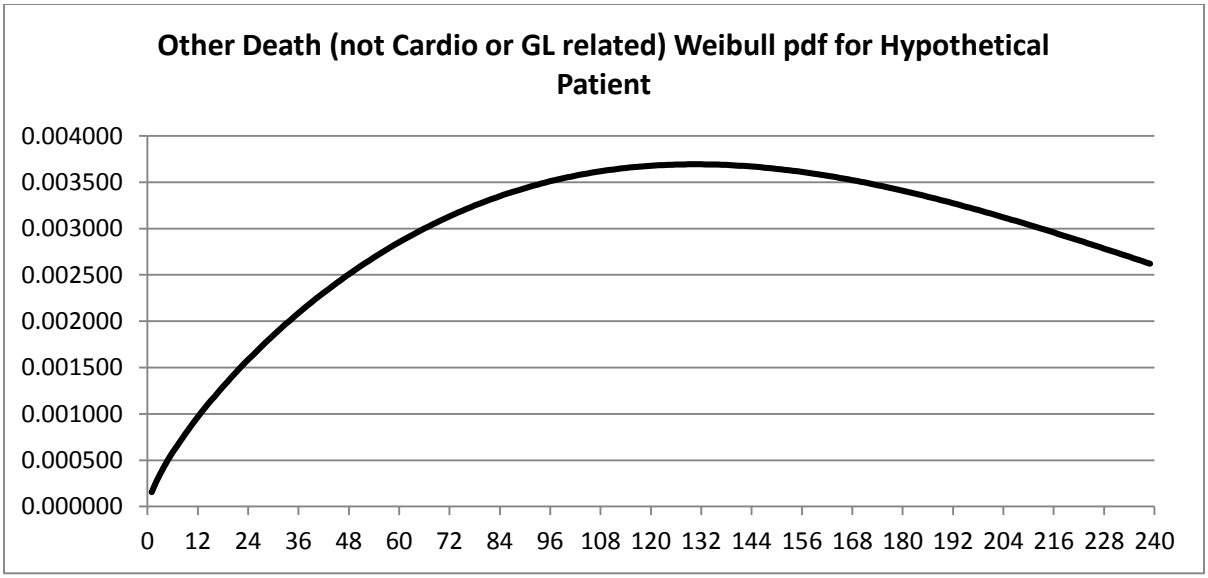
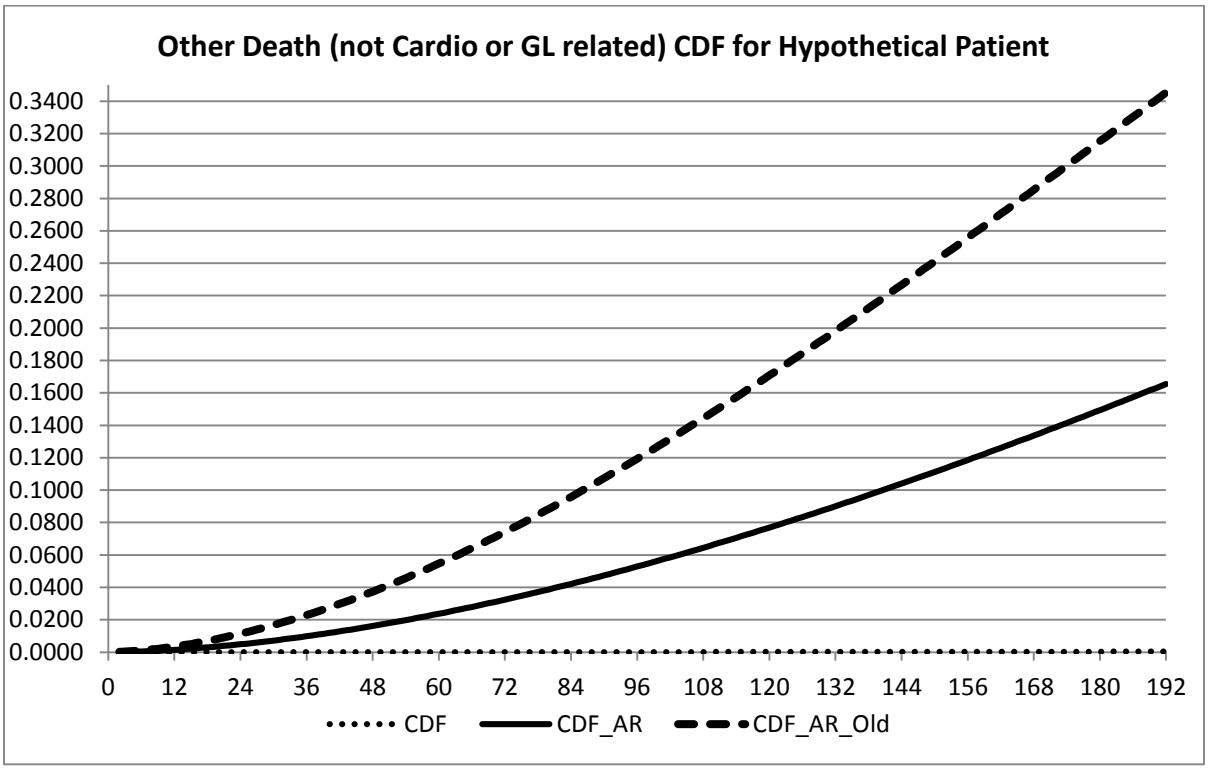


Figure J.2


Other Death (not Cardio or GL related) CDF for Hypothetical Patient
0.3400
0.3200
0.3000
0.2800
0.2600
0.2400
0.2200
0.2000
0.1800
0.1600
0.1400
0.1200
0.1000
0.0800
0.0600
0.0400
0.0200
0.0000
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
180
192
CDF
CDF_AR
CDF_AR_Old

7.2 Appendix II: ICD-9 codes

Events	**ICD-9 Codes**
Stroke	432.21, 432.29, 433.xx, 434.xx, 436.xx
Myocardial infarction	410.xx
Other cardiovascular diseases (angina, cardiac arrhythmia, ischemic heart disease, peripheral vascular disease)	411.xx-414.xx, 428.xx,427.xx, 443.9,420.xx-429.xx
New-onset diabetes mellitus	249.xx, 250.xx
Cancer	140.xx-239.xx
Bacterial infections (septicemia, kidney infections, skin infections, bacteremia)	038.42,038.1,038.0,599,590.xx,682.6,682.7,682.2,790.7
Cytomegalovirus infection	078.5

8. REFERENCES

1. Danovitch G. The kidney transplant waiting list. *UpToDate, Wolters Kluwer Health.* 2012.
2. Briggs JD. Causes of death after renal transplantation. *Nephrology Dialysis Transplantation.* 2001;16(8):1545-1549.
3. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. *Transplantation.* 2010;89(1):1-14.
4. Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P. *The role of modelling in prioritising and planning clinical trials.* Gray Publishing; 2003.
5. Ramwadhdoebe S, Buskens E, Sakkers RJ, Stahl JE. A tutorial on discrete-event simulation for health policy design and decision making: Optimizing pediatric ultrasound screening for hip dysplasia as an illustration. *Health policy.* 2009;93(2):143-150.
6. Tejada JJ, Ivy JS, King RE, et al. Combined des/sd model of breast cancer screening for older women, ii: screening-and-treatment simulation. *IIE Transactions.* 2014;46(7):707-727.
7. Vataire A-L, Aballéa S, Antonanzas F, et al. Core Discrete Event Simulation Model for the Evaluation of Health Care Technologies in Major Depressive Disorder. *Value in Health.* 2014;17(2):183-195.
8. Hoot NR, LeBlanc LJ, Jones I, et al. Forecasting emergency department crowding: a discrete event simulation. *Annals of emergency medicine.* 2008;52(2):116-125.
9. Caro J, Ward A, Moller J. Modelling the health benefits and economic implications of implanting dual-chamber vs. single-chamber ventricular pacemakers in the UK. *Europace.* 2006;8(6):449-455.
10. Pascual J, Quereda C, Zamora J, Hernández D, Transplantation SGfE-BMiR. Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. *Transplantation.* 2004;78(10):1548-1556.
11. Pascual J, Galeano C, Royuela A, Zamora J. A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation. *Transplantation.* 2010;90(4):343-349.
12. Lentine KL, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. *Journal of the American Society of Nephrology.* 2005;16(2):496-506.
13. Krämer BK, Klinger M, Wlodarczyk Z, et al. Tacrolimus combined with two different corticosteroid-free regimens compared with a standard triple regimen in renal transplantation: one year observational results. *Clinical transplantation.* 2010;24(1):E1-E9.
14. Morton RL, Howard K, Webster AC, Wong G, Craig JC. The cost-effectiveness of induction immunosuppression in kidney transplantation. *Nephrology Dialysis Transplantation.* 2009:gfp174.
15. McEwan P, Dixon S, Baboolal K, Conway P, Currie CJ. Evaluation of the cost effectiveness of sirolimus versus tacrolimus for immunosuppression following renal transplantation in the UK. *Pharmacoeconomics.* 2006;24(1):67-79.

16. Earnshaw SR, Graham CN, Irish WD, Sato R, Schnitzler MA. Lifetime cost-effectiveness of calcineurin inhibitor withdrawal after de novo renal transplantation. *Journal of the American Society of Nephrology.* 2008;19(9):1807-1816.
17. Thomas R, Kanso A, Sedor JR. Chronic kidney disease and its complications. *Primary care: Clinics in office practice.* 2008;35(2):329-344.
18. Berns JS. Patient information: Chronic kidney disease (Beyond the Basics). UpToDate. http://www.uptodate.com/contents/chronic-kidney-disease-beyond-the-basics. Last accessed on : 03/04/2014.
19. Fujisawa M, Ichikawa Y, Yoshiya K, et al. Assessment of health-related quality of life in renal transplant and hemodialysis patients using the SF-36 health survey. *Urology.* 2000;56(2):201-206.
20. National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). U.S. Department of Health and Human Services. http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/.
21. G. D. The Kidney Transplant Waiting List. UpToDate. http://www.uptodate.com/contents/the-kidney-transplant-waiting-list.
22. Kaufman DB BV, Aronoff GR., et al. . Assessment and Management of the Renal Transplant Patient. *Drugs, Diseases & Procedures.* 2013.
23. Subramanian S, Trence DL. Immunosuppressive agents: effects on glucose and lipid metabolism. *Endocrinology and metabolism clinics of North America.* 2007;36(4):891-905.
24. Marcén R, Pascual J, Teruel JL, et al. Outcome of cadaveric renal transplant patients treated for 10 years with cyclosporine: is chronic allograft nephropathy the major cause of late graft loss? *Transplantation.* 2001;72(1):57-62.
25. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. *Kidney international.* 2000;57(1):307-313.
26. Vanrenterghem Y, Lebranchu Y, Hené R, Oppenheimer F, Ekberg H, Group SDS. Double-Blind Comparison of Two Corticosteroid Regimens Plus Mycophenolate Mofetil and Cyclosporine for Prevention of Acute Renal Allograft Rejection1. *Transplantation.* 2000;70(9):1352-1359.
27. Hricik DE, WHALEN CC, Lautman J, et al. Withdrawal of Steroids After Renal Transplantation-Clinical Predictors of Outcome1. *Transplantation.* 1992;53(1):41-45.
28. Augustine JJ, Hricik DE. Steroid sparing in kidney transplantation: changing paradigms, improving outcomes, and remaining questions. *Clinical Journal of the American Society of Nephrology.* 2006;1(5):1080-1089.
29. Oh C-K, Kim SJ, Kim JH, Lee JH. Prospective Controlled Protocol for Three Months Steroid Withdrawal with Tacrolimus, Basiliximab, and Mycophenolate Mofetil in Renal Transplant Recipients. *Journal of Korean medical science.* 2012;27(4):337-342.
30. Phelan P, Moran A-M, O'Kelly P, et al. Steroid withdrawal in renal transplant patients: the Irish experience. *Irish journal of medical science.* 2011;180(2):429-433.
31. Woodle ES, First MR, Pirsch J, et al. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Annals of surgery.* 2008;248(4):564-577.

32. Laftavi MR, Stephan R, Stefanick B, et al. Randomized prospective trial of early steroid withdrawal compared with low-dose steroids in renal transplant recipients using serial protocol biopsies to assess efficacy and safety. *Surgery.* 2005;137(3):364-371.
33. Shihab F, Lee S, Smith L, et al. Effect of corticosteroid withdrawal on tacrolimus and mycophenolate mofetil exposure in a randomized multicenter study. *American Journal of Transplantation.* 2013;13(2):474-484.
34. Meulen CGt, Riemsdijk Iv, Hené RJ, et al. Steroid-Withdrawal at 3 Days After Renal Transplantation with Anti-IL-2 Receptor α Therapy: A Prospective, Randomized, Multicenter Study. *American journal of transplantation.* 2004;4(5):803-810.
35. Rostaing L, Cantarovich D, Mourad G, et al. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transplantation.* 2005;79(7):807-814.
36. Kumar MSA, Heifets M, Moritz MJ, et al. Safety and efficacy of steroid withdrawal two days after kidney transplantation: analysis of results at three years. *Transplantation.* 2006;81(6):832-839.
37. Cantarovich D, Hodemon-Corne B, Trébern-Launay K, Giral M, Foucher Y, Dantan E. Early Steroid Withdrawal Compared With Steroid Avoidance Correlates With Graft Failure Among Kidney Transplant Recipients With an History of Diabetes. Paper presented at: Transplantation proceedings2013.
38. Vítko S, Klinger M, Salmela K, et al. Two corticosteroid-free regimens—Tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil—In comparison with a standard triple regimen in renal transplantation: Results of the Atlas Study. *Transplantation.* 2005;80(12):1734-1741.
39. JT B. Using Decision Analysis to Facilitate Pharmacoeconomic Studies
40. Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment. *Pharmacoeconomics.* 2008;26(2):131-148.
41. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. 2004.
42. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *The New England journal of medicine.* 1997;337(14):1003.
43. Sonnenberg FA, Beck JR. Markov models in medical decision making a practical guide. *Medical decision making.* 1993;13(4):322-338.
44. Karnon J, Brown J. Selecting a decision model for economic evaluation: a case study and review. *Health care management science.* 1998;1(2):133-140.
45. Caro JJ, Möller J, Getsios D. Discrete event simulation: the preferred technique for health economic evaluations? *Value in health.* 2010;13(8):1056-1060.
46. Finkenstädt BF, Bjørnstad ON, Grenfell BT. A stochastic model for extinction and recurrence of epidemics: estimation and inference for measles outbreaks. *Biostatistics.* 2002;3(4):493-510.
47. Cooper K, Brailsford S, Davies R. Choice of modelling technique for evaluating health care interventions. *Journal of the operational research society.* 2007;58(2):168-176.
48. Rascati K. *Essentials of pharmacoeconomics.* Lippincott Williams & Wilkins; 2013.
49. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. *Health economics.* 2006;15(12):1295-1310.

50. Sculpher M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models. *Pharmacoeconomics.* 2000;17(5):461-477.
51. Halpern MT, Luce BR, Brown RE, Geneste B. Health and economic outcomes modeling practices: a suggested framework. *Value in Health.* 1998;1(2):131-147.
52. Basadonna G, Matas A, Gillingham K, et al. Early versus late acute renal allograft rejection: impact on chronic rejection. *Transplantation.* 1993;55(5):993-995.
53. Hughes GR, Currie CS, Corbett EL. Modeling tuberculosis in areas of high HIV prevalence. Paper presented at: Simulation Conference, 2006. WSC 06. Proceedings of the Winter2006.
54. Caro JJ. Pharmacoeconomic analyses using discrete event simulation. *Pharmacoeconomics.* 2005;23(4):323-332.
55. Kelton WD, Sadowski RP, Sadowski DA. *Simulation with ARENA.* Vol 3: McGraw-Hill New York; 2002.
56. Zhang D. Modeling Survival Data with Parametric Regression Models. North Carolina State University. Statistics. Chapter 5. http://www4.stat.ncsu.edu/~dzhang2/st745/chap5.pdf.
57. O'Hagan A, Stevenson M, Madan J. Monte Carlo probabilistic sensitivity analysis for patient level simulation models: efficient estimation of mean and variance using ANOVA. *Health economics.* 2007;16(10):1009-1023.
58. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J. Modeling Using Discrete Event Simulation A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–4. *Medical Decision Making.* 2012;32(5):701-711.
59. Gold M. Panel on cost-effectiveness in health and medicine. *Medical care.* 1996:DS197-DS199.
60. Duintjer Tebbens RJ, Pallansch MA, Kew OM, et al. Uncertainty and sensitivity analyses of a decision analytic model for posteradication polio risk management. *Risk Analysis.* 2008;28(4):855-876.
61. Collins BH KS, Johnston TD, Kim ED. Renal Transplantation Technique. Medscape. July 13, 2013.
62. Cecka JM. The UNOS Scientific Renal Transplant Registry--2000. *Clinical transplants.* 1999:1-18.
63. Opelz G, Döhler B. Association of HLA mismatch with death with a functioning graft after kidney transplantation: a collaborative transplant study report. *American Journal of Transplantation.* 2012;12(11):3031-3038.
64. Held PJ, Kahan BD, Hunsicker LG, et al. The impact of HLA mismatches on the survival of first cadaveric kidney transplants. *New England Journal of Medicine.* 1994;331(12):765-770.
65. Meier-Kriesche H-U, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. *Transplantation.* 2002;73(1):70-74.
66. Verani RR. Obesity-associated focal segmental glomerulosclerosis: pathological features of the lesion and relationship with cardiomegaly and hyperlipidemia. *American journal of kidney diseases.* 1992;20(6):629-634.
67. Kambham N, Markowitz GS, Valeri AM, Lin J, D D'Agati V. Obesity-related glomerulopathy: an emerging epidemic. *Kidney international.* 2001;59(4):1498-1509.

68. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *American Journal of Transplantation.* 2003;3(2):178-185.
69. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *American Journal of Transplantation.* 2004;4(6):905-913.
70. Gordon EJ, Caicedo JC. Ethnic advantages in kidney transplant outcomes: the Hispanic Paradox at work? *Nephrology Dialysis Transplantation.* 2009;24(4):1103-1109.
71. Wissing KM, Abramowicz D, Broeders N, Vereerstraeten P. Hypercholesterolemia is associated with increased kidney graft loss caused by chronic rejection in male patients with previous acute rejection. *Transplantation.* 2000;70(3):464-472.
72. Lindholm A, Albrechtsen D, Frödin L, Tufveson G, Persson NH, LUNDGREN G. Ischemic heart disease-major cause of death and graft loss after renal transplantation in Scandinavia. *Transplantation.* 1995;60(5):451-456.
73. SAGEDAL S, Hartmann A, Nordal KP, et al. Impact of early cytomegalovirus infection and disease on long-term recipient and kidney graft survival. *Kidney international.* 2004;66(1):329-337.
74. Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. *Jama.* 1989;261(24):3561-3566.
75. Shamanin V, zur Hausen H, Lavergne D, et al. Human papillomavirus infections in nonmelanoma skin cancers from renal transplant recipients and nonimmunosuppressed patients. *Journal of the National Cancer Institute.* 1996;88(12):802-811.
76. Heilman R, Nijim S, Chakkera H, et al. Impact of acute rejection on kidney allograft outcomes in recipients on rapid steroid withdrawal. *Journal of transplantation.* 2011;2011.
77. Solez K, Colvin R, Racusen L, et al. Banff'05 Meeting Report: Differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). *American Journal of Transplantation.* 2007;7(3):518-526.
78. El-Zoghby Z, Stegall M, Lager D, et al. Identifying specific causes of kidney allograft loss. *American Journal of Transplantation.* 2009;9(3):527-535.
79. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. *Diabetes/metabolism reviews.* 1988;4(1):17-30.
80. Burroughs TE, Swindle J, Takemoto S, et al. Diabetic complications associated with new-onset diabetes mellitus in renal transplant recipients. *Transplantation.* 2007;83(8):1027-1034.
81. Vincenti F, Friman S, Scheuermann E, Rostaing L. Glucose metabolism disorders after renal transplantation: Results of an international, randomized trial comparing cyclosporine versus tacrolimus. *Transplantation.* 2006;82(1):83.
82. Heit JJ. Calcineurin/NFAT signaling in the β-cell: From diabetes to new therapeutics. *Bioessays.* 2007;29(10):1011-1021.
83. Tamuka K, Fujimura T, Tsutsumi T, et al. Transcriptional inhibition of insulin by FK506 and possible invovlement of FK506 binding protein-12 in pancreatic [beta]-cell. *Transplantation.* 1995;59(11):1606-1612.
84. Ghisdal L, Bouchta NB, Broeders N, et al. Conversion from tacrolimus to cyclosporine A for new-onset diabetes after transplantation: a single-centre

experience in renal transplanted patients and review of the literature. *Transplant international.* 2008;21(2):146-151.
85. Bustami RT, Ojo AO, Wolfe RA, et al. Immunosuppression and the Risk of Post-Transplant Malignancy Among Cadaveric First Kidney Transplant Recipients. *American Journal of Transplantation.* 2004;4(1):87-93.
86. Flechner S. Cancer and renal transplantation. *Adv Stud Med.* 2007;7(13):411-419.
87. Patel S, Kwan JT, McCloskey E, et al. Prevalence and Causes of Low Bone Density and Fractures in Kidney Transplant Patients*. *Journal of Bone and Mineral Research.* 2001;16(10):1863-1870.
88. Nisbeth U, Lindh E, Ljunghall S, Backman U, Fellström B. Increased Fracture Rate in Diabetes Mellitus and Females After Renal Transplantation1. *Transplantation.* 1999;67(9):1218-1222.
89. Elmstedt E. Incidence of skeletal complications in renal graft recipients: effect of changes in pharmacotherapy. *Acta Orthopaedica.* 1982;53(6):853-856.
90. Grotz WH, Mundinger FA, Gugel B, Exner V, Kirste G, Schollmeyer PJ. Bone fracture and osteodensitometry with dual energy X-ray absorptiometry in kidney transplant recipients. *Transplantation.* 1994;58(8):912-915.
91. Gonzalez-Molina M, Gentil MA, Burgos D, et al. Effect of long-term steroid withdrawal in renal transplant recipients: a retrospective cohort study. *NDT plus.* 2010;3(suppl 2):ii32-ii36.