

# Validation of a mathematical model of renal disease

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## Abstract

Archimedes is a trial-validated model simulating human physiology, diseases (such as diabetes and its complications), and healthcare systems. Archimedes' mathematical representation of renal disease incorporates the progression of glomerular filtration rate, urinary albumin, and serum creatinine, which are dependent on demographic characteristics as well as diabetes status and social habits. The interactions among these variables are continuously recalculated as a person ages, starts or stops medications, or undergoes diagnostic tests and interventional procedures. The accuracy of Archimedes is tested by simulating real clinical trials. Two randomized controlled trials, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan in Diabetic Nephropathy Trial (IDNT) were used to validate the progression of renal disease. The RENAAL trial was used to inform the model and thus its control arm provided a dependent validation. The IDNT's control and treatment (Irbesartan) arms provided independent validations of Archimedes for the time-series primary outcomes, as well as the end of trial secondary cardiovascular outcomes. Log rank analysis estimated the likelihood that simulated results were statistically different ( $\alpha=0.05$ ) from those of the comparison trials (a p-value above 0.05 indicates no statistically significant difference). In the simulated control arms of both trials, all primary outcomes were not statistically different from those observed in the respective trials (RENAAL: composite outcome  $p=0.09$ , ESRD  $p=0.051$ , creatinine doubling  $p=0.24$ , death or ESRD  $p=0.051$ ; IDNT: composite outcome  $p=0.24$ , ESRD  $p=0.31$ , creatinine doubling  $p=0.14$ , and death  $p=0.29$ ). In the irbesartan arm of the IDNT trial, all primary outcomes predicted by Archimedes were again not found to be statistically different from the actual study results (composite outcome  $p=0.073$ , ESRD  $p=0.43$ , creatinine doubling  $p=0.051$ , and death  $p=0.21$ ). Archimedes provides accurate, trial-validated estimates of the progression of nephropathy and its complications, as well as effects of therapy in diabetics.

## Introduction

- Chronic kidney disease (particularly in diabetics) is a worldwide public health problem. The number of US persons with kidney failure who are treated with dialysis and transplantation is projected to increase from 340,000 in 1999 to 651,000 in 2010.<sup>1</sup>
- One of the keys to combating chronic kidney disease is to develop a better understanding of who is at risk.
  - It was previously believed that individuals progress through stages of albuminuria before developing kidney dysfunction.
  - However, recent studies have shown that >50% of those developing renal impairment did not have preceding albuminuria.<sup>2</sup>
  - These findings suggest that there are several different pathways to the progression of kidney dysfunction not captured by the previously existing Archimedes model for renal impairment.
- The Archimedes Model has virtual people with virtual physiologies who get virtual diseases, go to virtual doctors, get virtual tests and treatments and have virtual outcomes. [see Figure 1]
  - The physiology of a virtual person is described by mathematical equations which link biomarkers, organs, and diseases.
  - Each biomarker can change as a result of interventions, procedures, or lifestyle choices, resulting in changes in outcomes.
  - Simulated nurses, doctors, and physicians then interact with this person through modeled clinical guidelines. Medications, tests, and procedures like cardiac catheterization or kidney transplants may be performed by the doctors at this time.
- These features make Archimedes an excellent tool to analyze this worldwide public health problem.
- We developed a mathematical representation of renal disease and incorporated it into the full Archimedes Model.

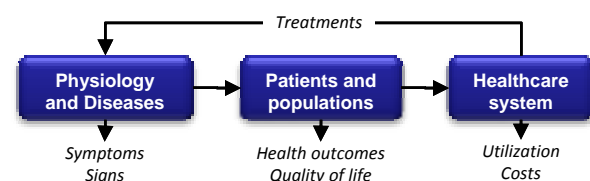


Figure 1: A representation of the Archimedes model. We start by modeling physiology and diseases in an individual, we then simulate a population of desired individuals each different from the next. Each individual can develop symptoms or health outcomes based on their physiology. Archimedes patients also seek care for their symptoms and diseases, get treatments which affect their physiology, and accrue cost as they move through the health care system.

## Objective

- Our objective was to update our nephropathy model based on the developing understanding of the risk factors involved in the progression to both diabetic and non-diabetic renal disease.
- We also sought to integrate symptoms associated with various stages of chronic kidney disease, as well as health care processes reflective of K/DOQI guidelines set forth by the National Kidney Foundation.<sup>3</sup>
- Lastly, we sought to validate the renal disease model against two clinical trials: IDNT<sup>4</sup> and RENAAL<sup>5</sup>.

## Methods

Data:

- The model for GFR and creatinine progression was built with the help of longitudinal data from the Framingham Heart Study.
- The model for albumin progression was built with the help of the Framingham Offspring Heart Study.
- NHANES III was used to correct for the race covariates in the models since both Framingham and Framingham Offspring participants were predominantly caucasian.
- The processes were built following the K/DOQI guidelines set forth by the National Kidney Foundation. These medical processes detail when to start a person on dialysis, how often to schedule appointments for each stage of CKD, what medication to dispense at what frequencies, distribution of wait times for kidney transplant candidates, etc.
- The model was validated for the outcomes ESRD, creatinine doubling, and death using the randomized controlled trials IDNT and RENAAL.

Analytical Methods:

- Stepwise Cox proportional hazards multivariate regressions on the Framingham Original and Framingham Offspring datasets were generated using SAS to inform the model on the significant risk factors in the progression to albuminuria and low values of GFR.
- Kaplan Meier curves for the comparisons of the outcomes between IDNT and RENAAL were generated using SAS. Log rank analysis was used to estimate the likelihood that simulated results were statistically different ( $\alpha=0.05$ ) from those of the comparison trials (a p-value above 0.05 indicates no statistically significant difference).

## Results

- The analysis suggests that the significant risk factors in deterioration of GFR are age, gender, race, creatinine, systolic blood pressure, body mass index, and diabetic status.
  - Diabetic status in the model reflects the underlying efficiency of insulin use. Controlling glucose does not cause someone to become "un-diabetic".
  - FPG does not show up as a significant covariate after diabetic status is taken into account. This implies that once someone becomes diabetic, tight glycemic control on its own does not improve renal function.
- The analysis suggests that the significant risk factors in the development of albuminuria are age, race, systolic blood pressure, body mass index, fasting plasma glucose, and smoking history.
- Validation results against IDNT and RENAAL for the primary end point of ESRD, creatinine doubling, or death are shown in Figures 2-4.
- In the simulated control arms of both trials, all primary outcomes were not statistically different than those observed in the respective trials.
- In the irbesartan arm of the IDNT trial, all primary outcomes predicted by Archimedes were again not found to be statistically different from the actual study results.

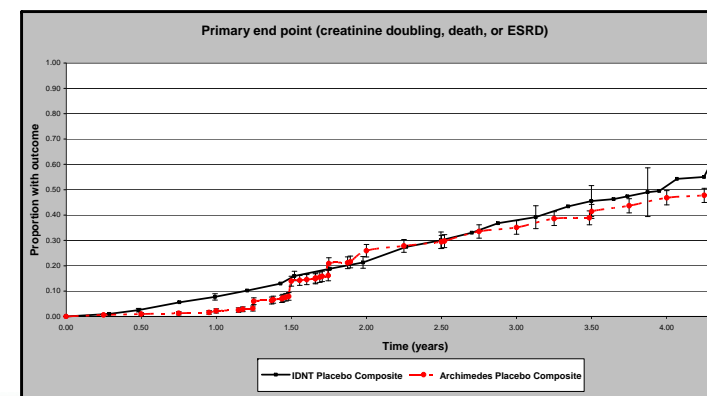


Figure 2: Kaplan Meier curve for the composite primary outcome comparing the placebo arm in IDNT (solid black line) versus the placebo arm in Archimedes (dashed red line). The error bars are +/- one standard error. Log rank  $p=0.24$  (not statistically significantly different).

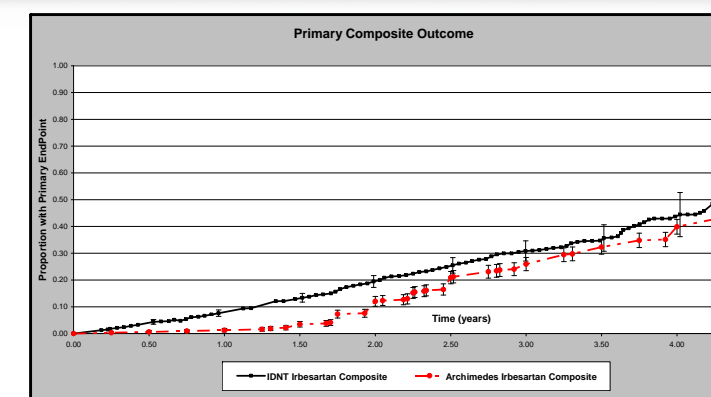


Figure 3: Kaplan Meier curve for the composite primary outcome comparing the Irbesartan arm in IDNT (solid black line) versus the Irbesartan arm in Archimedes (dashed red line). The error bars are +/- one standard error. Log rank  $p=0.073$  (not statistically significantly different).

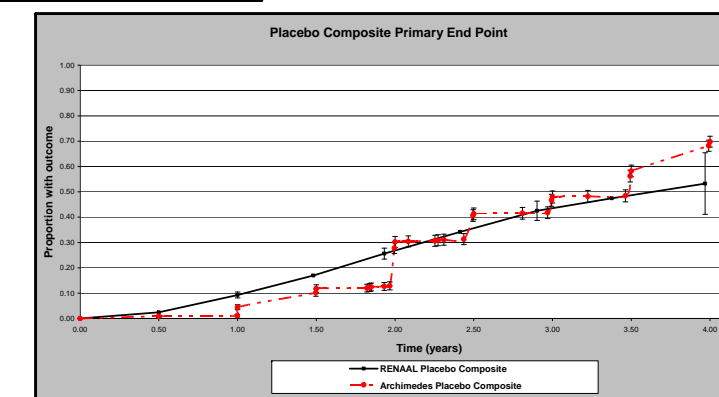


Figure 4: Kaplan Meier curve for the composite primary outcome comparing the placebo arm in RENAAL (solid black line) versus the placebo arm in Archimedes (dashed red line). The error bars are +/- one standard error. Log rank  $p=0.09$  (not statistically significantly different).

## Conclusions

- We have developed and validated a model for renal disease that is dependent on a person's demographic characteristics, standard risk factors, and diabetes status. The health care processes in this model reflect K/DOQI guidelines.
- Fasting plasma glucose does not appear as a significant covariate in the degeneration of GFR after diabetic status is taken into account. Lack of an effect on GFR of controlling glucose once diabetic may seem counterintuitive; however other studies like UKPDS 74 also do not find FPG an independent risk factor in a multivariate analysis for renal insufficiency.
- Future research will include further investigation of whether FPG or other measures of glucose burden can truly be disregarded as an independent risk factor. We also plan to validate the model against other datasets and clinical trials.

## References

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