# A Predictive Validation of the CARDS Trial

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The Archimedes Model has been subjected to two predictive validations: the Diabetes Prevention Program (DPP)[1] and the CARDS trial[2]. While both were presented publically before the results were known, the CARDS predictive validation was conducted under formal supervision by two independent reviewers, and the predictions were submitted in a sealed, dated envelope more than a month before the results were known even to the principal investigators.

This report summarizes the predictive validation of that trial. Details of the results put in the envelope, the results later provided by the Principal Investigator of the trial, and the steps taken to ensure that the validation was completely blinded are available by request to info@archimedesmodel.com.

Two simulations were performed, on March 23 and 25, 2004. The results were sent to the Chief Science Officer of the American Diabetes Association and the Principal Investigator of the CARDS trial on March 26, 2004. The results of the real trial were sent to Archimedes by a trial statistician on May 6, 2004. The results were eventually published in Lancet on August 21, 2004[2]. The results shown are in Figure 1 and Figure 2 for major coronary outcomes and strokes respectively. The lines with open circles show the cumulative hazard rate (Kaplan Meier) in the control group. The lines with closed circles show the results for the treatment group. The real results are in solid lines. The results predicted in the 3/23/2004 run are shown in dotted lines, and the results predicted in the 3/25/2004 runs are shown in dashed lines.

The results indicated that the Model's predictions of the rates of myocardial infarctions and strokes without atorvastatin were quite accurate. This is the most important validation, because calculation of outcome rates in the control group draws on every part of the physiology model relating to that outcome – scores of variables and equations. The Model's representation of the effect of atorvastatin on myocardial infarctions was also quite accurate (Figure 1). However, the Model's representation of the effect of atorvastatin on strokes (Figure 2) severely underestimated the effect observed in the trial. At the time this validation was done (March 23-25, 2004), there were no previous trials of the effects of atorvastatin on either myocardial infarctions or strokes in people with diabetes at high risk of CVD (the CARDS population). Nor were there any data on the effects of atorvastatin on biomarkers such as cholesterol levels in this population. (Those data were eventually published in August 2004.) We based our assumptions on the effectiveness of other statins such as simvastatin and pravastatin on short-term studies in other populations. We assumed that atorvastatin would decrease LDL levels approximately 40%, decrease triglycerides approximately 12%, and have no appreciable effect on HDL. We did not assume any effect other than that mediated through the cholesterol biomarkers. (That is, we did not assume any pleiotropic effect). The results indicate that there may well be a pleiotropic effect of atorvastatin on strokes. Based on data from CARDS and other trials, diabetes and cardiology experts also concluded that statins have pleiotropic effects, and we now include those effects in current versions of the Model.

[1] Diabetes Prevention Program Research Group, "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin," vol. 356, pp. 393-402, 2002.

[2] Colhoun HM, et al., "Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial," *Lancet*, vol. 364, no. 9435, pp. 685-696, 2004.

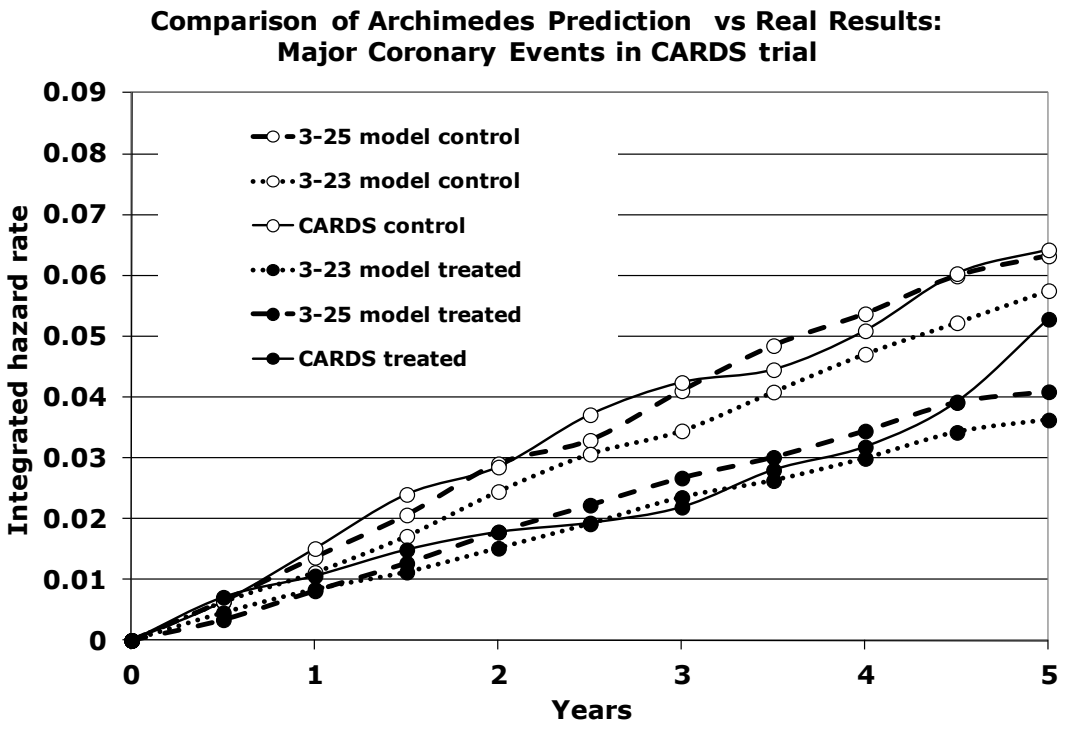


Figure 1. Comparison of Archimedes Prediction vs Real Results: Major Coronary Events in CARDS Trial

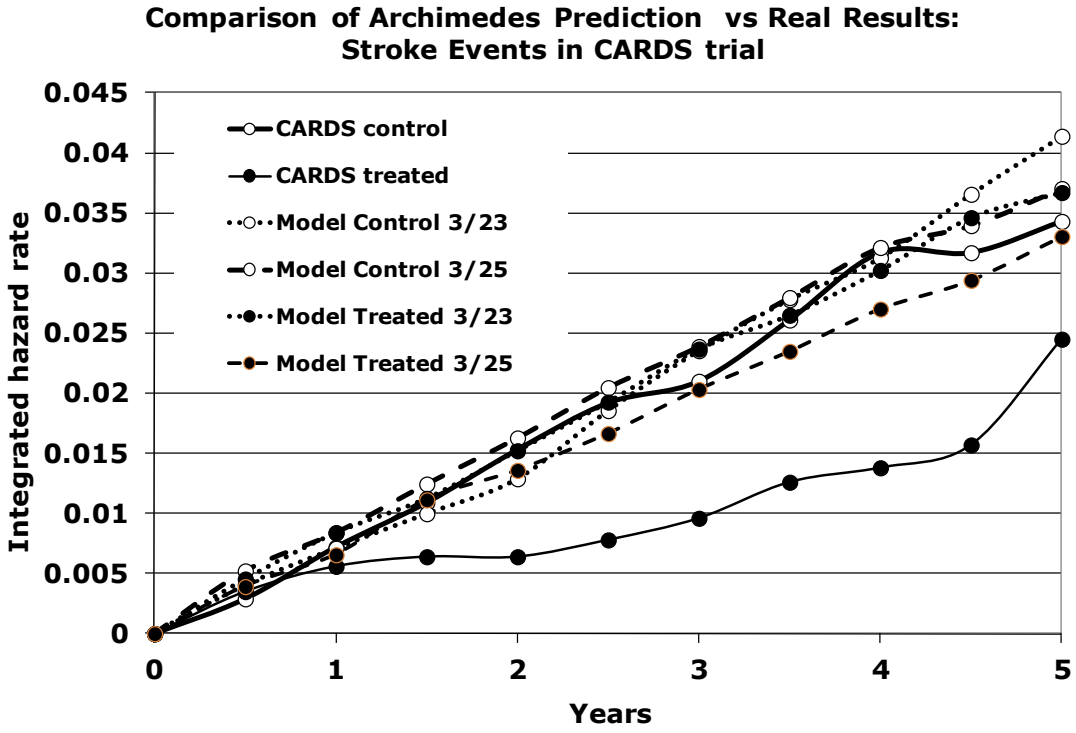


Figure 2. Comparison of Archimedes Prediction vs Real Results: Stroke Events in CARDS Trial

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