The role of simulation modeling in planning long-term clinical trials in type 2 diabetes.

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Introduction

Longer-term cardiovascular outcomes studies are routinely undertaken to demonstrate safety in all new diabetes therapies. Given that diabetes models are extensively validated to contemporary outcomes trials they offer the potential to inform on design of new trials and help explain observed results in those trials already completed.

The objective of this study was to use an established diabetes model to explore the relationship between levels of glycaemic control, major adverse cardiovascular events (MACE) and sample size.

Methods

This study used the IMS CORE Diabetes Model (CDM) [1,2], a lifetime simulation model designed to assess the health outcomes and economic consequences of interventions in type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM).

The model was initialized with patient level data (PLD) from subjects with T2DM drawn from NHANES (Table 1) and run with a five-year time horizon with the following treatment effects applied to HbA1c: 0% (Baseline); -0.5%; -1.0% and --1.5%.

Over the five-year time-horizon the expected cumulative proportion of MACE events (defined as myocardial infarction, stroke or CV death) were calculated for each treatment reduction in HbA1c (-0.5%, -1.0% and -1.5%) compared to baseline (no reduction in HbA1c) and sample sizes determined using a two sided Z-test of the difference in the cumulative proportions with 80% power and a 5% significance level.

To first demonstrate the CDM's general predictive capabilities the model was initially validated to the following outcomes trials: UKPDS 33 [3]; ASPEN [4]; VADT [5]; ADVANCE [6]; ACCORD [7, 8]; ADDITION-Europe [9]; ASCOT [10]; CARDS [11]; UKPDS 80 [12] and DCCT [13,14].

Table 1) Summary statistics for NHANES T2DM patient level data extract (n=1,859) used for the sample size analysis

Variable	Mean	SD
Age (years)	63.6	12.1
Male (%)	53	
Duration (years)	9.5	8.5
Smoker (%)	16	
HbA1c (%)	7.4	1.8
SBP (mmHg)	134.9	22.0
Cholesterol (mg/dl)	195	50.5
HDL (mg/dl)	47.9	13.8
BMI (kg/m2)	30.6	6.3

Results

PLD from NHANES was available on 1853 subjects with mean (SD) age 63.6(12.1) years, 53% male, duration of diabetes 9.6(8.5) years, baseline HbA1c 7.4% (1.8), systolic blood pressure 134.9mmHg (22.0) and total cholesterol of 189.8 mg/dl (48.7).

The expected five-year cumulative MACE event rate was 9.4% (baseline) and 9.2%, 8.7% and 8.3% for HbA1c reductions of 0.5%, 1.0% and 1.5% respectively (Figure 2). This figure also illustrates that a steady-state estimate of the cumulative proportion is only obtained when at least 6,000 subjects are recruited into each arm (total study size of 12,000).

Relative risk reductions for HbA1c reductions of 0.5%, 1.0% and 1.5% were 2.1%, 7.9% and 12.5% respectively.

Figures 3, 4 and 5 show the expected five-year cumulative MACE event rate for HbA1c reductions of 1.5%, 1.0% and 0.5% respectively, compared to baseline; also shown are 95% confidence intervals. Only a treatment reduction of 1.5% (Figure 3) shows confidence intervals not overlapping.

At the 5% level with 80% power, the total number of study patients required to detect a significant reduction in MACE events for HbA1c reduction of 0.5%, 1.0% and 1.5% are 661,304, 52,670 and 20,899 respectively.

Figure 1) Scatterplot of observed versus predicted endpoints across studies identified to validate the IMS CDM. Results are stratified by year of study, trial, endpoint and diabetes type. Validation coefficient of determination, (R2 = 0.89)

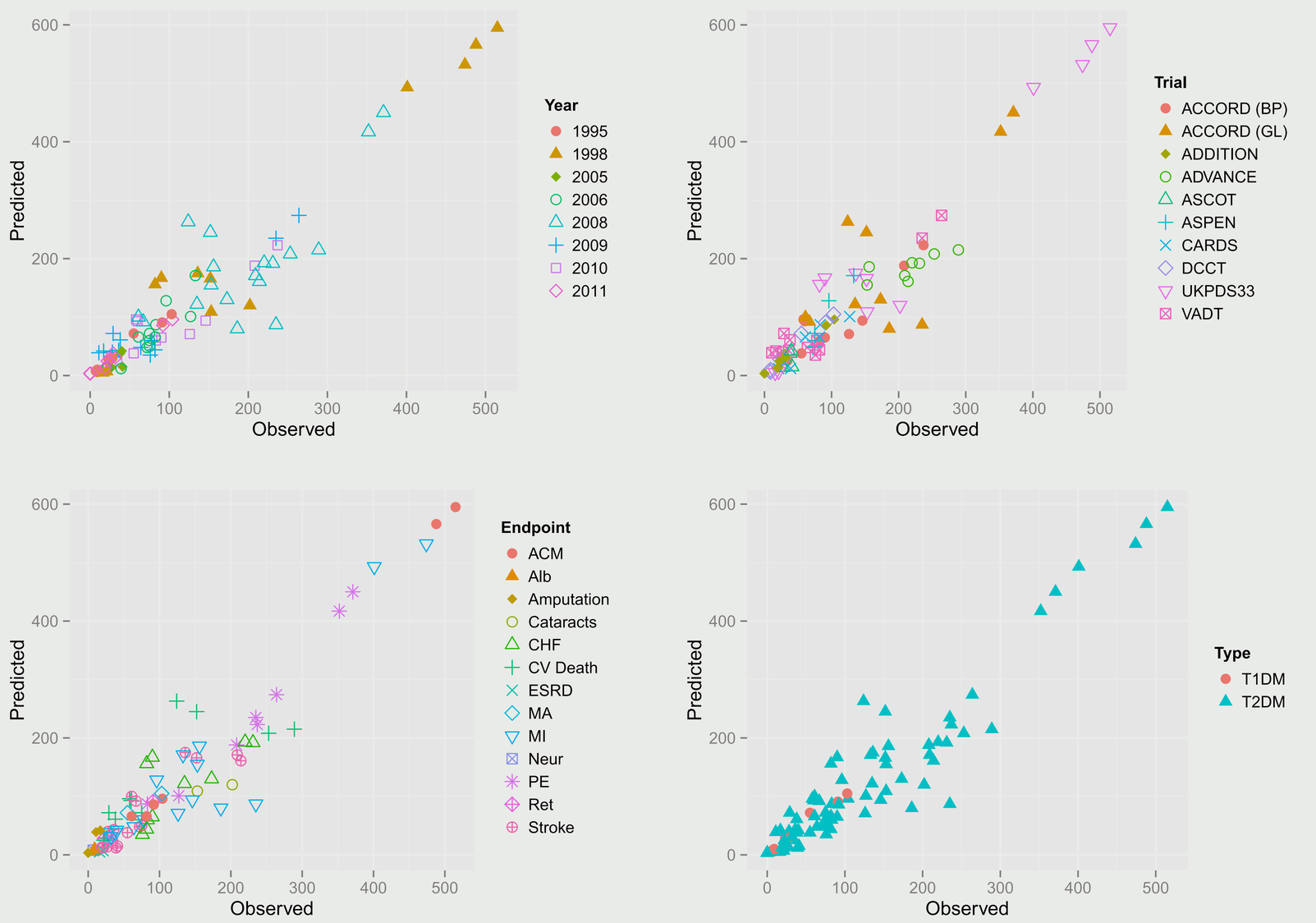
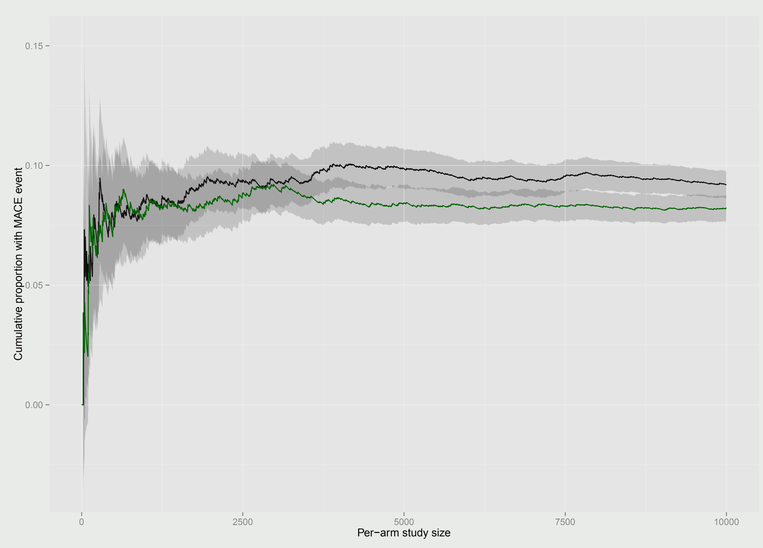


Figure 2) Expected cumulative proportion of MACE events as a function of study sample size for...

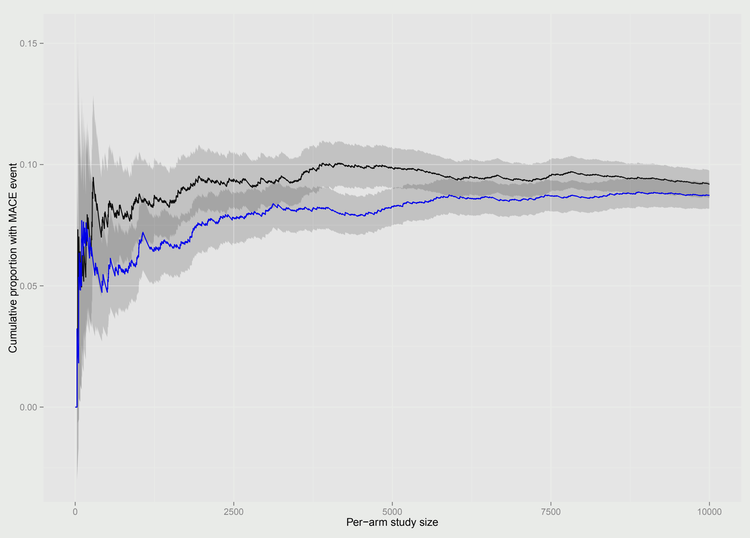
a baseline (black); -0.5% HbA1c (red); -1.0% HbA1c (blue) and -1.5% HbA1c (green)

Figure 3) Expected cumulative proportion of MACE events and 95% confidence intervals for...



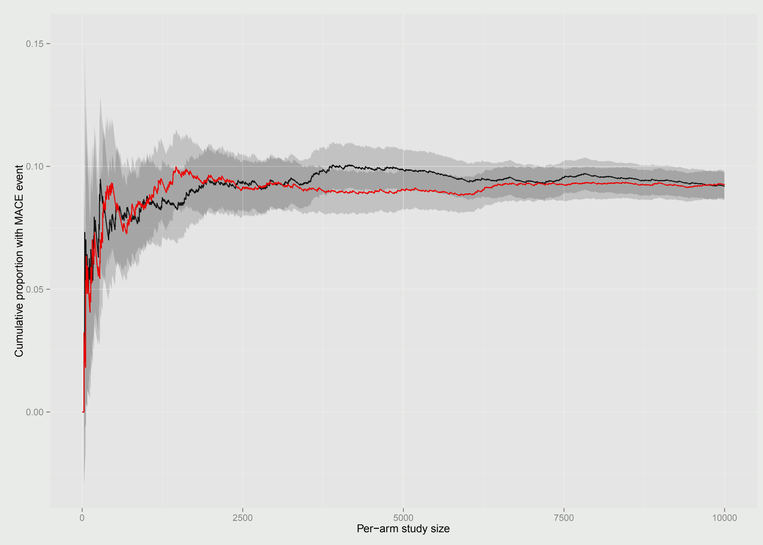
a 1.5% reduction in HbA1c (green) compared to baseline (black)

Figure 4) Expected cumulative proportion of MACE events and 95% confidence intervals for...



a 1.0% reduction in HbA1c (blue) compared to baseline (black)

Figure 5) Expected cumulative proportion of MACE events and 95% confidence intervals for...



a 0.5% reduction in HbA1c (red) compared to baseline (black)

Conclusion

Given the requirement to extensively validate health economic models to contemporary outcomes studies it is an obvious extension to use these models to inform on the design of clinical trials and interpret their results.

This study demonstrates how the sample sizes required to detect a significant reduction in MACE events as a function of HbA1c lowering in isolation are prohibitively excessive. It is only when a reduction in HbA1c of at least 1.5% is expected that sample sizes begin to become feasible.

This study also demonstrates how random variability (when per arm sample sizes are less than 6,000) can easily provide spurious and misleading results.

Long term disease models, such as the CDM, offer considerable flexibility in the evaluation of sample size requirements in terms of expected changes in modifiable risk factors.

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