

Clinical trial simulation methods for estimating the impact of DPP-4 inhibitors on cardiovascular disease

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Introduction: Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral antidiabetic agents for the treatment of type 2 diabetes mellitus, which lower blood glucose without causing severe hypoglycemia. However, the first cardiovascular (CV) safety trials have only recently reported their results, and our understanding of these therapies remains incomplete. Using clinical trial simulations, we estimated the effectiveness of DPP-4 inhibitors in preventing major adverse cardiovascular events (MACE) in a population like that enrolled in the SAVOR-TIMI (the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction) 53 trial.

Methods: We used the Archimedes Model to simulate a clinical trial of individuals (N=11,000) with diagnosed type 2 diabetes and elevated CV risk, based on established disease or multiple risk factors. The DPP-4 class was modeled with a meta-analysis of HbA_{1c} and weight change, pooling results from published trials of alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin. The study treatments were added-on to standard care, and outcomes were tracked for 20 years.

Results: The DPP-4 class was associated with an HbA_{1c} drop of 0.66% (0.71%, 0.62%) and a weight drop of 0.14 (–0.07, 0.36) kg. These biomarker improvements produced a relative risk (RR) for MACE at 5 years of 0.977 (0.968, 0.986). The number needed to treat to prevent one occurrence of MACE at 5 years was 327 (233, 550) in the elevated CV risk population.

Conclusion: Consistent with recent trial publications, our analysis indicates that DPP-4 inhibitors do not increase the risk of MACE relative to the standard of care. This study provides insights about the long-term benefits of DPP-4 inhibitors and supports the interpretation of the published CV safety trial results.

Keywords: cardiovascular, DPP-4 inhibitors, simulation

Introduction

Regulatory agencies, such as the US Food and Drug Administration's Center for Drug Evaluation and Research, require that drugs be established as safe and effective prior to approval. The approval process relies on the evidence-based medicine hierarchy of evidence quality, in which the randomized controlled clinical trial (RCT) is the gold standard method for quantifying the efficacy and safety of therapeutic agents.¹ In recent years, regulatory agencies have taken a more conservative position on approving new medicines that potentially have negative effects on cardiovascular (CV) risk. For example, the approval of antidiabetic agents now often requires a large CV safety trial,² creating a substantial barrier to the development of new therapies. Prospective RCTs are considered to be the only approach that is "hypothesis validating",³ thus the only way to establish safety and efficacy. However, in practice, RCTs can be used to

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test only a limited number of hypotheses because they are expensive and time-consuming to perform.

Clinical trial simulation represents a complementary, “hypothesis generating”, approach for forecasting the findings of RCTs yet to be completed, and exploring the possible drivers of RCT results.⁴ Clinical trial simulation cannot replace the RCT, but could be valuable in disease areas such as type 2 diabetes and cardiovascular disease (CVD), where trial protocols are often complex, and powering trials require large populations with multiyear follow-up. These critically important trials sometimes yield results that are challenging to interpret.

A number of clinical trial simulation methods have been used to predict or interpret the results from trials of type 2 diabetes and CVD. Individual-level Markov models are the least mathematically complex technique for clinical trial simulation, and have been applied to problems in health care for over four decades.⁵ In a simple Markov model, an individual's health is categorized by discrete states, and individuals move from state to state with invariant probabilities at fixed time intervals. However, describing an individual's health with a small number of discrete states is a coarse approximation because human physiology is complex and continuous in nature.⁶ A related limitation of simple Markov models is the invariant state transition probability. In reality, an individual's health evolves continuously over time, but the time evolution of risk is lost in the Markov framework.

These limitations have been addressed by extending the Markov model framework with tracker variables (such as glycated hemoglobin [HbA_{1c}]) that evolve over the course of a simulation and disease submodels that capture a richer representation of comorbidities. The United Kingdom Prospective Diabetes Study (UKPDS) outcomes model⁷ is one of the more commonly used examples of this class of model. The UKPDS model is an individual-level state transition model with annual cycles, functionalized transition probabilities based on disease status, four biomarkers as continuous variables (HbA_{1c} , blood pressure, total cholesterol, high-density lipoprotein cholesterol [$HDL-C$]), and a discrete smoking status risk factor. The risks of adverse events during each 1-year period are computed as functions of the individual's disease status and biomarkers.

The UKPDS model has a number of strengths. The UKPDS outcomes model is based on the UKPDS, the longest follow-up study of patients with type 2 diabetes. Hayes et al have recently published the UKPDS outcomes model 2,⁸ based on an updated data set with more data from

the subjects followed up after the clinical trial period had ended. Thus, UKPDS provides a data set of exceptional quality, spanning several diabetes-related comorbidities. Including tracker variables in the model provides time-varying risk and some measure of disease “history”. To a degree, the inclusion of second events improves the applicability of the model to higher-risk diabetic cohorts, as these cohorts often have substantial prevalence of prior CV events at baseline. The UKPDS model is available to researchers in easy-to-use forms (such as an Excel file) and is broadly accepted. That said, this class of model's representation of health by a limited number of discrete health states and rigidly defined annual event cycles remains a coarse approximation. Also, the model is based exclusively on the UKPDS trial, and as such, the model is confined by the parameters collected by the UKPDS protocol. For example, the model cannot be used to study important, related problems such as diabetes onset, and it cannot capture a second recurrent event (such as a third myocardial infarction [MI]). Further, the UKPDS cohort was recruited between 1977 and 1991, so aspects of the population do not represent modern patients duly (eg, rising body mass index and evolving standards of care). Finally, some investigators have observed that the UKPDS risk equations are not accurate for ethnically diverse populations, which could be a consequence of the model's dependence on one trial cohort.⁹ The CORE Diabetes Model^{10,11} and the Michigan model for diabetes^{12,13} are also examples of Markov models with tracker variables and disease submodels, with strengths and limitations similar to those of the UKPDS outcomes model, and some even borrow from the UKPDS risk equations. It is noteworthy that the CORE model group has published some trial validations.¹⁴

Meta-simulation of clinical trials using observational patient records represents a novel approach to clinical trial simulation. Chan et al employed meta-simulation of a published landmark clinical trial and compared the meta-simulation and trial results.⁴ The meta-simulated trial replicated the protocol of the Die Deutsche Diabetes Dialyse Studie (The German Diabetes Dialysis Study, 4D Study),¹⁵ and estimated the effectiveness of statins in preventing CV outcomes among dialysis patients. By mimicking the protocol of the 4D Study, the investigators vetted their approach by comparing their findings to those from a published RCT. In the meta-simulation, the cohort was constructed by applying the inclusion criteria of the 4D Study to a large observational data set containing longitudinal records for 115,000 patients with end-stage renal disease. The investigators allocated

individuals who began taking statins at some point during their dialysis treatment to a hypothetical intervention arm. Individuals who never took statins in the database were matched to individuals in the intervention arm, on the basis of similar risk factors, forming a matched control arm.

The Chan study demonstrates that meta-simulation can produce treatment effect hazard ratios that are numerically similar to those of a prospective RCT. Further, the 4D Study's findings for the primary outcome were not statistically significant, whereas the meta-simulation findings were significant due to a sample size nearly ten times larger than that of the RCT. This underscores the strength of leveraging large observational data sets.¹⁶ The apparent simplicity of the approach is attractive when communicating results, as a "simulated trial" based on observed real individuals is intuitive.

Observational studies are at risk of selection bias, because the subjects are not randomized to the control and intervention groups as they are in an RCT. Indeed, in the Chan study, simulated statin users were found to have a nonsignificant 15% increase in nonfatal angina or revascularization. This suggests that there may be residual confounding not addressed by the propensity scoring methods used by the investigators. A related challenge is database availability and suitability. For example, the 4D Study ran in a German setting, yet the simulated trial cohort was extracted from the US database, and the implication of a US versus European setting is difficult to fully quantify. Further, approaches based on observational data are less applicable to simulating trials with complex treatment protocols (eg, crossover designs) and novel therapies (eg, a new compound not present in observational data).

The aforementioned clinical trial simulation methods have been used with some success. However, their limitations motivate a model-based simulation methodology that supports a richer representation of human physiology, that can accurately forecast the impact of novel interventions, and that is less prone to the biases of observational data. In the present analysis, we applied the Archimedes Model to prospectively simulate the SAVOR-TIMI (The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus [SAVOR]–Thrombolysis in Myocardial Infarction [TIMI]) 53 trial.¹⁷ Our objective was to explore how the simulation approach may improve trial planning and support the interpretation of trial results. In the present case, the trial findings were published shortly following our simulation work. (Our simulation results were submitted to the 16th Annual European Congress on June 25, 2013. The outcomes

from the SAVOR-TIMI 53 trial were published in the *New England Journal of Medicine* on September 2, 2013.¹⁸)

Materials and methods

The Archimedes Model

The Archimedes Model is a rigorously validated simulation model of human physiology, chronic disease, and health care delivery systems.^{19,20} The model is based on a set of coupled mathematical equations that represent the physiological pathways of chronic diseases and their complications. The model includes CVDs, diabetes, respiratory conditions, and a number of cancers. One unique feature of the Archimedes Model is that it spans multiple diseases and captures the linkages between diseases and disease outcomes. Within this framework, interventions are modeled so as to operate on both the disease pathways and long-term health outcomes. Being an integrated system, the Archimedes Model is suitable for addressing diseases and syndromes that span multiple organ systems, drugs that have complex effects, and combinations of drugs. Within the simulated health care system, care is delivered according to guidelines (National Cholesterol Education Program Adult Treatment Panel III, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, etc). Further, the quality of care delivered and rates of treatment are calibrated to align with US statistics, and a full report is available on the Archimedes website (<http://www.archimedesmodel.com>). The model also provides a suitable platform for simulating clinical trials with complex protocols and subtle interactions with routine health care delivery.

The Archimedes Model is well suited to simulating clinical trials because simulated patients are based on the profiles of real people and, consequently, have correlated risk factors and biomarkers that evolve continuously over the trial period. A simulated cohort of individuals generated with the Archimedes Model has distributions and correlations of risk factors, medication usage, and medical histories reflective of real populations. The model provides facilities for selecting a cohort of simulated subjects meeting trial inclusion/exclusion criteria and then simulating each subject's life for the duration of the trial according to the specified trial protocol.

The Archimedes Model has been extensively validated, using more than 50 epidemiological and clinical studies. The model has been validated against clinical trials conducted in US, European, and multinational settings, and a detailed report of the validations is provided on the Archimedes website.²¹ Of note is the fact that some of the validations were performed prospectively (meaning the model predictions

were finalized before the trials were completed). One prospective validation of the Archimedes Model was the Collaborative Atorvastatin Diabetes Study which enrolled a UK population with type 2 diabetes. Further descriptions of the Archimedes Model are available on the Archimedes website and in prior publications.^{20,22–24}

Clinical trial simulation methods

We simulated a virtual clinical trial reflective of the SAVOR-TIMI 53 trial that was underway at the time of the analysis.¹⁷ Virtual subjects were eligible for inclusion if they had been previously diagnosed with type 2 diabetes, had an HbA_{1c} of at least 6.5% but not exceeding 12%, and had elevated CV risk. Elevated CV risk was defined as one or more of the following: at least 40 years of age and having had a previous MI or stroke; or at least 55 years old (male) or 60 years old (female) and having one of the following additional risk factors: low-density lipoprotein cholesterol over 130 mg/dL or HDL-C less than 40 mg/dL for men or less than 50 mg/dL for women, blood pressure >140/90 mmHg or >130/80 mmHg if on antihypertensive agent(s); or currently smoking.

The simulated trial cohort matched the published mean baseline risk factors: age, rising body mass index, blood pressure, HbA_{1c}, male fraction, smokers, subjects with prior MI, hypertension prevalence, as well as aspirin, insulin, and statin usage.²⁵ These risk factors were selected for matching from the randomization publication because they are direct drivers of CV risk in the Archimedes Model.²⁵

In the treatment arm, the trial DPP-4 inhibitor, representative of the class-level effects, was added on to standard diabetes care. In the comparator arm, standard diabetes care was delivered. However in all arms, no incretin-based therapies other than the target DPP-4 inhibitor were permitted. The target treatment was initiated immediately after baseline, and subjects were 100% adherent throughout the simulation. Individuals were tracked for 20 years. No loss to follow-up or other censoring was assumed, except for that due to mortality.

The trial simulations were designed and analyzed using the ARChES suite, version 2.4, which provides a Web-based interface for setting up and analyzing Archimedes Model simulations.²¹ The simulated population consisted of a sample of 11,000 patients, which is the prespecified sample size of the ARChES platform. The same sample of patients is run through each trial arm, substantially reducing the stochastic variability between arms; thus, this sample size was more than sufficient to derive statistically sound estimates of the primary end point.

DPP-4 inhibitor model

The trial DPP-4 inhibitor was a class-level treatment model, based on a meta-analysis of biomarker effects reported in the studies identified in a recent systematic review.²⁶ Studies were eligible to be included in the analysis if they were RCTs published in a peer reviewed journal and met the following criteria:

- Report data on nonpregnant participants aged 18 years and older with type 2 diabetes
 - Report the effect of the addition of any noninsulin diabetes medication on the HbA_{1c} level in subjects who were either drug naive or on background therapy with other agents
 - Include at least 30 subjects in each arm
 - Report the effect of therapy on the HbA_{1c} levels after a minimum of 12 weeks
- RCTs were excluded if:
- They reported data on subjects who did not have type 2 diabetes
 - The intervention included the initiation of two agents at the same time
 - The doses of any antidiabetic drug, except insulin, were different from the maximum dose currently recommended in clinical practice.

These criteria corresponded to the following compounds and doses: alogliptin 25 mg QD, linagliptin 5 mg QD, saxagliptin 5 mg QD, sitagliptin 100 mg QD, and vildagliptin 50 mg BID and 100 mg QD. In the meta-analysis, studies were weighted by the inverse of the sample variance. Absolute HbA_{1c} change from baseline was analyzed with a mixed effects model including a moderator for baseline HbA_{1c}. A random effects analysis was employed for absolute weight change from baseline. Meta-analyses were performed with the package metafor and R version 2.13.0.

We found that effects on lipids were not consistently reported and were often not statistically significant in literature. Effects on triglycerides were the most consistently statistically significant in the trials examined. However, the direct lipid CV risk factors in the Archimedes Model are total cholesterol and HDL-C. Therefore, effects on lipids were not included in the primary analysis, but were explored in the sensitivity analysis.

Efficacy outcomes

The primary study outcome was the occurrence of MACE, defined as the first occurrence of MI, stroke, or death from CV causes. The cumulative incidence of the first occurrence of MACE in each trial arm was reported as a Kaplan–Meier survival estimate, starting from study initiation. The relative

effectiveness of each treatment scenario was evaluated using relative risk (RR), and the absolute benefit was evaluated using the number needed to treat (NNT) to prevent one additional event over 5 years of follow-up. The RR estimates were computed as the ratio of the number of events in the intervention scenario by the number of events in the standard of care scenario. The standard error of the RR was estimated accounting for the correlation between arms due to the fact that identical sets of patients were simulated in each arm. This leads to smaller confidence intervals and *P*-values than might be expected for a similar RCT in which the arms are independent. The NNT values were derived from the Kaplan–Meier survival estimates using the method of Altman and Andersen,²⁷ comparing add-on DPP-4 inhibitor to standard of care. Standard error computations for comparative statistics also took into account correlation between trial arms. All confidence estimates reflect the statistical uncertainty resulting from the stochastic nature of the Archimedes Model. The uncertainty associated with the modeling assumptions is explored through sensitivity analyses.

Sensitivity analyses

In the sensitivity analysis, we explored the impact of variations on key modeling assumptions and meta-analysis results. The base case model for the DPP-4 inhibitor followed from the point estimate obtained in the meta-analysis. As sensitivity analyses, we also simulated DPP-4 inhibitor treatment scenarios corresponding to the upper and lower limits of the 95% confidence intervals around the HbA_{1c} and weight effects obtained from the meta-analysis. We also examined the weight and HbA_{1c} effects individually. Finally, we explored the base case model with the addition of effects on lipids, based on the estimates reported in the meta-analysis by Monami et al.²⁸

Results

Modeled interventions

Our meta-analysis yielded an estimate of the DPP-4 inhibitor class effect on HbA_{1c} of -0.66% (-0.71% , -0.62%), for a population with a baseline HbA_{1c} of 8.0% ($\tau^2=0.02$). The estimated effect on weight was -0.14 (-0.36 , 0.07) kg ($P=90$). A list of the studies included in the meta-analysis is provided in Table S1. These effects were used as the base case DPP-4 inhibitor class treatment model in the subsequent clinical trial simulations.

Simulation results

The baseline characteristics of the simulated cohort reflected those of the actual SAVOR-TIMI 53 cohort, as shown in Table S2. Treatment with the DPP-4 inhibitor class was

associated with an HbA_{1c} drop of 0.66% (0.71% , 0.62%) and a weight reduction of 0.14 (0.36 , -0.07) kg at 1 year, consistent with the meta-analysis and simulated study design.

At 5 years, the cumulative number of MACE was 1,507 (1,355, 1,658) and 1,467 (1,319, 1,616) in the comparator and intervention arms, respectively. At 5 years, the incidence of MACE was 0.134 (0.128 , 0.141) and 0.131 (0.125 , 0.138) in the comparator and intervention arms, respectively, as shown in Figure 1. This corresponded to a 5-year RR for MACE of 0.977 (0.968 , 0.986). The CV neutrality of the DPP-4 inhibitor was fairly consistent with a 20-year RR for MACE of 0.982 (0.977 , 0.986). The modest effect of the DPP-4 inhibitor on the primary end point yielded a 5-year NNT of 327 (233, 550).

Simulation sensitivity analysis

Results from the sensitivity analyses quantifying how our modeling assumptions impacted the simulation results are presented in Table S3. Each sensitivity analysis constituted an alternate treatment scenario. The sensitivity of the results to variations in the assumptions was evaluated based on the absolute change in the cumulative incidence of MACE at 5 years.

Discussion

Four decades ago, researches began to employ state transition models to better understand the most complex processes in health care.⁵ Today, the planning, execution, and interpretation of the clinical trials required to establish drug safety and efficacy stand as one of the major barriers to improving the treatment of chronic diseases such as diabetes. The potential

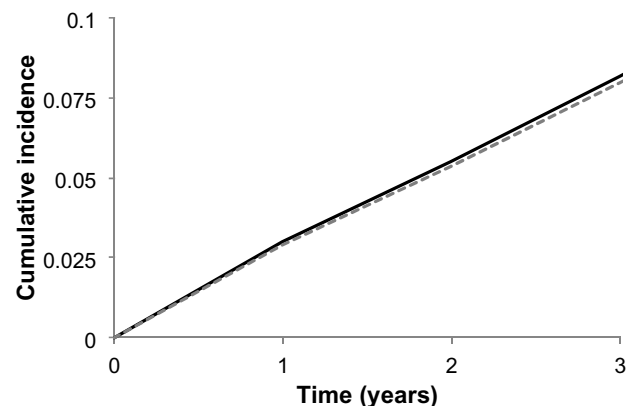


Figure 1 The Kaplan–Meier cumulative incidence of MACE.

Notes: The solid black and dashed gray lines correspond to the standard of care and DPP-4 inhibitor treatment arms, respectively. MACE was defined as the first occurrence of MI, stroke, or cardiovascular death.

Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction.

health benefits associated with new therapeutics for diabetes and CVD, as well as the staggering resource consumption associated with bringing new compounds to market, motivate advancements in simulation methods for clinical trials.

The restrictions imposed by the Markov modeling framework limit their utility for clinical trial simulation, particularly when predictions are needed over longer time scales and in cases of interacting diseases, such as diabetes and CVD, which cannot be represented effectively with a limited number of “states”. Meta-simulation based on observational data represents an emerging area of clinical trial simulation. If suitable observational data sets are available, then this approach is an attractive option due to the simplicity of the methodology (both in statistical modeling and in communication). However, conclusions obtained with this approach can be biased, as with all observational studies.

The Archimedes Model, a continuous-time/discrete-event simulation model, can provide a rich representation of human physiology and health care systems. However, the model is more complex than most other methods, and thus is best suited to research problems where accuracy and clinical detail are required. One such application is simulating the outcomes of trials where the underlying disease evolution is complex, such as the present analysis of diabetes and CVD. For this application, the Archimedes Model is unique in its ability to capture trial protocols and forecast event rates in the high-risk populations typical of CV safety RCTs.

In this analysis, we simulated the SAVOR-TIMI 53 study, prospectively, and first reported our results at the International Society for Pharmacoeconomics and Outcomes Research Annual European Congress (abstract with findings submitted on June 25, 2013). Our simulated study suggests that DPP-4 inhibitors do not increase the risk of MACE relative to the standard of care in a population with elevated CV risk. These findings agree with the CV neutral findings of the SAVOR-TIMI 53 (hazard ratio for treatment with saxagliptin of 1.00 [95% CI, 0.89–1.12]) and those of the EXAMINE trials (hazard ratio for treatment with alogliptin, 0.96; upper boundary of the one-sided repeated confidence interval, 1.16)²⁹ for the respective primary composite CV end points. Further, our analysis estimates the clinical impact of DPP-4 inhibitor treatment over a time horizon of 20 years, which is substantially longer than the trial follow-up times. Both of these trials reported their results after our simulation work was complete.

The agreement between the simulations and trial findings suggests that the benefits of DPP-4 inhibitors are largely consistent with the traditional linkages between HbA_{1c}, weight, and CV outcomes captured in the Archimedes Model.

Our sensitivity analyses explored the potential variability of our findings to alternate DPP-4 inhibitor modeling assumptions, and all sensitivity analyses lead to the conclusion that DPP-4 inhibitors are CV neutral.

Clinical trial simulations, like the present analysis, are valuable, yet they do have limitations and cannot yet replace RCTs. First, models that are largely statistical in nature, like the Archimedes Model, cannot predict intervention effects that have not yet been observed. In particular, the approach we have employed did not consider the occurrence of serious adverse drug events. Our simulation would not have been consistent with the SAVOR-TIMI 53 trial results, should there have been a substantial additional CV effect of DPP-4 inhibitors (beneficial or harmful) beyond those previously associated with HbA_{1c} and weight changes. In fact, in the SAVOR-TIMI 53 trial, more patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (HF) (hazard ratio, 1.27; 95% CI, 1.07–1.51; $P=0.007$), yet our simulations forecast lower rates of HF in the DPP-4 inhibitor group in sharp contrast to the trial findings. Additionally, a recent retrospective analysis of claims data found that sitagliptin use was associated with an increased risk of HF-related hospitalizations among patients with type 2 diabetes with preexisting HF.³⁰ Resolving this possible association between some DPP-4 inhibitors and HF will require additional trials and potentially more simulations. In such cases, clinical trial simulation may still be valuable, quantifying the magnitude of newly discovered effects, versus those associated with traditional risk factor changes. Second, clinical trial simulation depends on data inputs typically obtained through evidence synthesis and meta-analysis. In the present analysis, we observed substantial heterogeneity between the trials. We used standard meta-regression techniques to mitigate the heterogeneity, but the presence of heterogeneity suggests some uncertainty in the magnitude of the DPP-4 class effects on biomarkers, which propagates through to our final event rate estimates. Third, our simulation does not account for secular trends in either the impact of DPP-4 inhibitors or in the treatment guidelines that determine standard of care.

All told, this study provides insights about the long-term benefits of DPP-4 inhibitors for individuals with diabetes and supports the interpretation of the CV safety trial results now available.

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Supplementary materials

Table S1 Characteristics of the studies included in the meta-analysis

Source	Number	Follow-up (week)	Group	Design	Added to	Baseline HbA _{1c} (%)	Change in HbA _{1c} (%)	Change in weight (kg)	Change in SBP (mmHg)
Pratley, 2010 ¹	219	26	Staglipitin 100 mg	R, O, P	Metformin	8.50	-0.9	-0.96	-0.94
Bergental, 2010 ²	166	26	Staglipitin 100 mg	R, DB, P	Metformin	8.50	-0.9	-0.8	0.2
Ristic, 2005 ³	63	12	Vildagliptin 100 mg qd	R, DB, P	None	7.64	-0.53	"Not significant"	
Pi-Sunyer, 2007 ⁴	83	24	Vildagliptin 50 mg bid	R, DB, P	Naive	8.40	-0.7	0	
Pi-Sunyer, 2007 ⁴	91	24	Vildagliptin 100 mg qd	R, DB, P	Naive	8.30	-0.8	-0.4	
Schweizer, 2007 ⁵	526	52	Vildagliptin 100 mg qd	R, DB, P	Naive	8.70	-1	0.3	
Dejager, 2007 ⁶	92	24	Vildagliptin 100 mg qd	R, DB, P	Naive	8.40	-0.9		
Dejager, 2007 ⁶	90	24	Vildagliptin 50 mg bid	R, DB, P	Naive	8.60	-0.8		
Rosenstock, 2007 ⁷	154	24	Vildagliptin 100 mg qd	R, DB, P	Naive	8.60	-1.1	0.2	
Garber, 2007 ⁸	136	24	Vildagliptin 50 mg bid	R, DB, P	Pio	8.70	-1	"Only between group values"	
Rosenstock, 2007 ⁹	459	24	Vildagliptin 100 mg qd	R, DB, P	Naive	8.70	-1.1	"Only between group values"	
Bosi, 2007 ¹⁰	143	24	Vildagliptin 50 mg bid	R, DB, P	Metformin	8.40	-0.9	0.2	
Garber, 2008 ¹¹	132	24	Vildagliptin 100 mg qd	R, DB, P	Su	8.60	-0.63	1.3	
Bolli, 2008 ¹²	295	24	Vildagliptin 50 mg bid	R, DB, P	Metformin	8.40	-0.88	"No change"	
Pan, 2008 ¹³	441	24	Vildagliptin 50 mg bid	R, DB, P	None	8.60	-1.4	-0.4	
Ferrannini, 2009 ¹⁴	1,118	52	Vildagliptin 50 mg bid	R, DB, P	Metformin	7.30	-0.44	-0.23	
Goodman, 2009 ¹⁵	119	24	Vildagliptin 100 mg qd	R, DB, P	Metformin	8.50	-0.66		
Goodman, 2009 ¹⁵	119	24	Vildagliptin 100 mg qd	R, DB, P	Metformin	8.50	-0.53		
Bosi, 2009 ¹⁶	300	24	Vildagliptin 50 mg bid	R, DB, P	None	8.68	-1.1	-0.59	
Schweizer, 2009 ¹⁷	167	24	Vildagliptin 100 mg qd	R, DB, P	Naive	7.80	-0.64	-0.45	
Filozof, 2010 ¹⁸	513	52	Vildagliptin 50 mg bid	R, DB, P	Metformin	8.50	-0.81	0.08	
Charbonnel, 2006 ¹⁹	453	24	Staglipitin 100 mg	R, DB, P	Metformin	7.90	-0.67	"Not significant"	
Raz, 2006 ²⁰	193	18	Staglipitin 100 mg	R, DB, P	None	8.04	-0.48	-0.6	
Rosenstock, 2006 ²¹	163	24	Staglipitin 100 mg	R, DB, P	Pio	8.10	-0.85	1.8	
Aschner, 2006 ²²	229	24	Staglipitin 100 mg	R, DB, P	None	8.01	-0.61	1.5	
Hermansen, 2007 ²³	222	24	Staglipitin 100 mg	R, SB, P	Met/Met + Su	8.34	-0.45	0.8	
Goldstein, 2007 ²⁴	175	24	Staglipitin 100 mg	R, DB, P	None	8.87	-0.66	0	
Hanefeld, 2007 ²⁵	107	12	Staglipitin 100 mg	R, DB, P	None	7.78	-0.44	"No change"	
Nauck, 2007 ²⁶	382	52	Staglipitin 100 mg	R, DB, P	Metformin	7.48	-0.67	-1.5	
Scott, 2006 ²⁷	124	12	Staglipitin 100 mg	R, DB, P	None	7.80	-0.54	"Not significant"	
Scott, 2008 ²⁸	91	12	Staglipitin 100 mg	R, DB, P	Metformin	7.75	-0.73	"Not significant"	
Raz, 2008 ²⁹	95	30	Staglipitin 100 mg	R, DB, P	Metformin	9.30	-1	-0.5	
Nonaka, 2008 ³⁰	75	12	Staglipitin 100 mg	R, DB, P	None	7.50	-0.65	-0.1	
Mohan, 2009 ³¹	339	18	Staglipitin 100 mg	R, DB, P	None	8.70	-0.7	0.6	
Derosa, 2010 ³²	75	52	Staglipitin 100 mg	R, DB, P	Pio	8.50	-1.4	"Not significant"	
Rigby, 2010 ³³	56	16	Staglipitin 100 mg	R, O, P	Metformin	8.17	-0.4	-1.15	

Seck, 2010 ³⁴	248	104	Sitagliptin 100 mg	R, DB, O	Metformin	7.30	–0.54	–1.6
Aschner, 2010 ³⁵	455	24	Sitagliptin 100 mg	R, DB, O	Naive	7.20	–0.43	–0.6
Arechavaleta, 2011 ³⁶	433	30	Sitagliptin 100 mg	R, DB, P	Metformin	7.50	–0.47	–0.8
Scheen, 2010 ³⁷	334	18	Sitagliptin 100 mg	R, DB, P	Metformin	7.70	–0.62	–0.4
Scheen, 2010 ³⁷	343	18	Saxagliptin 5 mg	R, DB, P	Metformin	7.68	–0.52	–0.4
Rosenstock, 2008 ³⁸	47	12	Saxagliptin 5 mg	R, DB, P	Naive	7.90	–0.9	–0.1
DeFronzo, 2009 ³⁹	186	24	Saxagliptin 5 mg	R, DB, P	Met	8.10	–0.69	–0.87
Hollander, 2009 ⁴⁰	183	24	Saxagliptin 5 mg	R, DB, P	Tzd	8.40	–0.94	1.4
Rosenstock, 2009 ⁴¹	106	24	Saxagliptin 5 mg	R, DB, P	Naive	8.00	–0.46	–0.1
Chacra, 2009 ⁴²	253	24	Saxagliptin 5 mg	R, DB, P	Su	8.50	–0.64	0.8
Göke, 2010 ⁴³	293	52	Saxagliptin 5 mg	R, DB, P	Metformin	7.46	–0.74	–1.1
DeFronzo, 2008 ⁴⁴	131	26	Alogliptin 25 mg	R, DB, P	Naive	7.90	–0.59	–0.22
Nauck, 2008 ⁴⁵	210	26	Alogliptin 25 mg	R, DB, P	Metformin	7.90	–0.6	“Not significant”
Pratley, 2009 ⁴⁶	198	26	Alogliptin 25 mg	R, DB, P	Su	8.09	–0.53	0.68
Pratley, 2009 ⁴⁷	198	26	Alogliptin 25 mg	R, DB, P	Pio/+Met/+Su	100.00	–0.8	
Rosenstock, 2010 ⁴⁸	164	26	Alogliptin 25 mg	R, DB, P	Naive	8.80	–0.96	–0.3
Del Prato, 2011 ⁴⁹	333	26	Linagliptin 5 mg	R, DB, P	None	8.00	–0.44	
Taskinen, 2011 ⁵⁰	523	24	Linagliptin 5 mg	R, DB, P	Met	8.09	–0.49	
Forst, 2010 ⁵¹	66	12	Linagliptin 5 mg	R, DB, P	Met	8.50	–0.5	

Abbreviations: HbA_{1c}, glycated hemoglobin; Tzd, thiazolidinediones; Met, metformin; Su, sulfonylurea; Pio, pioglitazone; SBP, systolic blood pressure; R, randomized trial; DB, double-blind trial; O, open-label trial; P, parallel-group trial.

Table S2 Baseline characteristics of the simulated cohort, based on the actual SAVOR-TIMI 53 cohort

Characteristics	CV safety trial population
N	11,000
Age (years)	65.0 (8.67)
Male	0.67
SBP (mmHg)	137 (19.76)
DBP (mmHg)	79 (9.417)
TC (mg/dL)	187.7 (37.8)
HDL (mg/dL)	49.2 (14.16)
LDL (mg/dL)	100.4 (29.25)
TG (mg/dL)	191.7 (121.3)
HbA _{1c} (%)	8.0 (1.23)
BMI (kg/m ²)	31.2 (5.02)
Smoker (fraction)	0.13
Prior MI	0.38
Prior stroke	0.09
Stage 3 CKD and above	0.29
ESRD	0.02
CHF	0.10

Notes: Values are means with standard deviations in parentheses unless otherwise indicated.

Abbreviations: N, number in sample; BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; CKD, chronic kidney disease; ESRD, end-stage renal disease; CHF, chronic heart failure; CV, cardiovascular; HbA_{1c}, glycated hemoglobin; SAVOR-TIMI, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction.

Table S3 Sensitivity of the absolute MACE risk reduction associated with the DPP-4 inhibitor class, at 5 years, to different effect assumptions

Intervention sensitivity analysis	Absolute MACE incidence reduction at 5 years
DPP-4 inhibitor class (base case)	–0.0027 (–0.0038; –0.0016)
DPP-4 inhibitor class with HbA _{1c} effect only (no weight effect)	–0.0027 (–0.0038; –0.0016)
DPP-4 inhibitor class + lipid effects	–0.0035 (–0.0047; –0.0022)
DPP-4 inhibitor class based on lower 95% confidence limit effects from meta-analysis	–0.0026 (–0.0037; –0.0015)
DPP-4 inhibitor class based on upper 95% confidence limit effects from meta-analysis	–0.0030 (–0.0041; –0.0018)

Notes: For reference, in the standard of care arm the incidence of MACE at 5 years was 0.1253 (0.1189; 0.1316). MACE was defined as the first occurrence of MI, stroke, or cardiovascular death.

Abbreviations: MACE, major adverse cardiovascular events; DPP-4, dipeptidyl peptidase-4; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction.

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